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From cyclins to CDKIs: cell cycle regulation of skeletal muscle stem cell quiescence and activation

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Abstract

After extensive proliferation during development, the adult skeletal muscle cells remain outside the cell cycle, either as post-mitotic myofibers or as quiescent muscle stem cells (MuSCs). Despite its terminally differentiated state, adult skeletal muscle has a remarkable regeneration potential, driven by MuSCs. Upon injury, MuSC quiescence is reversed to support tissue growth and repair and it is re-established after the completion of muscle regeneration. The distinct cell cycle states and transitions observed in the different myogenic populations are orchestrated by elements of the cell cycle machinery. This consists of i) complexes of cyclins and Cyclin-Dependent Kinases (CDKs) that ensure cell cycle progression and ii) their negative regulators, the Cyclin-Dependent Kinase Inhibitors (CKIs). In this review we discuss the roles of these factors in developmental and adult myogenesis, with a focus on CKIs that have emerging roles in stem cell functions.

Cell cycle and myogenesis overview

Tight control of the cell cycle is imperative throughout the life of multicellular organisms. Deregulation of the cell cycle has been associated with cancer [1,2], age-related pathologies [1,3], developmental abnormalities [4,5], defective stem cell self-renewal [1,6] and stem cell loss [7]. Appropriate embryonic growth and patterning depend on a balance between proliferation and differentiation, to ensure sufficient cell propagation but not at the expense of formation of differentiated structures [8]. Once growth or tissue repair are completed, cell division plays a minor role in the homeostasis of many tissues, including skeletal muscle.

The cell cycle includes the phases of DNA synthesis and mitosis, separated by the transition G1 and G2 phases. After division, cells return to G1 and will either proceed to a new division or exit the cell cycle. In the latter case they remain in a resting, non-proliferative phase either permanently (terminal differentiation, senescence) or reversibly (quiescence). Quiescence allows cells to start cycling given specific needs. In contrast, cells driven to terminal differentiation do not re-enter the cell cycle in physiological conditions [9]. Similarly, cells can irreversibly stop dividing and go into senescence in response to developmental or regenerative cues [10–12] or to pathological damage/stress [13]. When it comes to muscle, after extensive proliferation of muscle progenitors prenatally and early postnatally, the adult skeletal muscle is mainly comprised of multinucleated myofibers, which are post-mitotic syncytial cells [14]. In addition, skeletal muscle always contains several mononucleated cell populations, with muscle stem cells (MuSCs) being central among them (see below). MuSCs exist in quiescence, a reversible state of cell cycle exit [15,16]. Despite cell cycle arrest, adult skeletal muscle can efficiently regenerate, and this regenerative capacity is largely driven by MuSCs [17–20]. Under both physiological (e.g. cellular turnover) and pathological (e.g. physical or chemical injuries, muscular dystrophies, etc) conditions, MuSCs play a pivotal role in the remodeling and regeneration processes of muscle tissue, to restore muscle mass, architecture, and function [21].

During myogenesis, activation of a complex repertoire of transcription factors is crucial for the acquisition of the myogenic fate and skeletal muscle differentiation. The myogenic lineage initially expresses the transcription factors PAX3 and PAX7, which are maintained in adult quiescent MuSCs (PAX7) or a subset of them (PAX3) [22–24]. Myogenic determination and differentiation largely rely on the Myogenic Regulatory Factors (MRFs), a family of basic helix-loop-helix transcription factors that includes MYF5, MYOD, MRF4/MYF6, and MYOG (reviewed in

[25]). As shown in **Fig. 1**, most quiescent MuSCs express MYF5 [26]; in addition, when muscle regeneration is required, MuSCs are rapidly activated, reenter the cell cycle, expand, and robustly express MRFs (MYF5 upregulation, followed by MYOD expression, followed by MYOG expression). The activated population initially co-expresses PAX7 and MYOD [27]. Subsequently, most myoblasts downregulate PAX7 but maintain MYOD, express MYOG, and follow the myogenic program to supply differentiated progeny for muscle repair (**Fig. 1**) [27]. It was recently shown that MYOG expression corresponds to limited further mitosis, as evidenced by live imaging [28]. Importantly, a subpopulation of activated satellite cells does not engage in terminal differentiation, maintains PAX7 (while losing MYOD) and returns to the quiescent state (**Fig. 1**) [27].

Disruption of MuSC quiescence leads to their exhaustion, which compromises their regenerative potential [29]. It is therefore essential to understand the mechanisms of cell cycle control and self-renewal of MuSCs through repeated cycles of growth and regeneration. These findings can lead to the development of more efficient methods to manipulate stem cells and maximize our ability to expand them *in vitro* for tissue regeneration, while avoiding malignant transformation.

Cell cycle progression and withdrawal are controlled by the same core molecular machinery across cell types, consisting of a network of Cyclin-Dependent Kinases (CDKs), Cyclins, Cyclin-Dependent Kinase Inhibitors (CKIs), retinoblastoma protein (Rb) and E2F factors (**Fig. 2**). Briefly, cell cycle progression is achieved by an array of CDKs and their activating subunits named Cyclins [30]. The regulation of these CDK-Cyclin complexes depends on the CKIs, which are classified in two families based on their structural homology and specificity of action [31]: the INK4 family that includes p15^{Ink4b} (p15), p16^{Ink4a} (p16), p18^{Ink4c} (p18), and p19^{Ink4d} (p19) and the CIP/KIP family that includes p21^{Cip1} (p21), p27^{Kip1} (p27) and p57^{Kip2} (p57). In case of CKI-mediated inhibition, the CDK-Cyclin complexes lose the capacity to phosphorylate Rb [32]. In its hypophosphorylated form, Rb can target E2F family factors, negatively affecting E2F-responsive genes that promote cell cycle progression [33]. Apart from their functions in cell proliferation, many other roles have been described for the majority of these factors, including regulation of transcription, control of translation, cell migration and apoptosis, reviewed elsewhere [34–38].

Substantial work has identified essential participants of *in vitro* cell cycle exit and differentiation of muscle cells, based on studies of the mouse myogenic cell line C2C12 or primary myoblast cultures. Nevertheless, information is generally lacking to confirm these interactions *in vivo*,

notably to understand the mechanism of MuSC entry into quiescence. In the following sections, after a brief presentation of each group of factors, relevant discoveries in the muscle field are summarized.

CDK-Cyclin complexes: cell cycle progression

General features in cell cycle regulation

The cell cycle is orchestrated by a cascade of CDKs and their associated Cyclin subunits. CDKs are serine/threonine kinases that acquire their catalytic activity via binding to a Cyclin molecule which results in conformational modifications [30]. Cyclins are structurally defined by a 100-residue domain termed the Cyclin box, which is required to bind and activate CDKs [39–41] and their expression is subject to oscillations during the cell cycle [42,43]. The mechanisms governing CDK activity involve i) activation by Cyclin binding and by CDK phosphorylation at a conserved threonine site and ii) repression by either CDKI binding (see next section), phosphorylation at inhibitory sites near the N terminus [44] or through inhibition of phosphorylation at activating sites [42]. To acquire full activation, the CDK-Cyclin complex is then phosphorylated by the CDK-Activating Kinase (CAK) [45]. The importance of CDK-Cyclin complexes in promoting transitions through the cell cycle was established in the 1990s. Less than a decade later, the Nobel prize in Physiology or Medicine (LH Hartwell, T Hunt, PM Nurse; 2001) acknowledged these key cell cycle players of all eukaryotic organisms, from yeasts to plants and animals. Studies performed in single and double knock-out mouse models showed redundant roles among some CDKs and Cyclins, with the exceptions of CDK1 [46], CyclinA2 [47] and CyclinB1 [48], the loss of which results in lethality at very early stages of embryonic development.

Mitogen availability throughout the cell cycle is an important determinant of the quiescence-proliferation decision [49]. Briefly, in the absence of signals that would impose return to quiescence, CDK4/6-CyclinD operate in G1 to bind the alpha-helix of Rb [50–52] and these complexes are followed in S-phase by CDK2-CyclinE complexes and then CDK2-CyclinA, while CyclinA further regulates important aspects of mitosis including spindle geometry (**Fig. 2**) [38,52–58] An alternative non-canonical model suggests that Rb protein phosphorylation by CDK2 rather than CDK4/6 is the critical step for the G1/S transition [59]. Finally, CDK1 (CDC2) is involved in the S/G2 checkpoint and transition, where it forms complexes with CyclinB or CyclinA [53,60–62].

Finally, non-canonical CyclinF is involved in the degradation of cell cycle proteins such as E2Fs [63] and its proteolysis ensures timely mitotic progression [64].

Apart from their canonical roles, some CDK and cyclin families have been implicated in translation [65,66], telomere protection [67], and transcription [68,69]. Some family members may exceptionally play a role in the control of proliferation, such as the requirement of CyclinK for prereplicative-complex assembly [70] or CDK9 involvement in cancer [71]. These CDK families are more conserved and their ablation results in embryonic lethality, suggesting non-redundant roles [72].

Implications in skeletal muscle cell cycle regulation

Dividing and differentiating myoblasts have been extensively analyzed for the presence and activity of various CDK-Cyclin complexes. Among CDKs, CDK4 has been broadly studied (**Table 1**). CDK4 is expressed in both myoblasts and myotubes [73,74], but in myotubes it is associated with the cell cycle inhibitors p21 and p27 rather than with Cyclins [75]. Moreover, CDK4 subcellular localization depends on CyclinD1: nuclear in dividing myoblasts expressing CyclinD1, and cytoplasmic in myotubes, which lack CyclinD1 [76]. This subcellular pattern is opposite to that observed for the cell cycle inhibitor p57 [77]. Chemical inhibition of CDK4/6 activity by PD 0332991 promotes accumulation at G1 at the expense of S phase and it enhances muscle-specific gene expression [78] (**Table 2**). Conversely, forced expression of CDK4 and CyclinD1 in C2C12 or primary myoblast cultures triggers DNA synthesis in myotubes, alters muscle-specific gene expression [79] and represses MEF2 activity [80] (**Table 2**). Zhang and colleagues showed that MYOD-CDK4 binding can block the DNA binding capacity of MYOD [76] and the ability of CDK4 to phosphorylate Rb [81] (**Table 2**). These inhibitory interactions might depend on MYOD and/or CDK4 levels, involvement of other partners in the MYOD-CDK4 complexes or subcellular trafficking. It should be noted that MYOD-CDK4 complexes were observed in the nuclei of dividing myoblasts, but not in differentiated myogenic cultures [76]. Even though most CDK4/6 studies rely on the C2C12 cell line, the data are concordant with those coming from primary cells, when such cells were analyzed.

Levels of both CDK4 and CDK6 are constant during myocyte differentiation [75], while their CyclinD partners show divergent patterns in myogenic cell line cultures: i) CyclinD1 is high in the proliferating population and low in the differentiating one, ii) CyclinD2 is not detectable in any of

the populations, and iii) CyclinD3 surprisingly increases upon differentiation, although Cyclins are traditionally involved in proliferation rather than differentiation (**Table 1**) [73,75,82–86]. In line with these *in vitro* results, CyclinD1 protein levels are high prenatally and decline after birth, while CyclinD3 is high at fetal and early postnatal stages [86,87]. Studies on *CyclinD1* levels during aging have reached contradictory results depending on the cell activation status: the Brack lab showed through mouse MuSC single-cell RNAseq age-related (20-month-old vs. 3-month-old) upregulation of *CyclinD1* in activated and activated+quiescent MuSCs [88], while the Rando lab found decreased *CyclinD1* in quiescent old MuSCs (18-22 months of age), which was restored by exercise [89]. Lack of CyclinD1 causes defects in other organs [90–92], but not in skeletal muscle, which implies the presence of compensatory effects by other factors. However, MuSC-specific CyclinD1 deletion results in reduced MuSC activation post-injury (**Table 2**) [89]. As mentioned above, CyclinD3 is the only G1 Cyclin upregulated upon myogenic differentiation [73,75,82]. In fact, the myogenic regulatory factor MYOD activates CyclinD3 expression, assisted by the co-activator p300 [93]. CyclinD3 is involved in the induction but not the maintenance of muscle differentiation. Consistent with this, CyclinD3 is highly expressed during development and perinatal growth, but is absent in adult skeletal muscles [86,87,94]. Furthermore, when overexpressed, CyclinD3 primes C2C12 myoblasts for differentiation by enhancing the expression of myogenic differentiation and cell cycle exit factors [95]. Interestingly, ectopic expression of CyclinD3 rescues the differentiation phenotype of Myotonic Dystrophy type 1 myoblasts [96]. Studying CyclinD3 knock-out mouse muscles showed smaller fibers and lower MuSC numbers under homeostatic conditions as well as reduced MuSC renewal after *in vitro* or *in vivo* activation [86]. Furthermore, CyclinD3 is involved in muscle metabolism and myofiber type identity (**Table 2**) [97].

Fewer studies focused on the other CDK-Cyclin complexes. The mitotic complex of CDK1-Cyclin B phosphorylates MYOD, leading to the repression of MYOD-dependent transactivation as well as to diminished MYOD protein levels during mitosis (**Table 2**) [98]. CyclinB1 expression is induced by muscle injury (**Table 1**) [99]. Muscle-specific expression of different CDKs and Cyclins in *C.elegans* activates the cell cycle transcriptional program, without loss of the differentiated state. Under these experimental conditions, cell cycle reentry and S-phase induction are not driven by CDK2-CyclinE but rather by CDK4-CyclinD [100]. In line with this observation, ectopic CDK2-CyclinE does not reinforce cell cycle reentry in differentiated myotubes, as opposed to the G1 CDK4-CyclinD complex, in C2C12 and primary myoblasts [79]. CDK2-associated kinase activity was observed in lysates from proliferating C2C12 myoblasts, but not from differentiated myotubes

(**Table 1**), while inactive CDK2-CyclinE complexes persist in the latter [74,101]. CDK1 is found in dividing fractions of satellite cells/myoblasts rather than in their quiescent or differentiating counterparts [74,102]. Accordingly, CDK2 and CDK1 exhibit high kinase activity towards MYOD in C2.7 myoblasts but not in myotubes, regulating MYOD turnover; specifically, by phosphorylating Ser200, CDK1/2 promote MYOD degradation (**Table 2**) [103]. CDK2 immunoprecipitates with CyclinA in proliferating C2C12 myoblasts [84], in agreement with the role of this complex in S-phase (**Fig. 2**). However, upon differentiation there is evidence that CDK2 is sequestered away from CyclinA into inactive CDK2-CyclinD3-p27 complexes [84]. In addition, CDK2 regulates satellite cell migration following injury-induced activation during muscle regeneration (**Table 2**) [104]. CDK1 also controls satellite cell-mediated muscle regeneration and hypertrophy following injury and overload, respectively (**Table 2**) [74]. Finally, single-cell RNAseq analysis showed that *CyclinA2*, *CyclinB1*, and *CyclinE2* are present in clusters of activated but not quiescent MuSCs [105], while CyclinB and CyclinE are transiently upregulated at three days post-injury when MuSCs are generally activated (**Table 1**), possibly to allow myoblast expansion before differentiation to new muscle fibers [106]. In aged regenerating muscles, the CyclinB/E upregulation window spreads from day 1 to day 3, implying extensive or premature proliferation and exhaustion of myoblasts before efficient regeneration of the injured muscle [106].

Cyclin transcription is directly regulated at the epigenetic level by the PRC2 complex and more precisely by the EZH2 catalytic subunit of the complex. EZH2 represses the expression of several Cyclins and their associated CDKs in myogenic cells (C2C12 cell line and primary myoblasts) [107].

Regarding the CDK families that are implicated in transcription rather than cell cycle progression, scarce data are available. In contrast to cell cycle-related CDK-Cyclin complexes, CDK9-CyclinT2 enhance MYOD function and promote differentiation [108,109]. In addition, CDK12 is linked to transcription of DM1 expanded repeats in Myotonic Dystrophy type 1, which is counteracted by CDK12 selective inhibition, thus providing a druggable target for this disease (**Table 2**) [110].

CDKs: negative regulators of CDK-Cyclin activity

General features in cell cycle regulation

The control of CDK-Cyclin complex formation and activity is largely dependent on the CDKs, which fall into two broad categories based on their structural and functional profile. Proteins of

the INK4 family contain conserved ankyrin repeats [111–113], a motif participating in protein recognition and interaction [114]. CIP/KIP family members show partial structural homology. They share a kinase inhibitory domain in their N-terminal region and a nuclear localization signal in their C-terminal region [115–117]. In addition, p21 and p57 contain a C-terminal PCNA-binding domain that allows interaction with PCNA and prevents DNA replication [118–120]. Moreover, p27 and p57 contain a C-terminal QT box with a consensus CDK phosphorylation site [115–117], involved in their SCF/Skp2-mediated degradation [121].

These structural differences underlie the divergent specificity of action between the two CDKI families at two levels:

- 1) the INK4 family members are selective inhibitors of CDK4 and CDK6, leaving the other CDKs unaffected [111–113,122,123]. In contrast, CIP/KIP proteins bind and inhibit all CDK-Cyclin complexes that are formed throughout the cell cycle [115–117,124–127], consistent with the fact that these complexes exhibit intrinsic flexibility and are largely disordered before binding to other proteins [128].
- 2) INK4 inhibitors can bind to untethered or Cyclin-associated CDK subunits, causing a strong inhibition of CDK catalytic activity and inducing G1 arrest [111–113,122,123]. In contrast, p21, p27, and p57 bind CDK-Cyclin heterodimers, with the affinity for CDKs increasing with Cyclin association [115,117,124–127,129].

Some exceptions to the standard dogma of CDKIs inhibiting CDK-Cyclin activity have been described. Briefly, there are sporadic reports of p21, p27 or p57 binding to CDK-Cyclin complexes without stopping their kinase activity [130], stabilizing CDK-Cyclin complexes (p21: [129,131–133], p27: [134–136], p57: [137]), or promoting their nuclear localization and thus substrate access [138]. Thus, CIP/KIP proteins might function as titratable buffers and repress CDKs in a concentration-dependent manner. It has also been proposed that sequestration of p21 and p27 in CDK4-CyclinD complexes early in G1 prevents these CDKIs from binding to CDK2-CyclinE complexes to allow cell cycle progression [44,139]. The above properties could explain the observations that p21 is among the most highly induced genes during early MuSC activation [140], even though MuSC activation signifies passing from quiescence to proliferation. Finally, contrary to its role in inhibiting the cell cycle, p57 was recently found to transactivate the proto-oncoprotein c-Jun and c-Jun-induced transcription [141].

Apart from their role in the cell cycle, CDKIs have been implicated in terminal differentiation of multiple lineages during organogenesis [142–145], cellular senescence [91,146–151], apoptosis (reviewed in [34]), transcription [141,152,153], and autophagy via an mTORC1-dependent mechanism [154].

Implications in skeletal muscle cell cycle regulation

Expression of CDKIs is generally increased during myogenesis, as shown in mouse embryos and myogenic cells. When the equilibrium is shifted to or against one of these factors, the differentiation and proliferation capacities are rapidly affected *in vitro*. More recently, *in vivo* data started to support the unique and redundant roles of CDKIs for muscle development, homeostasis, and regeneration. Further studies are expected to elucidate the currently poorly understood role of CDKIs in the entry (early postnatally) or re-entry (post-regeneration) of MuSC into quiescence.

A limited number of studies have evaluated the impact of the INK4 family on the muscle lineage. Terminally differentiated adult muscles or C2C12-derived myotubes lack p15 (**Table 1**) [155] and *p15*-null mice are not reported to display muscle defects (**Table 2**) [156]. However, p15 is elevated in MuSCs from aged animals along with other CDKIs and this could contribute to the defective regeneration of old muscle [157]. Similarly to p15, p16 is absent from proliferating C2C12 cells, myotubes or adult muscle samples (**Table 1**) [155,158]. However, during muscle regeneration both p15 and p16 proteins increase to reach a peak at day 3 post-injury (**Table 1**) [159], with p16 being upregulated in mesenchymal stromal cells at days 1 and 3 post-injury [160]. Furthermore, ectopic p16 is associated with increased muscle-specific gene expression (**Table 2**) [73] as well as protection of differentiating C2C12 from apoptosis [161], the latter occurring only in the presence of Rb [162]. p16 transcript and protein levels increase with aging in experimental models and human samples (**Table 1**), with its promoter exhibiting higher chromatin accessibility following injury-induced MuSC activation [157,163,164]. In addition, aging-associated p16 derepression ignites a switch of resting geriatric MuSCs from reversible quiescence to an irreversible pre-senescence state, compromising muscle regeneration [165]. p16 levels depend on the transcription factor Slug that represses p16 in MuSCs, inhibiting their entry into senescence, while Slug overexpression enhances muscle regeneration during aging [146]. The extent of p16/senescence in human MuSCs remains to be properly characterized, due to technical challenges [166,167], even though preliminary analyses show that *p16/p21/p14* mRNA

is present in some Duchenne muscular dystrophy samples as opposed to controls [168]. However, proper controls and quantifications are lacking in that study. In the context of muscle cancer rhabdomyosarcoma, p16 inactivation was found to not be important for pathogenesis [169]. Apart from MuSCs, p16 has also been found in endothelial progenitors (CD34+ intramuscular cells) and in cells infiltrating necrotic myofibers after exercise [170]. p18 shows a remarkable increase upon C2C12 differentiation, that is regulated transcriptionally (promoter switch to produce a different transcript) and translationally (**Table 1**) [155,171]. Furthermore, there is a continuing increase of p18-associated CDK4 and CDK6 [155]. In adult muscle tissue, p18 is abundant in mouse and human (**Table 1**) [122,155] and it is associated with all CDK6 molecules and half of the CDK4 ones (shared with p27) [155]. However, p18 deficiency is not reported to cause a muscle phenotype [156,172]. *In vivo* regeneration studies show an early transient increase in p18 levels (**Table 1**), although this effect was not further evaluated [159]. p19 is the only CDKI expressed at high levels in proliferating C2C12 myoblasts and declining following differentiation [155]. The reciprocal p19 decrease and p18 increase (**Table 1**) suggests either that p19 loss is compensated by p18 expression to induce cell cycle exit during differentiation or that p19 and p18 play distinct functions during myogenic cell cycle progression and exit. Finally, p19 (as well as p16 and other senescence markers) were found upregulated in the context of a muscular dystrophy [168].

Members of the CIP/KIP family have been more extensively explored in the myogenic lineage. Historically, most studies focused on p21, the first family member to be identified that showed early and robust skeletal muscle-specific expression (**Tables 1-2**). When C2C12 myoblasts are maintained in proliferation conditions, p21 is generally low [101]. p21 protein reaches detectable levels close to G1, but at mitosis entry it rapidly decreases [98]. After switching to differentiation conditions, p21 sharply increases [101,155,158,173,174], appearing in myocytes and myotubes [175,176]. Consistent with a role in differentiation-associated growth arrest, myotube p21 (a) immunoprecipitates with CDK2 and CDK4, (b) shows increased interaction with CDK2, CDK4, and CDK6 compared to myoblasts, and (c) exceeds the quantity of active CDK4-Cyclin [75,155,162,177]. In fact, p21 overexpression in C2C12 cells is sufficient for cell cycle withdrawal under growth conditions [178], while p21-deficient primary myoblasts show increased proliferation [179] and siRNA-mediated p21 suppression stimulates S phase entry in myotubes [180]. p21 maintains CDK4/6-CyclinD3 inactive in differentiating C2C12 myogenic cells [180], while CyclinD3 regulates p21 expression at the post-transcriptional level in C2.7 myoblasts [86]. It has been suggested that the interaction of p21 and CDK4 in differentiating C2C12 cells is

inhibitory, whereas p21 stabilizes CDK4-CyclinD1 activity when myogenic cells undergo hypertrophy [85].

Apart from the effects on muscle cell proliferation, p21 has also been studied in the context of myogenic differentiation (**Tables 1-2**). *In vivo*, it was shown that when myogenic nuclei fuse with myofibers, they present terminal differentiation characteristics and p21 protein expression once they are in the myofiber [181]. Forced p21 expression promotes muscle-specific gene expression, rescues CyclinD1-mediated *MyoD* repression and exerts protection against apoptosis in myogenic cell lines [73,161]. It would be interesting to verify if these results are reproducible *in vivo* with the newly generated mice that allow Cre/Dre-inducible p21 overexpression [182]. Conversely, primary myoblast cultures from *p21*-null animals show differentiation defects and increased apoptosis [179]. MYOD transcriptionally activates *p21* [98,173] and p21 is able to inhibit MYOD phosphorylation, stabilizing it [158]. A MYOD version that cannot be phosphorylated sustains *p21* expression, which interferes with M-phase entry [98]. However, in the absence of MYOD, p21 expression is delayed during muscle development [142]. MYOD-mediated p21 induction and p21 expression in the developing muscle are p53-independent [142,173], although p21 is transcriptionally regulated by p53 in other cell types [183]. Overexpression and silencing approaches established CyclinD3 as another factor that enhances p21 expression [86,95]. This is in agreement with the notion that CyclinD3 is the only G1 Cyclin that promotes myogenic differentiation rather than proliferation. p21 has been postulated to be a direct target of MYOG because (a) MYOG binding sites are detected in the *p21* promoter [184] and (b) on a protein level, p21 expression follows MYOG upon differentiation [185]. However, when myoblasts are induced to differentiate, *p21* transcripts appear before *Myog*, while MYOG knock-out embryos provided unequivocal evidence that MYOG is not required for p21 induction [142]. *p21* has also been identified as a target gene of the histone deacetylase HDAC4, which represses *p21* to allow MuSC amplification [186]. Finally, it was shown that the protein arginine methyltransferases PRMT5 and PRMT7 participate in the epigenetic silencing of p21 in MuSCs [187,188]. The effect of PRMT7 is mediated by the methyltransferase DNMT3b [188]. In addition, DNMT3a has been implicated in the epigenetic control of p57 in MuSCs [189].

The *in vivo* profiling of p21 expression in muscle reveals age-related differences. During development and the establishment of the muscle lineage, *p21* mRNA first appears in the forming myotome of E8.5 embryo somites [142]. From E10 it follows the *Myog* expression pattern [142]. In the adult, p21 protein is not detected in skeletal muscles [155]; our unpublished observation],

while mRNA expression is unclear. Very high [142,190] or undetectable [191] transcripts were reported in adult skeletal muscles; differences in analyzed muscles, mouse background, age window, or probes could partially explain these differences. In the *mdx* mouse model of Duchenne Muscular Dystrophy, elevated *p21* transcripts have been reported [192], while trans-differentiating fibroblasts from a rare human congenital myopathy also show upregulated *p21* [193]. MuSC-focused analysis revealed *p21* increases with aging along with increased chromatin accessibility at the *p21* locus and high *p21* protein expression post-injury [157,163,164,194]. The interplay of TGF β and Notch seems to ensure low *p21* (and also *p15*, *p16*, *p27*) in young muscles as opposed to their upregulation upon aging [195]. However, a more recent study reported a striking 90% reduction in *p21* protein levels in aged human muscles, with the reduction being unaffected by exercise training [196]. Rat primary myoblasts from aged animals also show a delay in expressing *p21* when cultured [197].

Although *p21* has been shown to play important roles in the regulation of the muscle lineage cell cycle *in vitro*, ablation of *p21* in mice does not affect skeletal muscle development, proliferation or differentiation nor the establishment of the MuSC compartment [179,198–200], our unpublished observation]. In addition, AAV-mediated transient suppression of *p21* does not affect the differentiation capacity of myoblasts nor does it induce genotoxic effects [201]. In injury-induced activation of MuSCs, *p21* seems to exert its function during the early period of the regeneration process. Specifically, during the first few days post-injury, *p21*-deficient mice display increased proliferation, cell numbers, and inflammation, accompanied by decreased expression of myogenic differentiation markers. However, one month post-injury *p21*-null muscles are comparable to controls [159,179,199,200], our unpublished observation]. It was recently shown that *p21* is part of the transient stress response core [202], which suggests that it may play an early function in promoting assembly of the CDK-Cyclin complexes to drive entry into proliferation, as previously proposed for *p57* (see below).

Searching for alternative cell cycle regulators in cells undergoing G1 arrest and myogenic differentiation, the groups of Maione, Lanfranchi, and Leibovitch independently identified *p57* [158,177,203]. *p57* increases when C2C12 cells are stimulated to differentiate (**Table 1**) [158,174] and when embryonic muscle progenitors proceed to myogenic determination and differentiation [204]. *p57* also translocates from the cytoplasm to the nucleus during differentiation of adult satellite cells [77]. During development, *p57* is present in most nuclei of limb and abdominal wall muscles [5,204,205], but *p57* knock-out mice do not manifest a severe muscle phenotype

[4,5,205], implying the presence of compensatory mechanisms (see below). In the adult muscle, p57 progressively decreases as mice age based on whole-muscle analyses [190]. Furthermore, p57 is barely detectable in adult mouse MuSCs at the protein level [77,189,199] with the exception of one study of FACS-isolated MuSCs [206]. A recent single-cell RNAseq screen found *p57* transcripts in clusters of quiescent human MuSCs [105]. It remains to be established whether this reflects specific flow cytometry gating, a difference in human versus mouse samples, and/or activation artifacts that are commonly induced by sample preparation [140,207,208]. In contrast to resting quiescent mouse MuSCs, p57 peaks soon after muscle regeneration is initiated and is maintained at higher than homeostasis levels throughout regeneration (**Table 1**) [159,194], our unpublished observation]. p57 deletion in the MuSC lineage severely impairs muscle regeneration post-injury (**Table 2**) [77], while low expression of p57 is a marker of aggressive phenotype and poor prognosis in the context of the skeletal muscle cancer rhabdomyosarcoma [169].

p57 and MYOD have been implicated in a positive feedback loop *in vitro* and *in vivo*, whereby MYOD induces p57 which then enhances MYOD activity and stability (**Table 2**). Although three putative MYOD binding sites proximal and downstream from the transcription start site of p57 are not functional [203], MYOD-responsive regions upstream of the transcription start site of p57 were identified by us and others [203,204]. We found a muscle-specific *p57* regulatory element which contains MYOD-bound E-boxes that show transactivation in myogenic cells *in vivo* [204]. In addition, general (not muscle-specific) MYOD-regulated p57 regulatory elements have been identified *in vitro* i) within the imprinting control region KvDMR1 [209] and ii) in a new intragenic region [210]. *In vitro* studies, based mostly on fibroblasts converted to the myogenic lineage, suggested that MYOD plays a dual function in inducing p57. First, it counteracts *cis*-acting repression, by sequentially interacting with CTCF, disrupting the CTCF-mediated chromatin loop, and releasing the p57 promoter. Second, it assists upregulation by the intermediate factors p73, SP1, and EGR1 [211–214]. *MyoD* knock-down in zebrafish embryos reduces p57 expression, while MYOD overexpression promotes ectopic p57 in somatic and head mesoderm of zebrafish [215]. Notably, MYOD-induced myogenic conversion of fibroblasts upregulates p57 only in the absence of p21 [81,177], implying intrinsic differences between fibroblasts and myogenic cells. In the opposite direction, p57 was found to promote MYOD accumulation in the myogenic progenitors (adaxial cells) of zebrafish embryos [215]. Co-immunoprecipitation assays showed that p57 directly binds to MYOD, through the basic region of MYOD and the amino-terminal domain of p57 [216]. Remarkably, the same p57 helix domain that is indispensable for CDK-Cyclin inhibition

is also important for MYOD binding [216,217]. *In vitro* dissection of the underlying mechanism revealed that p57 increases MYOD stability by inhibiting its phosphorylation by CDK2-CyclinE complexes [158], while p57- MYOD binding is competed by CDK4-CyclinD1 complexes [216].

Based on the profile similarities of p21 and p57 during myogenesis, their colocalization in differentiating myotubes *in vitro*, and the normal muscle development of single p21 or p57 knock-out embryos, their possible redundancy during development was evaluated by concomitantly ablating both factors [218]. Simultaneous abrogation of p21 and p57 increases Rb phosphorylation by CDK2, increases myoblast proliferation and apoptosis, and induces endoreplication of residual myotubes at the fetal stage. Multiple muscle groups (head, trunk, limb) are severely diminished in double knock-out embryos, with the overall phenotype resembling that of *Myogenin*-deficient embryos. Molecular genetic experiments placed p21 and p57 in parallel to MYOG rather than upstream or downstream of this MRF. Whether the redundant functions of p21 and p57 are at play during adult myogenesis remains to be shown.

p27 was found to participate both in the differentiation program and in maintaining a subpopulation of MuSCs. During C2C12 myogenic differentiation, p27 protein levels increase (**Table 1**), even though the mRNA amount remains constant, implying posttranslational regulation [84,155,158,173,174,219]. Ectopic p27 inhibits proliferation and promotes differentiation, while p27 repression leads to opposite effects in C2C12 and primary myoblasts (**Table 2**) [174,220]. The β 2-adrenoceptor agonist clenbuterol that was tested in rodent models of dystrophy, denervation and aging for its anabolic effects, was shown to induce cell cycle arrest by increasing the levels and nuclear accumulation of p27 [219]. Co-IP experiments showed that p27 can associate with MYOD (**Table 2**), possibly regulating transcription [221]. During hypertrophy of myogenic cells *in vitro*, p27 was proposed to function primarily as a CDK2 inhibitor at the G1/S transition [85]. *p27* deficiency leads to general hyperplasia and increased body size and muscle mass (**Table 2**), with the latter being partially mediated by decreased Myostatin [222], a protein inhibiting muscle growth. An in-depth *in vivo* analysis of MuSC subpopulations was performed using the retention of a H2B-GFP label as a reporter of proliferative history. This study revealed that p27 is required to maintain the primitive fate of a subpopulation with label-retaining dormant behavior (**Table 1**) [199]. The same team showed that p21 is acting in the non-label-retaining MuSCs to promote lineage commitment [88,199]. These *in vivo* findings are in agreement with early *in vitro* observations, whereby p21 is enriched in differentiated myotubes and p27 in self-renewing reserve cells [176]. Further supporting this model, p27 is only transiently

expressed in the developing muscle masses between E10.5 and E11.5 and all p27+ cells co-expressed MYOD, while only a subset had MYOG [223]. During aging, hypophosphorylation of AMPK and its downstream target p27 were recently found to be associated with reduced autophagy and increased apoptosis that characterizes aged MuSCs [224]. Restoration of phosphorylated p27 is sufficient to suppress the apoptosis and cell cycle defects, leading to improved *in vivo* grafting capacity of aged MuSCs [224].

Concluding remarks

Skeletal muscle develops and repairs itself under fine molecular regulation, in which cell cycle control is central. The precise regulation of proliferation and cell cycle arrest (quiescence, differentiation) have been explored by many groups over the last 30 years, elucidating the complex interactions between factors that sustain (e.g. CDK-Cyclin complexes) or inhibit (e.g. CDKIs) proliferation of muscle cells. Few exceptions to this dogma have been noted and are summarized here. First, analysis of cell cycle factor expression during the first week post-injury has shown concomitant increase of proliferation-promoting and proliferation-inhibiting molecules. As this was based on bulk cell analysis at each day post-injury, single cell analysis or a finer time-course could elucidate whether proliferation-promoting and proliferation-inhibiting factors are restricted to activated/proliferating and differentiating cells, respectively. Second, CDK4 and p57 are found in differentiating and proliferating cells, respectively, but this unexpected finding is accompanied with cytoplasmic rather than nuclear presence. In contrast, both factors are nuclear when they are shown to promote (CDK4) or inhibit (p57) proliferation. Third, CyclinD3 is the only Cyclin that is expressed in differentiation conditions, and it was shown to actively block proliferation by sequestering CDK2 in inactive complexes. On a similar note, CDK2-CyclinE complexes were reported in differentiating myoblasts, but they were inactive. Lastly, the cell cycle inhibitor p19 is high in proliferating and low in differentiating C2C12 cells but its role has not been further investigated.

Historically, most studies of cell cycle factor effects on the muscle lineage have been initiated on the C2C12 myogenic cell line or on MYOD-converted fibroblasts, with results not being validated on primary myoblasts, freshly isolated MuSCs or *in vivo*. More recently, *in vivo* high-throughput transcriptomic analyses identified cell cycle regulators among differentially expressed genes, but validation of these findings is lacking. Furthermore, whereas many early studies focused on development, detailing expression patterns and knock-out phenotypes of cell cycle factors, less work has been published on their postnatal role in muscle homeostasis, regeneration, and aging,

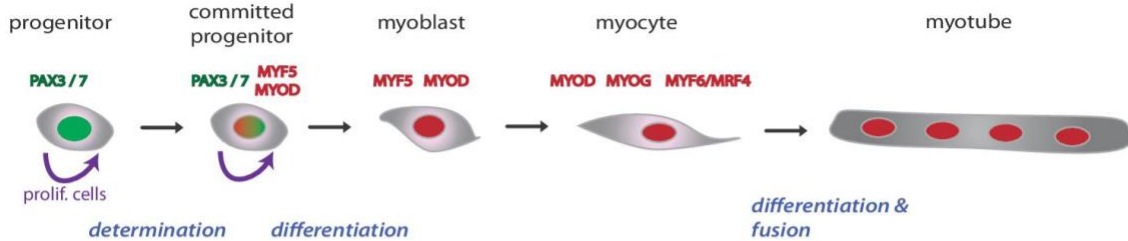
including MuSC quiescence (**Table 1**). Elucidating the gatekeepers of MuSC quiescence could have a major impact on the delivery of functional cells when cell therapies are considered as treatment for myopathies. Moreover, it would be interesting to develop a mathematical model describing the cell cycle dynamics of myogenic cells, as was recently done for the muscle regeneration process [225]. Finally, the field would benefit from confirmation of findings in human samples (normal or dystrophic muscle) which have been less studied than rodent models (**Table 1**). Overall, there has been substantial research on the cell cycle regulation of myogenesis, but many aspects remain to be characterized especially in postnatal and human muscle biology.

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Figures and Figure Legends

Development



Adult

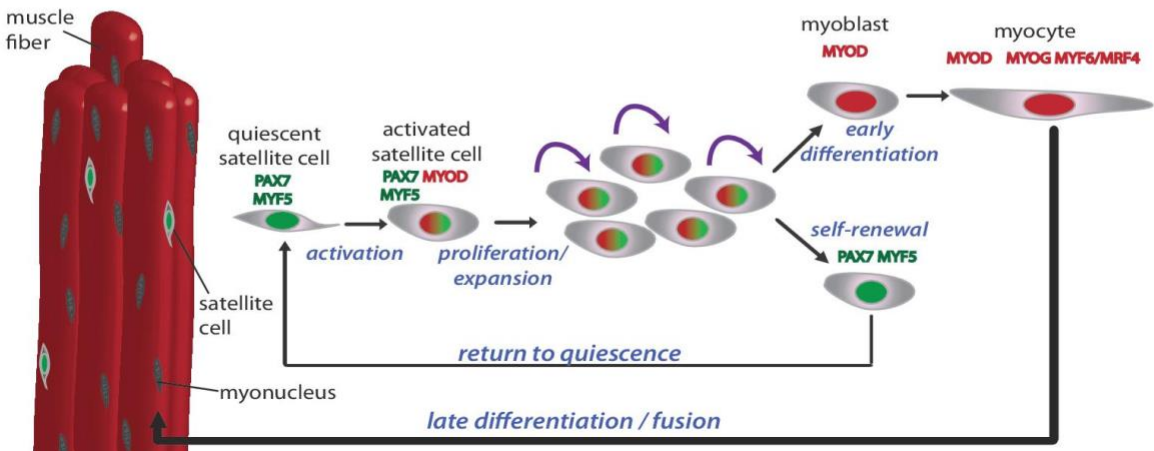


Figure 1. Cellular and molecular aspects of myogenic differentiation during development (top) or during postnatal skeletal muscle regeneration (bottom).

Top: embryonic and fetal progenitors are mitotically active and have not engaged in the myogenic program. The transcription factors MYF5, MYOD, and MYOG are sequentially expressed in progenitors that commit to the differentiated lineage and form the multinucleated myotubes that mature into myofibers.

Bottom: Myofibers of adult muscle are postmitotic and they are accompanied by muscle stem cells, termed satellite cells because of their anatomical position in the periphery of myofibers. Satellite cells are quiescent in resting muscle but enter the cell cycle to repair damaged muscle. Most of these activated cells will proceed to myogenic differentiation to form new myofibers, while a small subpopulation will self-renew to maintain the quiescent pool for future needs. Markers of muscle stem/progenitor cells are shown in green. Myogenic regulatory factors involved in myogenic progression during differentiation are shown in red. Cellular changes are shown in blue.

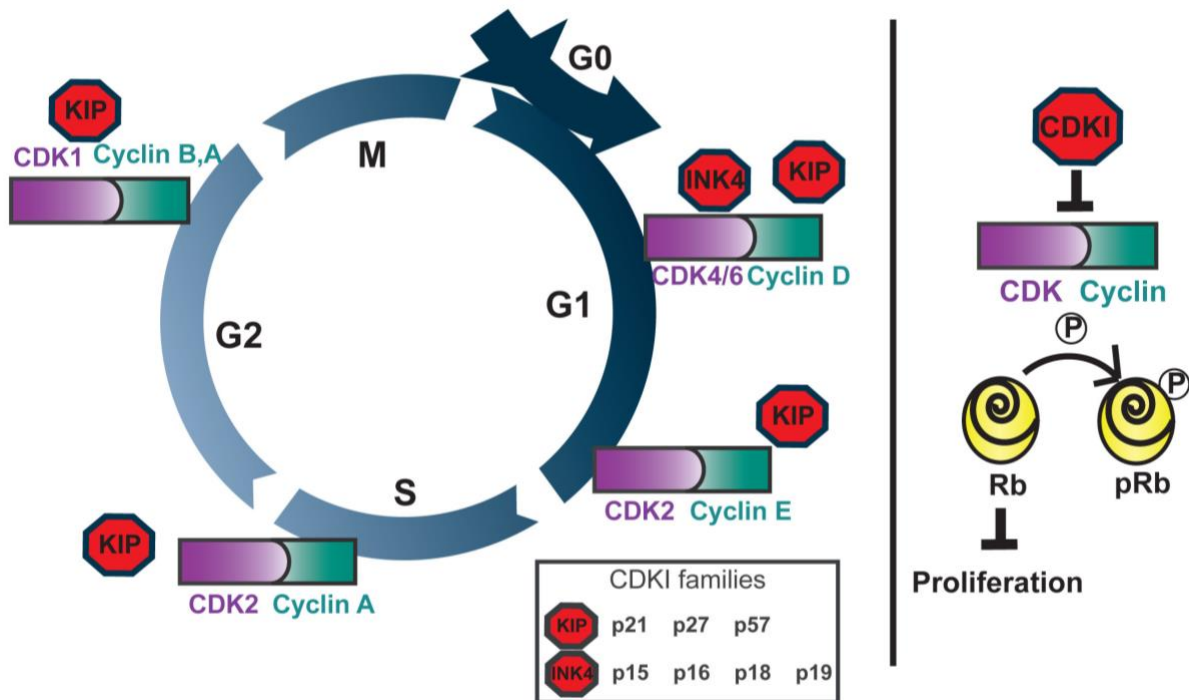


Figure 2. Cell cycle progression and arrest.

Non-cycling cells are maintained at the resting, non-proliferating phase called G₀, while cycling cells undergo S-phase (Synthesis; DNA replication step) and M-phase (Mitosis; division step), which are separated by two "gap phases" (G₁, G₂). Cell cycle progression depends on the activity of various complexes of Cyclin-Dependent Kinases (CDKs) and Cyclins, acting on different cell cycle transitions. When active, these complexes phosphorylate the retinoblastoma protein (Rb), blocking its inhibitory activity on proliferation. Two families of Cyclin-Dependent Kinase Inhibitors (CDKIs) counteract the activity of CDK-Cyclin complexes at early G₁ phase (family INK4, encompassing p15, p16, p18, p19) or throughout the cell cycle (family CIP/KIP, including p21, p27, p57).

Table 1. Expression pattern of cell cycle factors in different cell or tissue states of myogenesis

white: no data; /: not expressed; grey: low expression; black: high expression VR: variable results have been reported by different groups, please refer to text for details. In grey and black, subcellular expression is indicated when known: N (nuclear)/C (cytoplasmic)

Cell cycle factor		Cell level*			Tissue level**			Ag	References
		Q	AP	D	NI	AI/R	CP		
CDKs and Cyclins	CDK1								[74,79,102]
	CDK2			VR					[74,79,84,101]
	CDK4		N	C					[73–76,79]
	CDK6								[75]
	CyclinA								[79,84]
	CyclinA2								[105]
	CyclinB								[106]
	CyclinB1								[99,105]
	CyclinD1							VR	[73,75,79,82–86]
	CyclinD2								[73,75,82–86,88,89]
	CyclinD3								[73,75,82,86,87,94]
	CyclinE								[74,79,101,106]
	CyclinE2								[105]
CDKIs	p15								[155,157,159,195]
	p16				\$				[155,157–160,163–165,168,170,195]
	p18								[122,155,159,171]
	p19								[155,168]
	p21				VR			VR	[79,98,101,142,155,157,158,163,164,173–176,190–193,195–197,202]
	p27								[79,84,88,155,158,173,174,176,195,199,219,220,224]
	p57	VR	C	N					[77,105,158,159,174,189,190,199,206]

*Q: quiescence (*in vivo*: satellite cells, *ex vivo*: reserve cells that appear in differentiating cultures and have satellite-cell-like features); AP: activation and/or proliferation (myoblasts); D: differentiation (myocytes or myotubes or myofibers)

**NI: non-injured, resting healthy adult muscle; AI/R: acute muscular injury and regeneration in adult muscle; CP: clinically pathological muscle; Ag: aging muscle. Refer to the main text for details on the cell type(s) expressing each factor, in case data are not emanating from bulk analysis of the entire muscle tissue.

§ exercise-induced

Table 2. Deletion and overexpression phenotypes of cell cycle factors elucidating their function on myogenic cells or the skeletal muscle tissue

Cell cycle factor		Deletion (@MuSC: MuSC-specific genetic deletion) or inhibition	Ectopic expression	Interaction with myogenic factors	References
CDKs and Cyclins	CDK1	suppresses MuSC migration @MuSC: impairs regeneration post-injury and hypertrophy post-overload		CDK1 phosphorylates MYOD regulating its turnover	[74,98,103]
	CDK2			CDK2 phosphorylates MYOD regulating its turnover	[103]
	CDK4	induces G1 accumulation & muscle-specific gene expression	induces DNA synthesis in myotubes, represses MEF2 activity, impairs muscle-specific gene expression	CDK4 binds MYOD and blocks its DNA binding capacity, MYOD binds CDK4 and inhibits its ability to phosphorylate Rb	[76,78–81,100]
	CDK9-CyclinZ2*			the complex enhances MYOD function & promotes differentiation	[108,109]
	CDK12*	counteracts transcription of the DM1 expanded repeats in Myotonic Dystrophy type 1			[110]
	CyclinD1	knock-out: no muscle phenotypes @MuSC: reduced MuSC activation post-injury			[89–92,100]

	CyclinD3	knock-out: smaller fibers and less MuSCs, reduced MuSC renewal following activation, fiber-type shifting, hypermetabolism	promotes differentiation, rescues differentiation problems in Myotonic Dystrophy type 1	MYOD activates CyclinD3	[86,93,95–97]
	CyclinB			CDK1-CyclinB complex phosphorylates & represses MYOD	[98]
CDKIs	p15	knock-out: no muscle phenotypes reported			[156]
	p16		increases muscle-specific gene expression		[73]
	p18	knock-out: no muscle phenotypes reported			[156,172]
	p21	RNAi: stimulates S-phase entry in myotubes knock-out myoblasts: increased proliferation AAV-mediated transient p21 suppression: no myogenesis defect knock-out: no defect in muscle establishment (compensation by p57), delayed regeneration upon injury	induces C2C12 cell cycle withdrawal under growth conditions, induces muscle-specific gene expression, protects against apoptosis	MYOD transcriptionally activates p21, p21 inhibits MYOD phosphorylation stabilizing it	[73,98,158,161,173,178–180,198–201,218]
	p27	repression: inhibits differentiation & promotes proliferation knock-out: general hyperplasia & increased muscle mass, regeneration defects upon muscle injury	inhibits proliferation, promotes differentiation	p27 interacts with MYOD	[199,221,222]
	p57	knock-out: no defect in muscle establishment (compensation by		positive feedback loop with MYOD	[4,5,158,203–205,209–216,218]

		p21), regeneration impairment upon injury @MuSC: regeneration impairment upon injury			
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* non-canonical CDK-Cyclin complexes

References

- [1] C.J. Sherr, *Ink4-Arf* locus in cancer and aging: *Ink4-Arf* locus, *WIREs Dev Biol.* 1 (2012) 731–741. <https://doi.org/10.1002/wdev.40>.
- [2] K.S.A. Khabar, Hallmarks of cancer and AU-rich elements: Hallmarks of cancer and AU-rich elements, *WIREs RNA.* 8 (2017) e1368. <https://doi.org/10.1002/wrna.1368>.
- [3] H. Chandler, G. Peters, Stressing the cell cycle in senescence and aging, *Current Opinion in Cell Biology.* 25 (2013) 765–771. <https://doi.org/10.1016/j.ceb.2013.07.005>.
- [4] Y. Yan, J. Frisé, M.H. Lee, J. Massagué, M. Barbacid, Ablation of the CDK inhibitor p57Kip2 results in increased apoptosis and delayed differentiation during mouse development., *Genes & Development.* 11 (1997) 973–83.
- [5] P. Zhang, N.J. Liégeois, C. Wong, M. Finegold, H. Hou, J.C. Thompson, A. Silverman, J.W. Harper, R.A. DePinho, S.J. Elledge, Altered cell differentiation and proliferation in mice lacking p57KIP2 indicates a role in Beckwith-Wiedemann syndrome., *Nature.* 387 (1997) 151–8. <https://doi.org/10.1038/387151a0>.
- [6] A. Matsumoto, S. Takeishi, T. Kanie, E. Susaki, I. Onoyama, Y. Tateishi, K. Nakayama, K.I. Nakayama, p57 Is Required for Quiescence and Maintenance of Adult Hematopoietic Stem Cells, *Cell Stem Cell.* 9 (2011) 262–271. <https://doi.org/10.1016/j.stem.2011.06.014>.
- [7] K. Kozar, M.A. Ciemerych, V.I. Rebel, H. Shigematsu, A. Zagozdzon, E. Sicinska, Y. Geng, Q. Yu, S. Bhattacharya, R.T. Bronson, K. Akashi, P. Sicinski, Mouse Development and Cell Proliferation in the Absence of D-Cyclins, *Cell.* 118 (2004) 477–491. <https://doi.org/10.1016/j.cell.2004.07.025>.
- [8] M.A. Ciemerych, K. Archacka, I. Grabowska, M. Przewoźniak, Cell cycle regulation during proliferation and differentiation of mammalian muscle precursor cells, *Results Probl Cell Differ.* 53 (2011) 473–527. https://doi.org/10.1007/978-3-642-19065-0_20.
- [9] T.H. Cheung, T.A. Rando, Molecular regulation of stem cell quiescence, *Nat Rev Mol Cell Biol.* 14 (2013) 329–40. <https://doi.org/10.1038/nrm3591>.
- [10] D. Muñoz-Espín, M. Cañamero, A. Maraver, G. Gómez-López, J. Contreras, S. Murillo-Cuesta, A. Rodríguez-Baeza, I. Varela-Nieto, J. Ruberte, M. Collado, M. Serrano, Programmed Cell Senescence during Mammalian Embryonic Development, *Cell.* 155 (2013) 1104–1118. <https://doi.org/10.1016/j.cell.2013.10.019>.
- [11] M. Storer, A. Mas, A. Robert-Moreno, M. Pecoraro, M.C. Ortells, V. Di Giacomo, R. Yosef, N. Pilpel, V. Krizhanovsky, J. Sharpe, W.M. Keyes, Senescence Is a Developmental Mechanism that Contributes to Embryonic Growth and Patterning, *Cell.* 155 (2013) 1119–1130. <https://doi.org/10.1016/j.cell.2013.10.041>.
- [12] I. Le Roux, J. Konge, L. Le Cam, P. Flamant, S. Tajbakhsh, Numb is required to prevent p53-dependent senescence following skeletal muscle injury, *Nat Commun.* 6 (2015) 8528. <https://doi.org/10.1038/ncomms9528>.
- [13] D. Muñoz-Espín, M. Serrano, Cellular senescence: from physiology to pathology, *Nat Rev Mol Cell Biol.* 15 (2014) 482–496. <https://doi.org/10.1038/nrm3823>.
- [14] J. Esteves de Lima, M.-A. Bonnin, A. Bourgeois, A. Parisi, F. Le Grand, D. Duprez, Specific pattern of cell cycle during limb fetal myogenesis, *Developmental Biology.* 392 (2014) 308–323. <https://doi.org/10.1016/j.ydbio.2014.05.015>.
- [15] R.B. White, A.-S. Biérinx, V.F. Gnocchi, P.S. Zammit, Dynamics of muscle fibre growth during postnatal mouse development, *BMC Developmental Biology.* 10 (2010) 21. <https://doi.org/10.1186/1471-213X-10-21>.
- [16] F. Gattazzo, B. Laurent, F. Relaix, H. Rouard, N. Didier, Distinct Phases of Postnatal Skeletal Muscle Growth Govern the Progressive Establishment of Muscle Stem Cell Quiescence, *Stem Cell Reports.* 15 (2020) 597–611. <https://doi.org/10.1016/j.stemcr.2020.07.011>.

- [17] C. Lepper, T.A. Partridge, C.-M. Fan, An absolute requirement for Pax7-positive satellite cells in acute injury-induced skeletal muscle regeneration, *Development*. 138 (2011) 3639–3646. <https://doi.org/10.1242/dev.067595>.
- [18] J.J. McCarthy, J. Mula, M. Miyazaki, R. Erfani, K. Garrison, A.B. Farooqui, R. Srikuea, B.A. Lawson, B. Grimes, C. Keller, G. Van Zant, K.S. Campbell, K.A. Esser, E.E. Dupont-Versteegden, C.A. Peterson, Effective fiber hypertrophy in satellite cell-depleted skeletal muscle, *Development*. 138 (2011) 3657–3666. <https://doi.org/10.1242/dev.068858>.
- [19] M.M. Murphy, J.A. Lawson, S.J. Mathew, D.A. Hutcheson, G. Kardon, Satellite cells, connective tissue fibroblasts and their interactions are crucial for muscle regeneration, *Development*. 138 (2011) 3625–3637. <https://doi.org/10.1242/dev.064162>.
- [20] R. Sambasivan, R. Yao, A. Kissenpfennig, L. Van Wittenberghe, A. Paldi, B. Gayraud-Morel, H. Guenou, B. Malissen, S. Tajbakhsh, A. Galy, Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration, *Development*. 138 (2011) 3647–3656. <https://doi.org/10.1242/dev.067587>.
- [21] M.B. Baghdadi, S. Tajbakhsh, Regulation and phylogeny of skeletal muscle regeneration, *Developmental Biology*. 433 (2018) 200–209. <https://doi.org/10.1016/j.ydbio.2017.07.026>.
- [22] F. Relaix, D. Rocancourt, A. Mansouri, M. Buckingham, A Pax3/Pax7-dependent population of skeletal muscle progenitor cells, *Nature*. 435 (2005) 948–953. <https://doi.org/10.1038/nature03594>.
- [23] F. Relaix, D. Montarras, S. Zaffran, B. Gayraud-Morel, D. Rocancourt, S. Tajbakhsh, A. Mansouri, A. Cumano, M. Buckingham, Pax3 and Pax7 have distinct and overlapping functions in adult muscle progenitor cells, *J. Cell Biol.* 172 (2006) 91–102. <https://doi.org/10.1083/jcb.200508044>.
- [24] F. Calhabeu, S. Hayashi, J.E. Morgan, F. Relaix, P.S. Zammit, Alveolar rhabdomyosarcoma-associated proteins PAX3/FOXO1A and PAX7/FOXO1A suppress the transcriptional activity of MyoD-target genes in muscle stem cells, *Oncogene*. 32 (2013) 651–62. <https://doi.org/10.1038/onc.2012.73>.
- [25] N. Moncaut, P.W.J. Rigby, J.J. Carvajal, Dial M(RF) for myogenesis, *FEBS J.* 280 (2013) 3980–3990. <https://doi.org/10.1111/febs.12379>.
- [26] B. Gayraud-Morel, F. Chrétien, A. Jory, R. Sambasivan, E. Negroni, P. Flamant, G. Soubigou, J.-Y. Coppée, J. Di Santo, A. Cumano, V. Mouly, S. Tajbakhsh, Myf5 haploinsufficiency reveals distinct cell fate potentials for adult skeletal muscle stem cells, *Journal of Cell Science*. (2012) jcs.097006. <https://doi.org/10.1242/jcs.097006>.
- [27] F. Relaix, P.S. Zammit, Satellite cells are essential for skeletal muscle regeneration: the cell on the edge returns centre stage, *Development*. 139 (2012) 2845–2856. <https://doi.org/10.1242/dev.069088>.
- [28] M. Benavente-Diaz, G. Comai, D. Di Girolamo, F. Langa, S. Tajbakhsh, Dynamics of myogenic differentiation using a novel Myogenin knock-in reporter mouse, *Skeletal Muscle*. 11 (2021) 5. <https://doi.org/10.1186/s13395-021-00260-x>.
- [29] J.F. Bachman, J.V. Chakkalakal, Insights into muscle stem cell dynamics during postnatal development, *FEBS J.* (2021) febs.15856. <https://doi.org/10.1111/febs.15856>.
- [30] M. Malumbres, Cyclin-dependent kinases, *Genome Biol.* 15 (2014) 122. <https://doi.org/10.1186/gb4184>.
- [31] A. Borriello, I. Caldarelli, D. Bencivenga, M. Criscuolo, V. Cucciolla, A. Tramontano, A. Oliva, S. Perrotta, F. Della Ragione, p57^{Kip2} and Cancer: Time for a Critical Appraisal, *Mol Cancer Res.* 9 (2011) 1269–1284. <https://doi.org/10.1158/1541-7786.MCR-11-0220>.
- [32] D. Cobrinik, Pocket proteins and cell cycle control, *Oncogene*. 24 (2005) 2796–2809. <https://doi.org/10.1038/sj.onc.1208619>.

- [33] S. van den Heuvel, N.J. Dyson, Conserved functions of the pRB and E2F families, *Nat Rev Mol Cell Biol.* 9 (2008) 713–724. <https://doi.org/10.1038/nrm2469>.
- [34] A. Besson, S.F. Dowdy, J.M. Roberts, CDK Inhibitors: Cell Cycle Regulators and Beyond, *Developmental Cell.* 14 (2008) 159–169. <https://doi.org/10.1016/j.devcel.2008.01.013>.
- [35] H.-Z. Chen, S.-Y. Tsai, G. Leone, Emerging roles of E2Fs in cancer: an exit from cell cycle control, *Nat Rev Cancer.* 9 (2009) 785–797. <https://doi.org/10.1038/nrc2696>.
- [36] I.S. Pateras, K. Apostolopoulou, K. Niforou, A. Kotsinas, V.G. Gorgoulis, p57KIP2: “Kip”ing the cell under control, *Mol Cancer Res.* 7 (2009) 1902–19. <https://doi.org/10.1158/1541-7786.MCR-09-0317>.
- [37] N. Arsic, N. Bendris, M. Peter, C. Begon-Pescia, C. Rebouissou, G. Gadéa, N. Bouquier, F. Bibeau, B. Lemmers, J.M. Blanchard, A novel function for Cyclin A2: Control of cell invasion via RhoA signaling, *Journal of Cell Biology.* 196 (2012) 147–162. <https://doi.org/10.1083/jcb.201102085>.
- [38] A. Kanakkanthara, K.B. Jeganathan, J.F. Limzerwala, D.J. Baker, M. Hamada, H.-J. Nam, W.H. van Deursen, N. Hamada, R.M. Naylor, N.A. Becker, B.A. Davies, J.H. van Ree, G. Mer, V.S. Shapiro, L.J. Maher, D.J. Katzmann, J.M. van Deursen, Cyclin A2 is an RNA binding protein that controls *Mre11* mRNA translation, *Science.* 353 (2016) 1549–1552. <https://doi.org/10.1126/science.aaf7463>.
- [39] J.H. Nugent, C.E. Alfa, T. Young, J.S. Hyams, Conserved structural motifs in cyclins identified by sequence analysis, *J Cell Sci.* 99 (Pt 3) (1991) 669–674.
- [40] H. Kobayashi, E. Stewart, R. Poon, J.P. Adamczewski, J. Gannon, T. Hunt, Identification of the domains in cyclin A required for binding to, and activation of, p34cdc2 and p32cdk2 protein kinase subunits., *MBoC.* 3 (1992) 1279–1294. <https://doi.org/10.1091/mbc.3.11.1279>.
- [41] E.M. Lees, E. Harlow, Sequences within the conserved cyclin box of human cyclin A are sufficient for binding to and activation of cdc2 kinase., *Mol. Cell. Biol.* 13 (1993) 1194–1201. <https://doi.org/10.1128/MCB.13.2.1194>.
- [42] M. Lowe, J. Lage, E. Paatela, D. Munson, R. Hostager, C. Yuan, N. Katoku-Kikyo, M. Ruiz-Estevéz, Y. Asakura, J. Staats, M. Qahar, M. Lohman, A. Asakura, N. Kikyo, Cry2 Is Critical for Circadian Regulation of Myogenic Differentiation by Bclaf1-Mediated mRNA Stabilization of Cyclin D1 and Tmem176b, *Cell Reports.* 22 (2018) 2118–2132. <https://doi.org/10.1016/j.celrep.2018.01.077>.
- [43] M. Hirayama, F.-Y. Wei, T. Chujo, S. Oki, M. Yakita, D. Kobayashi, N. Araki, N. Takahashi, R. Yoshida, H. Nakayama, K. Tomizawa, FTO Demethylates Cyclin D1 mRNA and Controls Cell-Cycle Progression, *Cell Reports.* 31 (2020) 107464. <https://doi.org/10.1016/j.celrep.2020.03.028>.
- [44] S.J. Baker, E.P. Reddy, CDK4: A Key Player in the Cell Cycle, Development, and Cancer, *Genes & Cancer.* 3 (2012) 658–669. <https://doi.org/10.1177/1947601913478972>.
- [45] H.A. Collier, Regulation of Cell Cycle Entry and Exit: A Single Cell Perspective, in: R. Terjung (Ed.), *Comprehensive Physiology*, 1st ed., Wiley, 2019: pp. 317–344. <https://doi.org/10.1002/cphy.c190014>.
- [46] D. Santamaría, C. Barrière, A. Cerqueira, S. Hunt, C. Tardy, K. Newton, J.F. Cáceres, P. Dubus, M. Malumbres, M. Barbacid, Cdk1 is sufficient to drive the mammalian cell cycle, *Nature.* 448 (2007) 811–815. <https://doi.org/10.1038/nature06046>.
- [47] M. Murphy, M.-G. Stinnakre, C. Senamaud-Beaufort, N.J. Winston, C. Sweeney, M. Kubelka, M. Carrington, C. Bréchet, J. Sobczak-Thépot, Delayed early embryonic lethality following disruption of the murine cyclin A2 gene, *Nat Genet.* 15 (1997) 83–86. <https://doi.org/10.1038/ng0197-83>.
- [48] B. Strauss, A. Harrison, P.A. Coelho, K. Yata, M. Zernicka-Goetz, J. Pines, Cyclin B1 is essential for mitosis in mouse embryos, and its nuclear export sets the time for mitosis, *Journal of Cell Biology.* 217 (2018) 179–193. <https://doi.org/10.1083/jcb.201612147>.
- [49] M. Min, Y. Rong, C. Tian, S.L. Spencer, Temporal integration of mitogen history in mother cells controls proliferation of daughter cells, *Science.* 368 (2020) 1261–1265. <https://doi.org/10.1126/science.aay8241>.

- [50] D.E. Quelle, R.A. Ashmun, S.A. Shurtleff, J.Y. Kato, D. Bar-Sagi, M.F. Rousset, C.J. Sherr, Overexpression of mouse D-type cyclins accelerates G1 phase in rodent fibroblasts., *Genes & Development*. 7 (1993) 1559–1571. <https://doi.org/10.1101/gad.7.8.1559>.
- [51] B.R. Topacio, E. Zatulovskiy, S. Cristea, S. Xie, C.S. Tambo, S.M. Rubin, J. Sage, M. Kõivomägi, J.M. Skotheim, Cyclin D-Cdk4,6 Drives Cell-Cycle Progression via the Retinoblastoma Protein's C-Terminal Helix, *Molecular Cell*. 74 (2019) 758-770.e4. <https://doi.org/10.1016/j.molcel.2019.03.020>.
- [52] H.W. Yang, S.D. Cappell, A. Jaimovich, C. Liu, M. Chung, L.H. Daigh, L.R. Pack, Y. Fan, S. Regot, M. Covert, T. Meyer, Stress-mediated exit to quiescence restricted by increasing persistence in CDK4/6 activation, *ELife*. 9 (2020) e44571. <https://doi.org/10.7554/eLife.44571>.
- [53] M. Pagano, R. Pepperkok, F. Verde, W. Ansorge, G. Draetta, Cyclin A is required at two points in the human cell cycle, *EMBO J*. 11 (1992) 961–971.
- [54] D. Resnitzky, S.I. Reed, Different roles for cyclins D1 and E in regulation of the G1-to-S transition, *Mol Cell Biol*. 15 (1995) 3463–3469. <https://doi.org/10.1128/MCB.15.7.3463>.
- [55] H. Beamish, L. de Boer, N. Giles, F. Stevens, V. Oakes, B. Gabrielli, Cyclin A/cdk2 Regulates Adenomatous Polyposis Coli-dependent Mitotic Spindle Anchoring, *Journal of Biological Chemistry*. 284 (2009) 29015–29023. <https://doi.org/10.1074/jbc.M109.042820>.
- [56] L. Kabeche, D.A. Compton, Cyclin A regulates kinetochore microtubules to promote faithful chromosome segregation, *Nature*. 502 (2013) 110–113. <https://doi.org/10.1038/nature12507>.
- [57] S.L. Spencer, S.D. Cappell, F.-C. Tsai, K.W. Overton, C.L. Wang, T. Meyer, The Proliferation-Quiescence Decision Is Controlled by a Bifurcation in CDK2 Activity at Mitotic Exit, *Cell*. 155 (2013) 369–383. <https://doi.org/10.1016/j.cell.2013.08.062>.
- [58] J.P. Matson, J.G. Cook, Cell cycle proliferation decisions: the impact of single cell analyses, *FEBS J*. 284 (2017) 362–375. <https://doi.org/10.1111/febs.13898>.
- [59] S.M. Rubin, J. Sage, J.M. Skotheim, Integrating Old and New Paradigms of G1/S Control, *Molecular Cell*. 80 (2020) 183–192. <https://doi.org/10.1016/j.molcel.2020.08.020>.
- [60] G. Draetta, F. Luca, J. Westendorf, L. Brizuela, J. Ruderman, D. Beach, cdc2 protein kinase is complexed with both cyclin A and B: Evidence for proteolytic inactivation of MPF, *Cell*. 56 (1989) 829–838. [https://doi.org/10.1016/0092-8674\(89\)90687-9](https://doi.org/10.1016/0092-8674(89)90687-9).
- [61] T. Kishimoto, E. Okumura, In vivo regulation of the entry into M-phase: initial activation and nuclear translocation of cyclin B/Cdc2, in: L. Meijer, S. Guidet, M. Philippe (Eds.), *Progress in Cell Cycle Research*, Springer US, Boston, MA, 1997: pp. 241–249. https://doi.org/10.1007/978-1-4615-5371-7_19.
- [62] J.C. Saldivar, S. Hamperl, M.J. Bocek, M. Chung, T.E. Bass, F. Cisneros-Soberanis, K. Samejima, L. Xie, J.R. Paulson, W.C. Earnshaw, D. Cortez, T. Meyer, K.A. Cimprich, An intrinsic S/G₂ checkpoint enforced by ATR, *Science*. 361 (2018) 806–810. <https://doi.org/10.1126/science.aap9346>.
- [63] L. Clijsters, C. Hoencamp, J.J.A. Calis, A. Marzio, S.M. Handgraaf, M.C. Cuitino, B.R. Rosenberg, G. Leone, M. Pagano, Cyclin F Controls Cell-Cycle Transcriptional Outputs by Directing the Degradation of the Three Activator E2Fs, *Molecular Cell*. 74 (2019) 1264-1277.e7. <https://doi.org/10.1016/j.molcel.2019.04.010>.
- [64] I. Mavrommati, R. Faedda, G. Galasso, J. Li, K. Burdova, R. Fischer, B.M. Kessler, Z.I. Carrero, D. Guardavaccaro, M. Pagano, V. D'Angiolella, β -TrCP- and Casein Kinase II-Mediated Degradation of Cyclin F Controls Timely Mitotic Progression, *Cell Reports*. 24 (2018) 3404–3412. <https://doi.org/10.1016/j.celrep.2018.08.076>.
- [65] T. An, Y. Liu, S. Gourguechon, C.C. Wang, Z. Li, CDK Phosphorylation of Translation Initiation Factors Couples Protein Translation with Cell-Cycle Transition, *Cell Reports*. 25 (2018) 3204-3214.e5. <https://doi.org/10.1016/j.celrep.2018.11.063>.

- [66] I. Ryu, Y.-S. Won, H. Ha, E. Kim, Y. Park, M.K. Kim, D.H. Kwon, J. Choe, H.K. Song, H. Jung, Y.K. Kim, eIF4A3 Phosphorylation by CDKs Affects NMD during the Cell Cycle, *Cell Reports*. 26 (2019) 2126–2139.e9. <https://doi.org/10.1016/j.celrep.2019.01.101>.
- [67] G. Sarek, P. Kotsantis, P. Ruis, D. Van Ly, P. Margalef, V. Borel, X.-F. Zheng, H.R. Flynn, A.P. Snijders, D. Chowdhury, A.J. Cesare, S.J. Boulton, CDK phosphorylation of TRF2 controls t-loop dynamics during the cell cycle, *Nature*. 575 (2019) 523–527. <https://doi.org/10.1038/s41586-019-1744-8>.
- [68] P.K. Parua, G.T. Booth, M. Sansó, B. Benjamin, J.C. Tanny, J.T. Lis, R.P. Fisher, A Cdk9–PP1 switch regulates the elongation–termination transition of RNA polymerase II, *Nature*. 558 (2018) 460–464. <https://doi.org/10.1038/s41586-018-0214-z>.
- [69] S.J. Dubbury, P.L. Boutz, P.A. Sharp, CDK12 regulates DNA repair genes by suppressing intronic polyadenylation, *Nature*. 564 (2018) 141–145. <https://doi.org/10.1038/s41586-018-0758-y>.
- [70] T. Lei, P. Zhang, X. Zhang, X. Xiao, J. Zhang, T. Qiu, Q. Dai, Y. Zhang, L. Min, Q. Li, R. Yin, P. Ding, N. Li, Y. Qu, D. Mu, J. Qin, X. Zhu, Z.-X. Xiao, Q. Li, Cyclin K regulates prereplicative complex assembly to promote mammalian cell proliferation, *Nat Commun*. 9 (2018) 1876. <https://doi.org/10.1038/s41467-018-04258-w>.
- [71] H. Zhang, S. Pandey, M. Travers, H. Sun, G. Morton, J. Madzo, W. Chung, J. Khowsathit, O. Perez-Leal, C.A. Barrero, C. Merali, Y. Okamoto, T. Sato, J. Pan, J. Garriga, N.V. Bhanu, J. Simithy, B. Patel, J. Huang, N.J.-M. Raynal, B.A. Garcia, M.A. Jacobson, C. Kadoch, S. Merali, Y. Zhang, W. Childers, M. Abou-Gharbia, J. Karanicolas, S.B. Baylin, C.A. Zahnow, J. Jelinek, X. Graña, J.-P.J. Issa, Targeting CDK9 Reactivates Epigenetically Silenced Genes in Cancer, *Cell*. 175 (2018) 1244–1258.e26. <https://doi.org/10.1016/j.cell.2018.09.051>.
- [72] N. Bendris, B. Lemmers, J.M. Blanchard, Cell cycle, cytoskeleton dynamics and beyond: the many functions of cyclins and CDK inhibitors, *Cell Cycle*. 14 (2015) 1786–1798. <https://doi.org/10.1080/15384101.2014.998085>.
- [73] S.X. Skapek, J. Rhee, D.B. Spicer, A.B. Lassar, Inhibition of Myogenic Differentiation in Proliferating Myoblasts by Cyclin D1-Dependent Kinase, *Science*. 267 (1995) 1022–1024. <https://doi.org/10.1126/science.7863328>.
- [74] Y. Kobayashi, T. Tanaka, M. Mulati, H. Ochi, S. Sato, P. Kaldis, T. Yoshii, A. Okawa, H. Inose, Cyclin-Dependent Kinase 1 Is Essential for Muscle Regeneration and Overload Muscle Fiber Hypertrophy, *Front. Cell Dev. Biol.* 8 (2020) 564581. <https://doi.org/10.3389/fcell.2020.564581>.
- [75] J. Wang, K. Walsh, Inhibition of retinoblastoma protein phosphorylation by myogenesis-induced changes in the subunit composition of the cyclin-dependent kinase 4 complex, *Cell Growth Differ.* 7 (1996) 1471–1478.
- [76] J.-M. Zhang, Q. Wei, X. Zhao, B.M. Paterson, Coupling of the cell cycle and myogenesis through the cyclin D1-dependent interaction of MyoD with cdk4, *EMBO J.* 18 (1999) 926–933. <https://doi.org/10.1093/emboj/18.4.926>.
- [77] D. Mademtzoglou, Y. Asakura, M.J. Borok, S. Alonso-Martin, P. Mourikis, Y. Kodaka, A. Mohan, A. Asakura, F. Relaix, Cellular localization of the cell cycle inhibitor Cdkn1c controls growth arrest of adult skeletal muscle stem cells, *Elife*. 7 (2018). <https://doi.org/10.7554/eLife.33337>.
- [78] R. Saab, J.L. Bills, A.P. Miceli, C.M. Anderson, J.D. Houry, D.W. Fry, F. Navid, P.J. Houghton, S.X. Skapek, Pharmacologic inhibition of cyclin-dependent kinase 4/6 activity arrests proliferation in myoblasts and rhabdomyosarcoma-derived cells, *Mol Cancer Ther.* 5 (2006) 1299–1308. <https://doi.org/10.1158/1535-7163.MCT-05-0383>.
- [79] L. Latella, A. Sacco, D. Pajalunga, M. Tiainen, D. Macera, M. D’Angelo, A. Felici, A. Sacchi, M. Crescenzi, Reconstitution of Cyclin D1-Associated Kinase Activity Drives Terminally Differentiated Cells into the Cell Cycle, *Mol Cell Biol.* 21 (2001) 5631–5643. <https://doi.org/10.1128/MCB.21.16.5631-5643.2001>.

- [80] J.-B. Lazaro, Cyclin D-cdk4 activity modulates the subnuclear localization and interaction of MEF2 with SRC-family coactivators during skeletal muscle differentiation, *Genes & Development*. 16 (2002) 1792–1805. <https://doi.org/10.1101/gad.U-9988R>.
- [81] J.-M. Zhang, Direct inhibition of G1 cdk kinase activity by MyoD promotes myoblast cell cycle withdrawal and terminal differentiation, *The EMBO Journal*. 18 (1999) 6983–6993. <https://doi.org/10.1093/emboj/18.24.6983>.
- [82] S.S. Rao, C. Chu, D.S. Kohtz, Ectopic expression of cyclin D1 prevents activation of gene transcription by myogenic basic helix-loop-helix regulators., *Mol. Cell. Biol.* 14 (1994) 5259–5267. <https://doi.org/10.1128/MCB.14.8.5259>.
- [83] M. Kiess, R.M. Gill, P.A. Hamel, Expression and activity of the retinoblastoma protein (pRB)-family proteins, p107 and p130, during L6 myoblast differentiation, *Cell Growth Differ.* 6 (1995) 1287–1298.
- [84] C.Y. Chu, R.W. Lim, Involvement of p27kip1 and cyclin D3 in the regulation of cdk2 activity during skeletal muscle differentiation, *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*. 1497 (2000) 175–185. [https://doi.org/10.1016/S0167-4889\(00\)00064-1](https://doi.org/10.1016/S0167-4889(00)00064-1).
- [85] M. Hlaing, X. Shen, P. Dazin, H.S. Bernstein, The Hypertrophic Response in C2C12 Myoblasts Recruits the G1 Cell Cycle Machinery, *Journal of Biological Chemistry*. 277 (2002) 23794–23799. <https://doi.org/10.1074/jbc.M201980200>.
- [86] G. De Luca, R. Ferretti, M. Bruschi, E. Mezzaroma, M. Caruso, Cyclin D3 critically regulates the balance between self-renewal and differentiation in skeletal muscle stem cells: Cyclin D3 Regulates Muscle Stem Cell Function, *Stem Cells*. 31 (2013) 2478–2491. <https://doi.org/10.1002/stem.1487>.
- [87] J. Bartkova, J. Lukas, M. Strauss, J. Bartek, Cyclin D3: requirement for G1/S transition and high abundance in quiescent tissues suggest a dual role in proliferation and differentiation, *Oncogene*. 17 (1998) 1027–1037. <https://doi.org/10.1038/sj.onc.1202016>.
- [88] J.C. Kimmel, A.B. Hwang, A. Scaramozza, W.F. Marshall, A.S. Brack, Aging induces aberrant state transition kinetics in murine muscle stem cells, *Development*. (2020) dev.183855. <https://doi.org/10.1242/dev.183855>.
- [89] J.O. Brett, M. Arjona, M. Ikeda, M. Quarta, A. de Morrée, I.M. Egner, L.A. Perandini, H.D. Ishak, A. Goshayeshi, D.I. Benjamin, P. Both, C. Rodríguez-Mateo, M.J. Betley, T. Wyss-Coray, T.A. Rando, Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of Cyclin D1, *Nat Metab.* 2 (2020) 307–317. <https://doi.org/10.1038/s42255-020-0190-0>.
- [90] V. Fantl, G. Stamp, A. Andrews, I. Rosewell, C. Dickson, Mice lacking cyclin D1 are small and show defects in eye and mammary gland development., *Genes & Development*. 9 (1995) 2364–2372. <https://doi.org/10.1101/gad.9.19.2364>.
- [91] P. Sicinski, J.L. Donaher, S.B. Parker, T. Li, A. Fazeli, H. Gardner, S.Z. Haslam, R.T. Bronson, S.J. Elledge, R.A. Weinberg, Cyclin D1 provides a link between development and oncogenesis in the retina and breast, *Cell*. 82 (1995) 621–630. [https://doi.org/10.1016/0092-8674\(95\)90034-9](https://doi.org/10.1016/0092-8674(95)90034-9).
- [92] Y.J. Choi, X. Li, P. Hydbring, T. Sanda, J. Stefano, A.L. Christie, S. Signoretti, A.T. Look, A.L. Kung, H. von Boehmer, P. Sicinski, The Requirement for Cyclin D Function in Tumor Maintenance, *Cancer Cell*. 22 (2012) 438–451. <https://doi.org/10.1016/j.ccr.2012.09.015>.
- [93] C. Cenciarelli, F. De Santa, P.L. Puri, E. Mattei, L. Ricci, F. Bucci, A. Felsani, M. Caruso, Critical Role Played by Cyclin D3 in the MyoD-Mediated Arrest of Cell Cycle during Myoblast Differentiation, *Mol Cell Biol.* 19 (1999) 5203–5217. <https://doi.org/10.1128/MCB.19.7.5203>.
- [94] M.A. Ciemerych, Q. Yu, K. Szczepanska, P. Sicinski, CDK4 activity in mouse embryos expressing a single D-type cyclin, *Int. J. Dev. Biol.* 52 (2008) 299–305. <https://doi.org/10.1387/ijdb.072336mc>.
- [95] R. Gurung, V.K. Parnaik, Cyclin D3 promotes myogenic differentiation and Pax7 transcription, *J. Cell. Biochem.* 113 (2012) 209–219. <https://doi.org/10.1002/jcb.23346>.

- [96] E. Salisbury, K. Sakai, B. Schoser, C. Huichalaf, C. Schneider-Gold, H. Nguyen, G.-L. Wang, J.H. Albrecht, L.T. Timchenko, Ectopic expression of cyclin D3 corrects differentiation of DM1 myoblasts through activation of RNA CUG-binding protein, CUGBP1, *Experimental Cell Research*. 314 (2008) 2266–2278. <https://doi.org/10.1016/j.yexcr.2008.04.018>.
- [97] S. Giannattasio, G. Giacobuzzo, A. Bonato, C. Caruso, S. Luvisetto, R. Coccurello, M. Caruso, Lack of cyclin D3 induces skeletal muscle fiber-type shifting, increased endurance performance and hypermetabolism, *Sci Rep*. 8 (2018) 12792. <https://doi.org/10.1038/s41598-018-31090-5>.
- [98] L.A.J. Tintignac, V. Sirri, M.P. Leibovitch, Y. Lécluse, M. Castedo, D. Metivier, G. Kroemer, S.A. Leibovitch, Mutant MyoD Lacking Cdc2 Phosphorylation Sites Delays M-Phase Entry, *Mol Cell Biol*. 24 (2004) 1809–1821. <https://doi.org/10.1128/MCB.24.4.1809-1821.2004>.
- [99] Z. Chen, L. Li, S. Xu, Z. Liu, C. Zhou, Z. Li, Y. Liu, W. Wu, Y. Huang, M. Kuang, S. Fan, H. Li, X. Li, G. Song, W.-S. Wu, J. Chen, Y. Hou, A Cdh1–FoxM1–Apc axis controls muscle development and regeneration, *Cell Death Dis*. 11 (2020) 180. <https://doi.org/10.1038/s41419-020-2375-6>.
- [100] J. Korzelius, I. The, S. Ruijtenberg, M.B.W. Prinsen, V. Portegijs, T.C. Middelkoop, M.J. Groot Koerkamp, F.C.P. Holstege, M. Boxem, S. van den Heuvel, *Caenorhabditis elegans* Cyclin D/CDK4 and Cyclin E/CDK2 Induce Distinct Cell Cycle Re-Entry Programs in Differentiated Muscle Cells, *PLoS Genet*. 7 (2011) e1002362. <https://doi.org/10.1371/journal.pgen.1002362>.
- [101] A. Mal, D. Chattopadhyay, M.K. Ghosh, R.Y.C. Poon, T. Hunter, M.L. Harter, P21 and Retinoblastoma Protein Control the Absence of DNA Replication in Terminally Differentiated Muscle Cells, *Journal of Cell Biology*. 149 (2000) 281–292. <https://doi.org/10.1083/jcb.149.2.281>.
- [102] S.N. Opreescu, F. Yue, J. Qiu, L.F. Brito, S. Kuang, Temporal Dynamics and Heterogeneity of Cell Populations during Skeletal Muscle Regeneration, *IScience*. 23 (2020) 100993. <https://doi.org/10.1016/j.isci.2020.100993>.
- [103] M. Kitzmann, M. Vandromme, V. Schaeffer, G. Carnac, J.-C. Labbé, N. Lamb, A. Fernandez, cdk1- and cdk2-Mediated Phosphorylation of MyoD Ser200 in Growing C2 Myoblasts: Role in Modulating MyoD Half-Life and Myogenic Activity, *Mol Cell Biol*. 19 (1999) 3167–3176. <https://doi.org/10.1128/MCB.19.4.3167>.
- [104] Y. Konagaya, K. Takakura, M. Sogabe, A. Bisaria, C. Liu, T. Meyer, A. Sehara-Fujisawa, M. Matsuda, K. Terai, Intravital imaging reveals cell cycle-dependent myogenic cell migration during muscle regeneration, *Cell Cycle*. 19 (2020) 3167–3181. <https://doi.org/10.1080/15384101.2020.1838779>.
- [105] E. Barriet, S.M. Garcia, K. Striedinger, J. Wu, S. Lee, L. Byrnes, A. Wong, S. Xuefeng, S. Tamaki, A.S. Brack, J.H. Pomerantz, Functionally heterogeneous human satellite cells identified by single cell RNA sequencing, *ELife*. 9 (2020) e51576. <https://doi.org/10.7554/eLife.51576>.
- [106] A. Shcherbina, J. Larouche, P. Fraczek, B.A. Yang, L.A. Brown, J.F. Markworth, C.H. Chung, M. Khaliq, K. de Silva, J.J. Choi, M. Fallahi-Sichani, S. Chandrasekaran, Y.C. Jang, S.V. Brooks, C.A. Aguilar, Dissecting Murine Muscle Stem Cell Aging through Regeneration Using Integrative Genomic Analysis, *Cell Reports*. 32 (2020) 107964. <https://doi.org/10.1016/j.celrep.2020.107964>.
- [107] A. Adhikari, J.K. Davie, The PRC2 complex directly regulates the cell cycle and controls proliferation in skeletal muscle, *Cell Cycle*. 19 (2020) 2373–2394. <https://doi.org/10.1080/15384101.2020.1806448>.
- [108] C. Simone, P. Stiegler, L. Bagella, B. Pucci, C. Bellan, G. De Falco, A. De Luca, G. Guanti, P.L. Puri, A. Giordano, Activation of MyoD-dependent transcription by cdk9/cyclin T2, *Oncogene*. 21 (2002) 4137–4148. <https://doi.org/10.1038/sj.onc.1205493>.
- [109] I. Marchesi, V. Nieddu, V. Caracciolo, M. Maioli, L. Gaspa, A. Giordano, L. Bagella, Activation and function of murine Cyclin T2A and Cyclin T2B during skeletal muscle differentiation, *J. Cell. Biochem*. 114 (2013) 728–734. <https://doi.org/10.1002/jcb.24414>.
- [110] A. Ketley, M. Wojciechowska, S. Ghidelli-Disse, P. Bamborough, T.K. Ghosh, M.L. Morato, S. Sedehizadeh, N.A. Malik, Z. Tang, P. Pawalowska, M. Tanner, R. Billeter-Clark, R.C. Trueman, P.C.

- Geiszler, A. Agostini, O. Othman, M. Bösche, M. Bantscheff, M. Rüdiger, D.E. Mossakowska, D.H. Drewry, W.J. Zuercher, C.A. Thornton, G. Drewes, I. Uings, C.J. Hayes, J.D. Brook, CDK12 inhibition reduces abnormalities in cells from patients with myotonic dystrophy and in a mouse model, *Sci. Transl. Med.* 12 (2020) eaaz2415. <https://doi.org/10.1126/scitranslmed.aaz2415>.
- [111] M. Serrano, G.J. Hannon, D. Beach, A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4, *Nature*. 366 (1993) 704–707. <https://doi.org/10.1038/366704a0>.
- [112] G.J. Hannon, D. Beach, p15INK4B is a potential effector of TGF- β -induced cell cycle arrest, *Nature*. 371 (1994) 257–261. <https://doi.org/10.1038/371257a0>.
- [113] H. Hirai, M.F. Roussel, J.Y. Kato, R.A. Ashmun, C.J. Sherr, Novel INK4 proteins, p19 and p18, are specific inhibitors of the cyclin D-dependent kinases CDK4 and CDK6, *Mol Cell Biol.* 15 (1995) 2672–2681. <https://doi.org/10.1128/MCB.15.5.2672>.
- [114] P. Michaelis, V. Bennett, The ANK repeat: a ubiquitous motif involved in macromolecular recognition, *Trends in Cell Biology.* 2 (1992) 127–129. [https://doi.org/10.1016/0962-8924\(92\)90084-Z](https://doi.org/10.1016/0962-8924(92)90084-Z).
- [115] K. Polyak, M.-H. Lee, H. Erdjument-Bromage, A. Koff, J.M. Roberts, P. Tempst, J. Massagué, Cloning of p27Kip1, a cyclin-dependent kinase inhibitor and a potential mediator of extracellular antimitogenic signals, *Cell.* 78 (1994) 59–66. [https://doi.org/10.1016/0092-8674\(94\)90572-X](https://doi.org/10.1016/0092-8674(94)90572-X).
- [116] M.H. Lee, I. Reynisdottir, J. Massague, Cloning of p57KIP2, a cyclin-dependent kinase inhibitor with unique domain structure and tissue distribution., *Genes & Development.* 9 (1995) 639–649. <https://doi.org/10.1101/gad.9.6.639>.
- [117] S. Matsuoka, M.C. Edwards, C. Bai, S. Parker, P. Zhang, A. Baldini, J.W. Harper, S.J. Elledge, p57KIP2, a structurally distinct member of the p21CIP1 Cdk inhibitor family, is a candidate tumor suppressor gene., *Genes & Development.* 9 (1995) 650–662. <https://doi.org/10.1101/gad.9.6.650>.
- [118] R. Li, S. Waga, G.J. Hannon, D. Beach, B. Stillman, Differential effects by the p21 CDK inhibitor on PCNA-dependent DNA replication and repair, *Nature.* 371 (1994) 534–537. <https://doi.org/10.1038/371534a0>.
- [119] S. Waga, G.J. Hannon, D. Beach, B. Stillman, The p21 inhibitor of cyclin-dependent kinases controls DNA replication by interaction with PCNA, *Nature.* 369 (1994) 574–578. <https://doi.org/10.1038/369574a0>.
- [120] H. Watanabe, Z.-Q. Pan, N. Schreiber-Agus, R.A. DePinho, J. Hurwitz, Y. Xiong, Suppression of cell transformation by the cyclin-dependent kinase inhibitor p57KIP2 requires binding to proliferating cell nuclear antigen, *Proceedings of the National Academy of Sciences.* 95 (1998) 1392–1397. <https://doi.org/10.1073/pnas.95.4.1392>.
- [121] Z. Lu, T. Hunter, Ubiquitylation and proteasomal degradation of the p21^{Cip1}, p27^{Kip1} and p57^{Kip2} CDK inhibitors, *Cell Cycle.* 9 (2010) 2342–2352. <https://doi.org/10.4161/cc.9.12.11988>.
- [122] K.L. Guan, C.W. Jenkins, Y. Li, M.A. Nichols, X. Wu, C.L. O’Keefe, A.G. Matera, Y. Xiong, Growth suppression by p18, a p16INK4/MTS1- and p14INK4B/MTS2-related CDK6 inhibitor, correlates with wild-type pRb function., *Genes & Development.* 8 (1994) 2939–2952. <https://doi.org/10.1101/gad.8.24.2939>.
- [123] F.K. Chan, J. Zhang, L. Cheng, D.N. Shapiro, A. Winoto, Identification of human and mouse p19, a novel CDK4 and CDK6 inhibitor with homology to p16ink4, *Mol Cell Biol.* 15 (1995) 2682–2688. <https://doi.org/10.1128/MCB.15.5.2682>.
- [124] Y. Gu, C.W. Turck, D.O. Morgan, Inhibition of CDK2 activity in vivo by an associated 20K regulatory subunit, *Nature.* 366 (1993) 707–710. <https://doi.org/10.1038/366707a0>.
- [125] J. Wade Harper, The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases, *Cell.* 75 (1993) 805–816. [https://doi.org/10.1016/0092-8674\(93\)90499-G](https://doi.org/10.1016/0092-8674(93)90499-G).
- [126] Y. Xiong, G.J. Hannon, H. Zhang, D. Casso, R. Kobayashi, D. Beach, p21 is a universal inhibitor of cyclin kinases, *Nature.* 366 (1993) 701–704. <https://doi.org/10.1038/366701a0>.

- [127] K. Polyak, J.Y. Kato, M.J. Solomon, C.J. Sherr, J. Massague, J.M. Roberts, A. Koff, p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest., *Genes & Development*. 8 (1994) 9–22. <https://doi.org/10.1101/gad.8.1.9>.
- [128] C.A. Galea, Y. Wang, S.G. Sivakolundu, R.W. Kriwacki, Regulation of Cell Division by Intrinsically Unstructured Proteins: Intrinsic Flexibility, Modularity, and Signaling Conduits, *Biochemistry*. 47 (2008) 7598–7609. <https://doi.org/10.1021/bi8006803>.
- [129] J.W. Harper, S.J. Elledge, K. Keyomarsi, B. Dynlacht, L.H. Tsai, P. Zhang, S. Dobrowolski, C. Bai, L. Connell-Crowley, E. Swindell, Inhibition of cyclin-dependent kinases by p21., *MBoC*. 6 (1995) 387–400. <https://doi.org/10.1091/mbc.6.4.387>.
- [130] T.J. Soos, H. Kiyokawa, J.S. Yan, M.S. Rubin, A. Giordano, A. DeBlasio, S. Bottega, B. Wong, J. Mendelsohn, A. Koff, Formation of p27-CDK complexes during the human mitotic cell cycle, *Cell Growth Differ*. 7 (1996) 135–146.
- [131] P. Michieli, M. Chetid, D. Lin, J.H. Pierce, W.E. Mercer, D. Givol, Induction of WAF1/CIP1 by a p53-independent pathway, *Cancer Res*. 54 (1994) 3391–3395.
- [132] H. Zhang, G.J. Hannon, D. Beach, p21-containing cyclin kinases exist in both active and inactive states., *Genes & Development*. 8 (1994) 1750–1758. <https://doi.org/10.1101/gad.8.15.1750>.
- [133] J. LaBaer, M.D. Garrett, L.F. Stevenson, J.M. Slingerland, C. Sandhu, H.S. Chou, A. Fattaey, E. Harlow, New functional activities for the p21 family of CDK inhibitors., *Genes & Development*. 11 (1997) 847–862. <https://doi.org/10.1101/gad.11.7.847>.
- [134] M.K. James, A. Ray, D. Leznova, S.W. Blain, Differential Modification of p27^{Kip1} Controls Its Cyclin D-cdk4 Inhibitory Activity, *Mol Cell Biol*. 28 (2008) 498–510. <https://doi.org/10.1128/MCB.02171-06>.
- [135] M.D. Larrea, J. Liang, T. Da Silva, F. Hong, S.H. Shao, K. Han, D. Dumont, J.M. Slingerland, Phosphorylation of p27^{Kip1} Regulates Assembly and Activation of Cyclin D1-Cdk4, *Mol Cell Biol*. 28 (2008) 6462–6472. <https://doi.org/10.1128/MCB.02300-07>.
- [136] K.Z. Guiley, J.W. Stevenson, K. Lou, K.J. Barkovich, V. Kumarasamy, T.U. Wijeratne, K.L. Bunch, S. Tripathi, E.S. Knudsen, A.K. Witkiewicz, K.M. Shokat, S.M. Rubin, p27 allosterically activates cyclin-dependent kinase 4 and antagonizes palbociclib inhibition, *Science*. 366 (2019) eaaw2106. <https://doi.org/10.1126/science.aaw2106>.
- [137] A. Cerqueira, A. Martín, C.E. Symonds, J. Odajima, P. Dubus, M. Barbacid, D. Santamaría, Genetic Characterization of the Role of the Cip/Kip Family of Proteins as Cyclin-Dependent Kinase Inhibitors and Assembly Factors, *Mol Cell Biol*. 34 (2014) 1452–1459. <https://doi.org/10.1128/MCB.01163-13>.
- [138] G.D. Grant, J.G. Cook, The Temporal Regulation of S Phase Proteins During G1, in: H. Masai, M. Foiani (Eds.), *DNA Replication*, Springer Singapore, Singapore, 2017: pp. 335–369. https://doi.org/10.1007/978-981-10-6955-0_16.
- [139] M. Abbastabar, M. Kheyrollah, K. Azizian, N. Bagherlou, S.S. Tehrani, M. Maniati, A. Karimian, Multiple functions of p27 in cell cycle, apoptosis, epigenetic modification and transcriptional regulation for the control of cell growth: A double-edged sword protein, *DNA Repair*. 69 (2018) 63–72. <https://doi.org/10.1016/j.dnarep.2018.07.008>.
- [140] L. Machado, J.E. de Lima, O. Fabre, C. Proux, R. Legendre, A. Szegedi, H. Varet, L.R. Ingerslev, R. Barrès, F. Relaix, P. Mourikis, In Situ Fixation Redefines Quiescence and Early Activation of Skeletal Muscle Stem Cells, *Cell Reports*. 21 (2017) 1982–1993. <https://doi.org/10.1016/j.celrep.2017.10.080>.
- [141] M.K. Kullmann, F. Pegka, C. Ploner, L. Hengst, Stimulation of c-Jun/AP-1-Activity by the Cell Cycle Inhibitor p57Kip2, *Front. Cell Dev. Biol*. 9 (2021) 664609. <https://doi.org/10.3389/fcell.2021.664609>.

- [142] S.B. Parker, G. Eichele, P. Zhang, A. Rawls, A.T. Sands, A. Bradley, E.N. Olson, J.W. Harper, S.J. Elledge, p53-Independent Expression of p21^{Cip1} in Muscle and Other Terminally Differentiating Cells, *Science*. 267 (1995) 1024–1027. <https://doi.org/10.1126/science.7863329>.
- [143] F. Zindy, D.E. Quelle, M.F. Roussel, C.J. Sherr, Expression of the p16INK4a tumor suppressor versus other INK4 family members during mouse development and aging, *Oncogene*. 15 (1997) 203–211. <https://doi.org/10.1038/sj.onc.1201178>.
- [144] J. Westbury, M. Watkins, A.C. Ferguson-Smith, J. Smith, Dynamic temporal and spatial regulation of the cdk inhibitor p57kip2 during embryo morphogenesis, *Mechanisms of Development*. 109 (2001) 83–89. [https://doi.org/10.1016/S0925-4773\(01\)00512-3](https://doi.org/10.1016/S0925-4773(01)00512-3).
- [145] E. Susaki, K. Nakayama, L. Yamasaki, K.I. Nakayama, Common and specific roles of the related CDK inhibitors p27 and p57 revealed by a knock-in mouse model, *Proceedings of the National Academy of Sciences*. 106 (2009) 5192–5197. <https://doi.org/10.1073/pnas.0811712106>.
- [146] P. Zhu, C. Zhang, Y. Gao, F. Wu, Y. Zhou, W.-S. Wu, The transcription factor Slug represses p16Ink4a and regulates murine muscle stem cell aging, *Nat Commun*. 10 (2019) 2568. <https://doi.org/10.1038/s41467-019-10479-4>.
- [147] A. Tsugu, K. Sakai, P.B. Dirks, S. Jung, R. Weksberg, Y.-L. Fei, S. Mondal, S. Ivanchuk, C. Ackerley, P.A. Hamel, J.T. Rutka, Expression of p57KIP2 Potently Blocks the Growth of Human Astrocytomas and Induces Cell Senescence, *The American Journal of Pathology*. 157 (2000) 919–932. [https://doi.org/10.1016/S0002-9440\(10\)64605-6](https://doi.org/10.1016/S0002-9440(10)64605-6).
- [148] K. Alexander, P.W. Hinds, Requirement for p27^{KIP1} in Retinoblastoma Protein-Mediated Senescence, *Mol Cell Biol*. 21 (2001) 3616–3631. <https://doi.org/10.1128/MCB.21.11.3616-3631.2001>.
- [149] S. Gargica, S. Brookes, E. Anderton, J. Rowe, G. Peters, Contrasting Behavior of the p18^{INK4c} and p16^{INK4a} Tumor Suppressors in Both Replicative and Oncogene-Induced Senescence, *Cancer Res*. 72 (2012) 165–175. <https://doi.org/10.1158/0008-5472.CAN-11-2552>.
- [150] C. Giovannini, L. Gramantieri, M. Minguzzi, F. Fornari, P. Chieco, G.L. Grazi, L. Bolondi, CDKN1C/P57 is regulated by the Notch target gene Hes1 and induces senescence in human hepatocellular carcinoma., *The American Journal of Pathology*. 181 (2012) 413–22. <https://doi.org/10.1016/j.ajpath.2012.04.019>.
- [151] Cooperative role between p21cip1/waf1 and p27kip1 in premature senescence in glandular proliferative lesions in mice, *Histology and Histopathology*. (2014) 397–406. <https://doi.org/10.14670/HH-29.397>.
- [152] R. Pippa, L. Espinosa, G. Gundem, R. García-Escudero, A. Dominguez, S. Orlando, E. Gallastegui, C. Saiz, A. Besson, M.J. Pujol, N. López-Bigas, J.M. Paramio, A. Bigas, O. Bachs, p27Kip1 represses transcription by direct interaction with p130/E2F4 at the promoters of target genes, *Oncogene*. 31 (2012) 4207–4220. <https://doi.org/10.1038/onc.2011.582>.
- [153] S. Orlando, E. Gallastegui, A. Besson, G. Abril, R. Aligué, M.J. Pujol, O. Bachs, p27^{Kip1} and p21^{Cip1} collaborate in the regulation of transcription by recruiting cyclin–Cdk complexes on the promoters of target genes, *Nucleic Acids Res*. 43 (2015) 6860–6873. <https://doi.org/10.1093/nar/gkv593>.
- [154] A. Nowosad, P. Jeannot, C. Callot, J. Creff, R.T. Perchey, C. Joffre, P. Codogno, S. Manenti, A. Besson, p27 controls Ragulator and mTOR activity in amino acid-deprived cells to regulate the autophagy–lysosomal pathway and coordinate cell cycle and cell growth, *Nat Cell Biol*. 22 (2020) 1076–1090. <https://doi.org/10.1038/s41556-020-0554-4>.
- [155] D.S. Franklin, Y. Xiong, Induction of p18INK4c and its predominant association with CDK4 and CDK6 during myogenic differentiation., *MBoC*. 7 (1996) 1587–1599. <https://doi.org/10.1091/mbc.7.10.1587>.

- [156] E. Latres, Limited overlapping roles of P15INK4b and P18INK4c cell cycle inhibitors in proliferation and tumorigenesis, *The EMBO Journal*. 19 (2000) 3496–3506. <https://doi.org/10.1093/emboj/19.13.3496>.
- [157] J. Li, S. Han, W. Cousin, I.M. Conboy, Age-Specific Functional Epigenetic Changes in p21 and p16 in Injury-Activated Satellite Cells: Age-Specific Epigenetic Changes in Satellite Cells, *Stem Cells*. 33 (2015) 951–961. <https://doi.org/10.1002/stem.1908>.
- [158] E.G. Reynaud, K. Pospel, M. Guillier, M.P. Leibovitch, S.A. Leibovitch, p57Kip2 stabilizes the MyoD protein by inhibiting cyclin E-Cdk2 kinase activity in growing myoblasts, *Molecular and Cellular Biology*. 19 (1999) 7621–7629.
- [159] Z. Yan, S. Choi, X. Liu, M. Zhang, J.J. Schageman, S.Y. Lee, R. Hart, L. Lin, F.A. Thurmond, R.S. Williams, Highly Coordinated Gene Regulation in Mouse Skeletal Muscle Regeneration, *Journal of Biological Chemistry*. 278 (2003) 8826–8836. <https://doi.org/10.1074/jbc.M209879200>.
- [160] T.S. Chikenji, Y. Saito, N. Konari, M. Nakano, Y. Mizue, M. Otani, M. Fujimiya, p16INK4A-expressing mesenchymal stromal cells restore the senescence–clearance–regeneration sequence that is impaired in chronic muscle inflammation, *EBioMedicine*. 44 (2019) 86–97. <https://doi.org/10.1016/j.ebiom.2019.05.012>.
- [161] J. Wang, K. Walsh, Resistance to Apoptosis Conferred by Cdk Inhibitors During Myocyte Differentiation, *Science*. 273 (1996) 359–361. <https://doi.org/10.1126/science.273.5273.359>.
- [162] J. Wang, K. Guo, K.N. Wills, K. Walsh, Rb functions to inhibit apoptosis during myocyte differentiation, *Cancer Res*. 57 (1997) 351–354.
- [163] H. Kondo, H.W. Kim, L. Wang, M. Okada, C. Paul, R.W. Millard, Y. Wang, Blockade of senescence-associated micro RNA -195 in aged skeletal muscle cells facilitates reprogramming to produce induced pluripotent stem cells., *Aging Cell*. 15 (2016) 56–66. <https://doi.org/10.1111/accel.12411>.
- [164] E. Balan, E. De Groote, M. Bouillon, N. Viceconte, M. Mahieu, D. Naslain, H. Nielens, A. Decottignies, L. Deldicque, No effect of the endurance training status on senescence despite reduced inflammation in skeletal muscle of older individuals, *American Journal of Physiology-Endocrinology and Metabolism*. 319 (2020) E447–E454. <https://doi.org/10.1152/ajpendo.00149.2020>.
- [165] P. Sousa-Victor, S. Gutarra, L. García-Prat, J. Rodríguez-Ubveva, L. Ortet, V. Ruiz-Bonilla, M. Jardí, E. Ballestar, S. González, A.L. Serrano, E. Perdiguero, P. Muñoz-Cánoves, Geriatric muscle stem cells switch reversible quiescence into senescence, *Nature*. 506 (2014) 316–321. <https://doi.org/10.1038/nature13013>.
- [166] C.M. Dungan, B.D. Peck, R.G. Walton, Z. Huang, M.M. Bamman, P.A. Kern, C.A. Peterson, In vivo analysis of γ H2AX+ cells in skeletal muscle from aged and obese humans, *FASEB J*. 34 (2020) 7018–7035. <https://doi.org/10.1096/fj.202000111RR>.
- [167] M.L. Idda, W.G. McClusky, V. Lodde, R. Munk, K. Abdelmohsen, M. Rossi, M. Gorospe, Survey of senescent cell markers with age in human tissues, *Aging*. 12 (2020) 4052–4066. <https://doi.org/10.18632/aging.102903>.
- [168] H. Sugihara, N. Teramoto, K. Nakamura, T. Shiga, T. Shirakawa, M. Matsuo, M. Ogasawara, I. Nishino, T. Matsuwaki, M. Nishihara, K. Yamanouchi, Cellular senescence-mediated exacerbation of Duchenne muscular dystrophy, *Sci Rep*. 10 (2020) 16385. <https://doi.org/10.1038/s41598-020-73315-6>.
- [169] S. Glumac, R. Davidovic, B. Dozic, S. Hinic, I. Pavlovic, D. Drakulic, A. Todorović, M.M. Pavlovic, S.R. Skodric, I. Baralic, J. Sopta, S. Pejic, Immunohistochemical expression of cyclin-dependent kinase inhibitors p16 and p57 in rhabdomyosarcoma, *Pathology - Research and Practice*. 225 (2021) 153558. <https://doi.org/10.1016/j.prp.2021.153558>.

- [170] J. Wu, I.-S. Cheng, S. Saovieng, W.-H. Jean, C.-L. Kao, Y.-Y. Liu, C.-Y. Huang, T.X.Y. Lee, J.L. Ivy, C.-H. Kuo, Aerobic exercise induces tumor suppressor p16^{INK4a} expression of endothelial progenitor cells in human skeletal muscle, *Aging*. 12 (2020) 20226–20234. <https://doi.org/10.18632/aging.103763>.
- [171] D.E. Phelps, K.-M. Hsiao, Y. Li, N. Hu, D.S. Franklin, E. Westphal, E.Y.-H.P. Lee, Y. Xiong, Coupled Transcriptional and Translational Control of Cyclin-Dependent Kinase Inhibitor p18^{INK4c} Expression during Myogenesis, *Mol Cell Biol*. 18 (1998) 2334–2343. <https://doi.org/10.1128/MCB.18.4.2334>.
- [172] D.S. Franklin, V.L. Godfrey, H. Lee, G.I. Kovalev, R. Schoonhoven, S. Chen-Kiang, L. Su, Y. Xiong, CDK inhibitors p18INK4c and p27Kip1 mediate two separate pathways to collaboratively suppress pituitary tumorigenesis, *Genes & Development*. 12 (1998) 2899–2911. <https://doi.org/10.1101/gad.12.18.2899>.
- [173] O. Halevy, B.G. Novitch, D.B. Spicer, S.X. Skapek, J. Rhee, G.J. Hannon, D. Beach, A.B. Lassar, Correlation of Terminal Cell Cycle Arrest of Skeletal Muscle with Induction of p21 by MyoD, *Science*. 267 (1995) 1018–1021. <https://doi.org/10.1126/science.7863327>.
- [174] G. Messina, C. Blasi, S.A. La Rocca, M. Pompili, A. Calconi, M. Grossi, p27^{Kip1} Acts Downstream of N-Cadherin-mediated Cell Adhesion to Promote Myogenesis beyond Cell Cycle Regulation, *MBoC*. 16 (2005) 1469–1480. <https://doi.org/10.1091/mbc.e04-07-0612>.
- [175] N. Yoshida, S. Yoshida, K. Koishi, K. Masuda, Y. Nabeshima, Cell heterogeneity upon myogenic differentiation: down-regulation of MyoD and Myf-5 generates “reserve cells,” *J Cell Sci*. 111 (Pt 6) (1998) 769–779.
- [176] Y. Cao, Z. Zhao, J. Gruszczynska-Biegala, A. Zolkiewska, Role of Metalloprotease Disintegrin ADAM12 in Determination of Quiescent Reserve Cells during Myogenic Differentiation In Vitro, *Mol Cell Biol*. 23 (2003) 6725–6738. <https://doi.org/10.1128/MCB.23.19.6725-6738.2003>.
- [177] R. Figliola, R. Maione, MyoD induces the expression of p57Kip2 in cells lacking p21Cip1/Waf1: Overlapping and distinct functions of the two cdk inhibitors, *J. Cell. Physiol*. 200 (2004) 468–475. <https://doi.org/10.1002/jcp.20044>.
- [178] K. Guo, J. Wang, V. Andrés, R.C. Smith, K. Walsh, MyoD-induced expression of p21 inhibits cyclin-dependent kinase activity upon myocyte terminal differentiation, *Mol Cell Biol*. 15 (1995) 3823–3829. <https://doi.org/10.1128/MCB.15.7.3823>.
- [179] T.J. Hawke, A.P. Meeson, N. Jiang, S. Graham, K. Hutcheson, J.M. DiMaio, D.J. Garry, p21 is essential for normal myogenic progenitor cell function in regenerating skeletal muscle, *American Journal of Physiology-Cell Physiology*. 285 (2003) C1019–C1027. <https://doi.org/10.1152/ajpcell.00055.2003>.
- [180] D. Pajalunga, A. Mazzola, A.M. Salzano, M.G. Biferi, G. De Luca, M. Crescenzi, Critical requirement for cell cycle inhibitors in sustaining nonproliferative states, *Journal of Cell Biology*. 176 (2007) 807–818. <https://doi.org/10.1083/jcb.200608109>.
- [181] M. Marti, N. Montserrat, C. Pardo, L. Mulero, L. Miquel-Serra, A.M.C. Rodrigues, J. Andrés Vaquero, B. Kuebler, C. Morera, M.J. Barrero, J.C. Izpisua Belmonte, Mcad-mediated intercellular interactions activate satellite cell division, *Journal of Cell Science*. (2013) jcs.123562. <https://doi.org/10.1242/jcs.123562>.
- [182] W. Pu, X. Han, L. He, Y. Li, X. Huang, M. Zhang, Z. Lv, W. Yu, Q.-D. Wang, D. Cai, J. Wang, R. Sun, J. Fei, Y. Ji, Y. Nie, B. Zhou, A genetic system for tissue-specific inhibition of cell proliferation, *Development*. (2020) dev.183830. <https://doi.org/10.1242/dev.183830>.
- [183] W. El-Deiry, WAF1, a potential mediator of p53 tumor suppression, *Cell*. 75 (1993) 817–825. [https://doi.org/10.1016/0092-8674\(93\)90500-P](https://doi.org/10.1016/0092-8674(93)90500-P).
- [184] K. Singh, F.J. Dilworth, Differential modulation of cell cycle progression distinguishes members of the myogenic regulatory factor family of transcription factors, *FEBS J*. 280 (2013) 3991–4003. <https://doi.org/10.1111/febs.12188>.

- [185] V. Andrés, K. Walsh, Myogenin expression, cell cycle withdrawal, and phenotypic differentiation are temporally separable events that precede cell fusion upon myogenesis., *The Journal of Cell Biology*. 132 (1996) 657–666.
- [186] N. Marroncelli, M. Bianchi, M. Bertin, S. Consalvi, V. Saccone, M. De Bardi, P.L. Puri, D. Palacios, S. Adamo, V. Moresi, HDAC4 regulates satellite cell proliferation and differentiation by targeting P21 and Sharp1 genes, *Sci Rep*. 8 (2018) 3448. <https://doi.org/10.1038/s41598-018-21835-7>.
- [187] T. Zhang, S. Günther, M. Looso, C. Künne, M. Krüger, J. Kim, Y. Zhou, T. Braun, Prmt5 is a regulator of muscle stem cell expansion in adult mice, *Nat Commun*. 6 (2015) 7140. <https://doi.org/10.1038/ncomms8140>.
- [188] R.S. Blanc, G. Vogel, T. Chen, C. Crist, S. Richard, PRMT7 Preserves Satellite Cell Regenerative Capacity, *Cell Reports*. 14 (2016) 1528–1539. <https://doi.org/10.1016/j.celrep.2016.01.022>.
- [189] M. Naito, M. Mori, M. Inagawa, K. Miyata, N. Hashimoto, S. Tanaka, H. Asahara, Dnmt3a Regulates Proliferation of Muscle Satellite Cells via p57Kip2, *PLoS Genet*. 12 (2016) e1006167. <https://doi.org/10.1371/journal.pgen.1006167>.
- [190] C.W. Park, J.H. Chung, Age-dependent changes of p57Kip2 and p21Cip1/Waf1 expression in skeletal muscle and lung of mice, *Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression*. 1520 (2001) 163–168. [https://doi.org/10.1016/S0167-4781\(01\)00266-4](https://doi.org/10.1016/S0167-4781(01)00266-4).
- [191] K.F. Macleod, N. Sherry, G. Hannon, D. Beach, T. Tokino, K. Kinzler, B. Vogelstein, T. Jacks, p53-dependent and independent expression of p21 during cell growth, differentiation, and DNA damage., *Genes & Development*. 9 (1995) 935–944. <https://doi.org/10.1101/gad.9.8.935>.
- [192] S. Endesfelder, A. Krahn, K.-A. Kreuzer, U. Lass, C.A. Schmidt, C. Jahrmarkt, A. von Moers, A. Speer, Elevated p21 mRNA level in skeletal muscle of DMD patients and mdx mice indicates either an exhausted satellite cell pool or a higher p21 expression in dystrophin-deficient cells per se, *J Mol Med*. 78 (2000) 569–574. <https://doi.org/10.1007/s001090000153>.
- [193] C. Weise, F. Dai, F. Pröls, U.-P. Ketelsen, U. Dohrmann, M. Kirsch, B. Brand-Saberi, Myogenin (Myf4) upregulation in trans-differentiating fibroblasts from a congenital myopathy with arrest of myogenesis and defects of myotube formation, *Anat Embryol*. 211 (2006) 639–648. <https://doi.org/10.1007/s00429-006-0117-x>.
- [194] M. Borok, N. Didier, F. Gattazzo, T. Ozturk, A. Corneau, H. Rouard, F. Relaix, Progressive and Coordinated Mobilization of the Skeletal Muscle Niche throughout Tissue Repair Revealed by Single-Cell Proteomic Analysis, *Cells*. 10 (2021) 744. <https://doi.org/10.3390/cells10040744>.
- [195] M.E. Carlson, M. Hsu, I.M. Conboy, Imbalance between pSmad3 and Notch induces CDK inhibitors in old muscle stem cells, *Nature*. 454 (2008) 528–532. <https://doi.org/10.1038/nature07034>.
- [196] M.M. Dethlefsen, J.F. Halling, H.D. Møller, P. Plomgaard, B. Regenberg, S. Ringholm, H. Pilegaard, Regulation of apoptosis and autophagy in mouse and human skeletal muscle with aging and lifelong exercise training, *Experimental Gerontology*. 111 (2018) 141–153. <https://doi.org/10.1016/j.exger.2018.07.011>.
- [197] K.A. Zwetsloot, T.E. Childs, L.T. Gilpin, F.W. Booth, Non-passaged muscle precursor cells from 32-month old rat skeletal muscle have delayed proliferation and differentiation, *Cell Prolif*. 46 (2013) 45–57. <https://doi.org/10.1111/cpr.12007>.
- [198] C. Deng, P. Zhang, J. Wade Harper, S.J. Elledge, P. Leder, Mice Lacking p21CIP1/WAF1 undergo normal development, but are defective in G1 checkpoint control, *Cell*. 82 (1995) 675–684. [https://doi.org/10.1016/0092-8674\(95\)90039-X](https://doi.org/10.1016/0092-8674(95)90039-X).
- [199] J.V. Chakkalakal, J. Christensen, W. Xiang, M.T. Tierney, F.S. Boscolo, A. Sacco, A.S. Brack, Early forming label-retaining muscle stem cells require p27kip1 for maintenance of the primitive state, *Development*. 141 (2014) 1649–1659. <https://doi.org/10.1242/dev.100842>.

- [200] N. Chinzei, S. Hayashi, T. Ueha, T. Fujishiro, N. Kanzaki, S. Hashimoto, S. Sakata, S. Kihara, M. Haneda, Y. Sakai, R. Kuroda, M. Kurosaka, P21 Deficiency Delays Regeneration of Skeletal Muscular Tissue, *PLoS ONE*. 10 (2015) e0125765. <https://doi.org/10.1371/journal.pone.0125765>.
- [201] M.G. Biferi, C. Nicoletti, G. Falcone, E.M.R. Puggioni, N. Passaro, A. Mazzola, D. Pajalunga, G. Zaccagnini, E. Rizzuto, A. Auricchio, L. Zentilin, G. De Luca, M. Giacca, F. Martelli, A. Musio, A. Musarò, M. Crescenzi, Proliferation of Multiple Cell Types in the Skeletal Muscle Tissue Elicited by Acute p21 Suppression, *Molecular Therapy*. 23 (2015) 885–895. <https://doi.org/10.1038/mt.2015.27>.
- [202] L. Machado, P. Geara, J. Camps, M. Dos Santos, F. Teixeira-Clerc, J. Van Herck, H. Varet, R. Legendre, J.-M. Pawlotsky, M. Sampaolesi, T. Voet, P. Maire, F. Relaix, P. Mourikis, Tissue damage induces a conserved stress response that initiates quiescent muscle stem cell activation, *Cell Stem Cell*. 28 (2021) 1125–1135.e7. <https://doi.org/10.1016/j.stem.2021.01.017>.
- [203] C. Bean, M. Salamon, A. Raffaello, S. Campanaro, A. Pallavicini, G. Lanfranchi, The *Ankrd2*, *Cdkn1c* and *Calcyclin* Genes are Under the Control of MyoD During Myogenic Differentiation, *Journal of Molecular Biology*. 349 (2005) 349–366. <https://doi.org/10.1016/j.jmb.2005.03.063>.
- [204] A. Zalc, S. Hayashi, F. Auradé, D. Bröhl, T. Chang, D. Mademtzoglou, P. Mourikis, Z. Yao, Y. Cao, C. Birchmeier, F. Relaix, Antagonistic regulation of p57kip2 by Hes/Hey downstream of Notch signaling and muscle regulatory factors regulates skeletal muscle growth arrest, *Development*. 141 (2014) 2780–2790. <https://doi.org/10.1242/dev.110155>.
- [205] D. Mademtzoglou, S. Alonso-Martin, T.H. Chang, K. Bismuth, B. Drayton-Libotte, F. Aurade, F. Relaix, A p57 conditional mutant allele that allows tracking of p57-expressing cells, *Genesis*. 55 (2017). <https://doi.org/10.1002/dvg.23025>.
- [206] S. Fukada, A. Uezumi, M. Ikemoto, S. Masuda, M. Segawa, N. Tanimura, H. Yamamoto, Y. Miyagoe-Suzuki, S. Takeda, Molecular signature of quiescent satellite cells in adult skeletal muscle, *Stem Cells*. 25 (2007) 2448–2459. <https://doi.org/10.1634/stemcells.2007-0019>.
- [207] N. Pietrosevoli, S. Mella, S. Yennek, M.B. Baghdadi, H. Sakai, R. Sambasivan, F. Pala, D. Di Girolamo, S. Tajbakhsh, Comparison of multiple transcriptomes exposes unified and divergent features of quiescent and activated skeletal muscle stem cells, *Skeletal Muscle*. 7 (2017) 28. <https://doi.org/10.1186/s13395-017-0144-8>.
- [208] C.T.J. van Velthoven, A. de Morree, I.M. Egner, J.O. Brett, T.A. Rando, Transcriptional Profiling of Quiescent Muscle Stem Cells In Vivo, *Cell Reports*. 21 (2017) 1994–2004. <https://doi.org/10.1016/j.celrep.2017.10.037>.
- [209] O. Andresini, A. Ciotti, M.N. Rossi, C. Battistelli, M. Carbone, R. Maione, A cross-talk between DNA methylation and H3 lysine 9 dimethylation at the *KvDMR1* region controls the induction of *Cdkn1c* in muscle cells, *Epigenetics*. 11 (2016) 791–803. <https://doi.org/10.1080/15592294.2016.1230576>.
- [210] O. Andresini, M.N. Rossi, F. Matteini, S. Petrai, T. Santini, R. Maione, The long non-coding RNA *Kcnq1ot1* controls maternal p57 expression in muscle cells by promoting H3K27me3 accumulation to an intragenic MyoD-binding region, *Epigenetics & Chromatin*. 12 (2019) 8. <https://doi.org/10.1186/s13072-019-0253-1>.
- [211] G. Vaccarello, R. Figliola, S. Cramerotti, F. Novelli, R. Maione, p57Kip2 is Induced by MyoD Through a p73-dependent Pathway, *Journal of Molecular Biology*. 356 (2006) 578–588. <https://doi.org/10.1016/j.jmb.2005.12.024>.
- [212] R. Figliola, A. Busanello, G. Vaccarello, R. Maione, Regulation of p57KIP2 during Muscle Differentiation: Role of Egr1, Sp1 and DNA Hypomethylation, *Journal of Molecular Biology*. 380 (2008) 265–277. <https://doi.org/10.1016/j.jmb.2008.05.004>.
- [213] A. Busanello, C. Battistelli, M. Carbone, C. Mostocotto, R. Maione, MyoD regulates p57 kip2 expression by interacting with a distant cis -element and modifying a higher order chromatin structure, *Nucleic Acids Research*. 40 (2012) 8266–8275. <https://doi.org/10.1093/nar/gks619>.

- [214] C. Battistelli, A. Busanello, R. Maione, Functional interplay between MyoD and CTCF in regulating long-range chromatin interactions during differentiation, *Journal of Cell Science*. (2014) jcs.149427. <https://doi.org/10.1242/jcs.149427>.
- [215] D.P.S. Osborn, K. Li, Y. Hinitz, S.M. Hughes, Cdkn1c drives muscle differentiation through a positive feedback loop with Myod, *Developmental Biology*. 350 (2011) 464–475. <https://doi.org/10.1016/j.ydbio.2010.12.010>.
- [216] E.G. Reynaud, M.P. Leibovitch, L.A.J. Tintignac, K. Pospel, M. Guillier, S.A. Leibovitch, Stabilization of MyoD by Direct Binding to p57Kip2, *Journal of Biological Chemistry*. 275 (2000) 18767–18776. <https://doi.org/10.1074/jbc.M907412199>.
- [217] Y. Hashimoto, K. Kohri, Y. Kaneko, H. Morisaki, T. Kato, K. Ikeda, M. Nakanishi, Critical Role for the 310 Helix Region of p57Kip2 in Cyclin-dependent Kinase 2 Inhibition and Growth Suppression, *Journal of Biological Chemistry*. 273 (1998) 16544–16550. <https://doi.org/10.1074/jbc.273.26.16544>.
- [218] P. Zhang, C. Wong, D. Liu, M. Finegold, J.W. Harper, S.J. Elledge, p21(CIP1) and p57(KIP2) control muscle differentiation at the myogenin step., *Genes & Development*. 13 (1999) 213–24.
- [219] M. Chen, C. Liu, M. Wang, H. Wang, K. Zhang, Y. Zheng, Z. Yu, X. Li, W. Guo, N. Li, Q. Meng, Clenbuterol Induces Cell Cycle Arrest in C2C12 Myoblasts by Delaying p27 Degradation through β -arrestin 2 Signaling, *Int. J. Biol. Sci.* 13 (2017) 1341–1350. <https://doi.org/10.7150/ijbs.17948>.
- [220] M.V. Chakravarthy, T.W. Abraha, R.J. Schwartz, M.L. Fiorotto, F.W. Booth, Insulin-like Growth Factor-I Extends in Vitro Replicative Life Span of Skeletal Muscle Satellite Cells by Enhancing G1/S Cell Cycle Progression via the Activation of Phosphatidylinositol 3'-Kinase/Akt Signaling Pathway, *Journal of Biological Chemistry*. 275 (2000) 35942–35952. <https://doi.org/10.1074/jbc.M005832200>.
- [221] A. Biçer, S. Orlando, A.B.M.M.K. Islam, E. Gallastegui, A. Besson, R. Aligué, O. Bachs, M.J. Pujol, ChIP-Seq analysis identifies p27(Kip1)-target genes involved in cell adhesion and cell signalling in mouse embryonic fibroblasts, *PLoS ONE*. 12 (2017) e0187891. <https://doi.org/10.1371/journal.pone.0187891>.
- [222] J. Lin, M. Anne Della-Fera, C. Li, K. Page, Y. Ho Choi, D.L. Hartzell, C.A. Baile, P27 knockout mice: reduced myostatin in muscle and altered adipogenesis, *Biochemical and Biophysical Research Communications*. 300 (2003) 938–942. [https://doi.org/10.1016/S0006-291X\(02\)02949-2](https://doi.org/10.1016/S0006-291X(02)02949-2).
- [223] S.D. Zabudoff, M. Csete, R. Wagner, X. Yu, B.J. Wold, p27Kip1 is expressed transiently in developing myotomes and enhances myogenesis, *Cell Growth Differ.* 9 (1998) 1–11.
- [224] J.P. White, A.N. Billin, M.E. Campbell, A.J. Russell, K.M. Huffman, W.E. Kraus, The AMPK/p27Kip1 Axis Regulates Autophagy/Apoptosis Decisions in Aged Skeletal Muscle Stem Cells, *Stem Cell Reports*. 11 (2018) 425–439. <https://doi.org/10.1016/j.stemcr.2018.06.014>.
- [225] H.V. Kojouharov, B.M. Chen-Charpentier, F.J. Solis, C. Biguetti, M. Brotto, A simple model of immune and muscle cell crosstalk during muscle regeneration, *Mathematical Biosciences*. 333 (2021) 108543. <https://doi.org/10.1016/j.mbs.2021.108543>.