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Macrophage cell cycle

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Abstract

Macrophages are dynamic and plastic immune cells essential for tissue homeostasis and pathogen defense. Their cell cycle regulation is highly influenced by intrinsic and extrinsic signals facilitating rapid responses to infections and tissue damage. Dysregulation of their cell cycle leads to diseases like cancer and HIV. This chapter highlights aspects of the macrophage cell cycle crucial for the development of targeted therapies.

Keywords: Macrophage Cell Cycle, Plasticity, Disease Progression, Cellular Proliferation, Molecular Regulators

1. Introduction

Macrophages are highly dynamic immune cells that play a key role in tissue health, homeostasis, defense against pathogens, chronic rejection of transplants, and wound healing (Lucas et al. 2010; Wynn et al. 2013; Jiang et al. 2014; Gordon and Plüddemann 2017; Gossselin et al. 2014, 2017). They are distributed in almost all tissues of the body and originate from bone marrow-derived monocytes and embryonic precursors (Yona et al. 2013; Hoeffel and Ginhoux 2018). Their specific cell cycle regulation and ability to proliferate allow a rapid response to infections, organ transplantations, or tissue damage (Sieweke and Allen 2013).

Macrophages, like other proliferating cells, progress through the cell cycle phases – G1, S, G2, and M (Matsushime 1995; El Dika 2013; Ferreira et al. 2020; El Dika et al. 2022; Uzbekov and Prigent 2022). In tissues, the cell cycle is tightly regulated by extracellular signals that control cell proliferation, thus influencing tissue growth and expansion. Disruption of the cell cycle and cell proliferation is frequently implicated in various pathologies, including cancer (Malumbres and Barbacid 2009; Metcalfe et al. 2022). Macrophages in G1 and possibly in G2 phase can enter a permanent state of cell cycle arrest called senescence, which is characterized by irreversible growth arrest and changes in cellular morphology and function (Fig.1), (Wang et al. 2024). Key molecular changes associated with macrophage senescence include increased levels of Senescence-Associated Beta-Galactosidase (SA- β -Gal) and upregulation of the cyclin-dependent kinase inhibitor 2A (also known as CDKN2A or p16INK4a, (Wang et al. 2024). Senescent macrophages exhibit a Senescence-Associated Secretory Phenotype (SASP) and secrete pro-inflammatory factors. They are characterized by specific gene expression alterations, imbalanced polarization states, dysregulation of cholesterol homeostasis, and oxidative respiration (Wang et al. 2024).

Macrophages can also enter a resting stage or G0 phase. In the G0 phase macrophages are primarily in a non-dividing state of quiescence until prompted by specific stimuli such as growth factors, nutrients, pathogen invasion, or cytokines (Weiss and Schaible 2015). This state is crucial for maintaining a pool of ready-to-

activate macrophages that can respond quickly to infection or tissue damage. When activated, macrophages can exit the G0 phase to proliferate or differentiate into specialized forms, which are more effective at dealing with specific threats or injuries. Their ability to exit the G0 phase and become active is vital for effective immune responses and the resolution of inflammation. Recent research indicates that the shift from G0 to G1 creates an opportunity for HIV-1 infection (Ferreira et al. 2020). Macrophages are key targets for HIV-1, but they produce high levels of SAM domain and HD domain-containing protein 1 (SAMHD1), a deoxynucleotide-triphosphate hydrolase that restricts viral DNA synthesis by reducing dNTP levels (Laguetta et al. 2011; Ferreira et al. 2020). While the G0 state is resistant to HIV-1 infection, the G1 state becomes highly permissive (Fig.1). In the G1 state, macrophages deactivate the antiviral restriction factor SAMHD1 through the phosphorylation process, thereby facilitating effective HIV-1 infection (Laguetta et al. 2011; Kim et al. 2013; Mlcochova et al. 2017; Antonucci et al. 2017; Schott et al. 2018; Ferreira et al. 2020). The macrophages' internal molecular machinery regulating cell cycle progression is affected by extracellular signals that dictate proliferation, quiescence, or differentiation (Sieweke and Allen 2013; Pearce and Pearce 2013). These signals include interactions with microbial products such as lipopolysaccharides (LPS) or cytokines (e.g. IFN- γ), which can promote macrophages to exit the G0 phase and resume the cell cycle (Kawai and Akira 2010). These stimuli are essential for macrophages to respond effectively to environmental challenges, thus affirming their role as guardians of tissue health and integrity.

Transition in the macrophage cell cycle is also rigorously controlled to ensure proper DNA replication and integrity (Ferreira et al. 2020; Mlcochova et al. 2024). This regulation is vital in normal physiological conditions as well as in pathological contexts, such as mentioned HIV viral infections where the macrophage cell cycle greatly influences vulnerability to the infection of the organism (Dupont and Sattentau 2020; Ferreira et al. 2020; Mlcochova et al. 2024). In the context of cancer, the dynamics of macrophage proliferation and their interactions with tumor cells can influence tumor growth, thus highlighting the complexity of macrophage roles in diseases such as, for example, periodontal and oral cancer (Gosselin et al. 2014; Gosselin et al. 2017; Metcalfe et al. 2022).

2. Regulation of Macrophage Cell Cycle

The regulation of the macrophage cell cycle involves a network of signaling pathways, transcription factors, and external stimuli that govern their proliferation and differentiation. The ability of macrophages to join the cell cycle and undergo self-renewal shows their dynamic nature and plasticity.

2.1. Signaling Pathways

Macrophages have the unique ability to mature and specialize under the influence of two important growth factors: Macrophage Colony Stimulating Factor (M-CSF) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) (Mehta et al. 2015; Ushach and Zlotnik 2016; Munsif et al. 2023). M-CSF is found in most tissues and can be easily detected in the blood. In contrast, GM-CSF is primarily produced in the lungs and increases during inflammatory responses. These molecules are essential for the survival and growth of macrophages. When macrophages differentiate in response to M-CSF or GM-CSF, they exhibit different behaviors during the cell cycle, especially during the transition from the G1 to the S phase.

Recent research has shown that GM-CSF and M-CSF activate distinct pathways in macrophages – one responsible for proliferation and the other for survival (Vico et al. 2022). M-CSF is very effective in promoting macrophage proliferation, significantly increasing the growth and differentiation of monocytic/macrophage lineage cells when present. In contrast, although GM-CSF induces proliferation, it does so less efficiently than M-CSF. However, GM-CSF excels in protecting macrophages from DNA damage. After DNA breaks caused by substances such as etoposide or hydrogen peroxide, GM-CSF contributes to faster recovery and reduced proliferation, probably by activating genes that pause the cell cycle. The ability of GM-CSF to protect macrophages against DNA damage exceeds that of M-CSF.

Macrophages differentiated with M-CSF multiply faster than those with GM-CSF, as shown by intracellular Ki67 staining (also known as MKI67, a marker of proliferation) (Badia et al. 2016). The M-CSF-stimulation results in 7% of Ki67+ macrophages compared to GM-CSF-stimulation which results in 0.5% of Ki67+ macrophages (Badia et al. 2016). Also, the M-CSF-stimulated macrophage population has more cells in the active stages of the cell cycle (S/G2M). These differences also affect macrophages' vulnerability to HIV-1 infection. The M-CSF-stimulated macrophages are about ten

times more likely to be infected with HIV-1 compared to GM-CSF-stimulated (Badia et al. 2016). There are additionally higher levels of dNTPs in actively cycling M-CSF-treated macrophages, hinting that the dynamics of the cell cycle, especially progression through the S phase, are crucial for HIV-1 to infect and replicate within these cells.

Additionally, SAMHD1, a protein that restricts HIV-1 replication, plays a significant role in this process (Badia et al. 2016). Significant differences in SAMHD1 activity were observed between macrophages treated with M-CSF and those treated with GM-CSF. M-CSF-treated ones show changes in SAMHD1, which could make them more susceptible to HIV-1. When Viral Protein X (HIV-2 Vpx) degrades SAMHD1, HIV-1 replication increases, demonstrating the importance of SAMHD1 in limiting viral infection (Badia et al. 2016). This emphasizes how factors related to the cell cycle and proliferation can affect SAMHD1 and, consequently, the susceptibility of macrophages to HIV-1 infection.

2.2. Transcription Factors

Transcription factors are important in coordinating the gene expression programs that govern macrophage proliferation, differentiation, and self-renewal. They interact with specific DNA sequences to control the transcription of genes involved in cell cycle progression and maintenance of macrophage identity.

Several transcription factors are involved in this process:

- i. Kruppel-like factor 4 (KLF4), a zinc finger transcription factor critical for macrophage proliferation and differentiation (Liao et al. 2018). KLF4 binds to specific DNA sequences to control the expression of genes involved in the cell cycle progression and self-renewal. Its Inhibition results in aberrant macrophage proliferation and impaired differentiation.
- ii. Nuclear receptor signaling pathways such as liver X receptors (LXRs) and retinoid X receptors (RXRs) (Chen and Ross 2004; Pascual-García et al. 2011; A-Gonzalez et al. 2013; Menéndez-Gutiérrez et al. 2015). LXRs are lipid-activated transcription factors associated with lipid metabolism and inflammation. They inhibit macrophage cell cycle progression and form heterodimers with RXRs to modulate the macrophage gene expression during the cell cycle. Interactions of LXRs, RXRs, and other nuclear receptors also

provide a complex regulatory network that regulates macrophage function and self-renewal.

- iii. Sirtuin-1 (SIRT1), which is a member of the sirtuin family of NAD⁺-dependent deacetylases and is implicated in the regulation of macrophage self-renewal and proliferation (Imperatore et al. 2017; Röszer 2018). Its inhibition reduces alveolar and peritoneal macrophage self-renewal, thus suggesting a role for this transcriptional regulator in macrophage homeostasis. SIRT1 exerts its effects by deacetylating histone and non-histone proteins, thus modulating gene expression and cell cycle progression. However, the precise mechanisms by which SIRT1 regulates macrophage proliferation and differentiation warrant further investigation.
- iv. Nuclear Factor κ B (NF- κ B) and Signal Transducer and Activator of Transcription (STAT), which are important transcription factors that regulate the cell cycle and inflammatory responses (Aravindaram and Yang 2010; Pugazhenti et al. 2013; Dinasarapu et al. 2013; Pinheiro et al. 2019). They are activated by cytokines and other signals. Indeed, NF- κ B can both promote and inhibit the cell cycle, which affects many genes involved in cell proliferation and survival, like cyclin D1, crucial for the G1 phase of the cell cycle (Hinz et al. 1999; Joyce et al. 2001; Witzel et al. 2010; Hwang et al. 2010). Similarly, STAT, particularly STAT3, influences the cell cycle by enhancing the expression of genes like cyclin D1 and Myc (myelocytomatosis oncogene), which drive the transition from the G1 to the S phase (Sai et al. 2012; Zhou et al. 2018; Yu et al. 2022).
- v. Myc and Hypoxia-Inducible Factor Alpha (HIF1 α), a subunit of HIF-1. Myc facilitates the transition from the G1 phase to the S phase of the macrophage cell cycle by upregulating the expression of cyclins (like cyclin D1) and cyclin-dependent kinases (CDKs), (Liu et al. 2016). Under hypoxia, macrophages undergo HIF1 α -mediated transcriptional reprogramming that alters macrophage metabolism and function toward pathogen elimination and inflammatory responses, thus resulting in disruptions in cell cycle and proliferation. Moreover, mitogenic stimulation, such as by CSF-1, activates a Myc-dependent transcriptional program in macrophages to favor cell cycle entry and upregulate glucose and glutamine metabolism supporting growth and proliferation (Liu et al. 2016). Conversely, proinflammatory signals like LPS and IFN- γ shift metabolism towards glycolysis via a HIF1 α -dependent program, thus

suppressing Myc-driven proliferation while enhancing the proinflammatory response (Liu et al. 2016). M1 macrophages, under these conditions, experience cell cycle arrest, ensuring they maintain their effector functions without excessive proliferation (Fig. 1).

2.3. Cyclins, CDKs and Circadian Rhythm

Cyclins and cyclin-dependent kinases (CDKs) are key regulators of the cell cycle that control the progression through the different phases of cell division. In macrophages, the expression and activity of cyclins and CDKs are highly controlled to ensure proper cell cycle progression and proliferation (Matsushime 1995). Cyclins and CDKs are also important for the expression of cell cycle checkpoint genes. It has been demonstrated that the reduced gene expression of cyclin D1 in response to LPS blocks the macrophage cell cycle (Matsushime 1995; Röszer 2018). Thus, the dysregulation of the cyclin gene expression (or CDK activity) results in cell cycle arrest.

All cells and organisms function according to the circadian rhythm. The circadian rhythm is endogenous but is adjusted to the local environment by external cues (zeitgebers) such as light, temperature, and redox cycles. Because circadian rhythm oscillates cell processes over a 24-hour cycle, it is not surprising that macrophage functions and responses to pathogens and other stimuli also oscillate according to their circadian rhythm (Fig. 2).

It has been shown that, in macrophages, the circadian clock influences the expression of genes involved in cell cycle progression, such as cyclins and cyclin-dependent kinases (CDKs) (Fig.1); (Timmons et al. 2020; Shirato and Sato 2022; Lellupitiyage Don et al. 2022). The rhythmic expression of these regulators is essential for coordinating cell division and proliferation in a timely manner. Disruption of the circadian rhythms can then lead to dysregulation of the cell cycle, thus affecting macrophage proliferation and differentiation.

Furthermore, the circadian clock impacts the response of macrophages to external stimuli, such as pathogens or inflammatory signals, by modulating cell cycle progression and activation of immune responses (Timmons et al. 2020; Shirato and Sato 2022; Lellupitiyage Don et al. 2022). It has been demonstrated that deletion of the circadian gene *BMAL1* in macrophages alters their phagocytic activity and antimicrobial response. Disruptions in circadian rhythms, such as those caused by endotoxin exposure, affect the cell cycle of macrophages through the generation of

reactive oxygen species. Additionally, the clearance of apoptotic cells by macrophages, known as efferocytosis, is subject to circadian regulation. This process is crucial for maintaining tissue homeostasis and resolving inflammation. The activity of TAM receptors, a family of receptor tyrosine kinases that includes Tyro3, Axl, and Mer and known as efferocytosis mediators, shows circadian patterns, potentially influenced by oscillations in glucocorticoid levels and core clock genes like *BMAL1*.

2.4. TGF- β 's Interactions

The complex interaction between transforming growth factor- β (TGF- β) and macrophages impacts their functionality, polarization, and functions in tissue regeneration and immune regulation (Ruscetti et al. 1991; Ashcroft 1999; Vannella and Wynn 2017; Shapouri-Moghaddam et al. 2018; Chen et al. 2023). This cytokine impacts the cell cycle by causing a pause in the G1 phase (Derynck 1994; Ravitz and Wenner 1997; Hocevar and Howe 1998; Wolf 2000). This is primarily achieved by activating CDK inhibitors like p21 (also known as cyclin-dependent kinase inhibitor 1) and p15 (also known as cyclin-dependent kinase 4 inhibitor B), which play a critical role in cell cycle arrest in the G1 phase (Nagahara et al. 1999). The p21 and p15 suppress the expression of the cyclin D-CDK4/6 (D-type cyclins complexed with cyclin-dependent kinases 4 or 6) and cyclin E-CDK2 (E-type cyclins complexed with cyclin-dependent kinases 2) that both are required for progressing towards the S phase (Nagahara et al. 1999; El Dika 2013).

The Smad (Mothers Against Decapentaplegic Homolog), a protein complex induced by TGF- β , plays an essential role in controlling cell growth by suppressing specific cellular activities essential for cell cycle progression (Syed 2016). This suppression arrests the cell cycle in the G1 phase, preventing cells from progressing to the S phase, where DNA synthesis occurs. Both Smad-dependent and -independent pathways are involved in the TGF- β signaling cascade, contributing to its role in cell cycle regulation. As an example, TGF- β can trigger dephosphorylation Ribosomal protein S6 kinase beta-1 (S6K1, also known as p70S6) through protein phosphatase 2A, resulting in cell cycle disruption (Petritsch et al. 2000). This highlights the variety of signaling pathways that TGF- β can stimulate to exert its actions and the importance of TGF- β in cell cycle regulation by balancing proliferation and cell cycle arrest.

2.5. Inflammatory Signals

Inflammatory cytokines include tumor necrosis factor alpha (TNF α) and interferon gamma (IFN γ) (Holden et al. 2017; Shapouri-Moghaddam et al. 2018; Mily et al. 2020; Edris et al. 2022). They inhibit macrophage proliferation and induce cell cycle arrest by altering the expression of cell cycle checkpoint genes. These inflammatory mediators shift the transcriptional program of macrophages from a self-renewal state to an inflammatory response state. M1 macrophages (pro-inflammatory) are activated by signaling via Toll-like receptors (TLRs) and cytokines such as TNF- α and IFN- γ , resulting in the expression of pro-inflammatory genes controlled by transcription factors such as NF- κ B and STAT1 and release of antimicrobial and tumoricidal cytokines such as TNF- α , IL-1, and IL-6 (Holden et al. 2017; Shapouri-Moghaddam et al. 2018; Mily et al. 2020; Edris et al. 2022). However, the cell cycle regulation of M2 macrophages (anti-inflammatory) involves activating specific signaling pathways such as JAK/STAT, the IL-4, and IL-13 that impact macrophage proliferation, which in turn promotes not only anti-inflammatory responses but also cell growth and cell survival. Besides, STAT6 is activated by IL-4 and IL-13 and plays an important role in stimulating the growth of M2 macrophages. Advanced techniques are essential for investigating the nuanced roles and cell cycle behaviors of macrophages, especially in understanding how M1 and M2 phenotypes influence their proliferation and functionality.

3. Cell Cycle-Dependent Plasticity of Macrophages

Macrophage plasticity is critical for their roles in host protection, tissue repair, and immune regulation. Recent research on macrophage plasticity has shown that different phases of the cell cycle influence the macrophage activation states and functional properties (Daniel et al. 2023). For example, macrophages in the G1 phase are more likely to turn on a pro-inflammatory response, while those in the S or G2/M phases might adopt anti-inflammatory characteristics. So, this cell cycle-dependent plasticity permits macrophages to fine-track their responses to changing environmental stimuli, therefore ensuring effective immune function and tissue homeostasis.

Interestingly, single-cell approaches have been recently used to characterize the heterogeneity in macrophage responses based on their cell cycle state (Daniel et al. 2023). It has been shown that macrophages in different phases exhibit distinct gene expression profiles and functional properties. For example, macrophages analyzed at

the single-cell level show a wide range of activation states beyond the traditional M1 and M2 classifications. This diversity is influenced by local cytokine milieus, tissue-specific signals, and the cell cycle phase. The authors also showed that IL-4 can induce S-G2/M-biased gene expression, including tissue remodeling genes, in macrophages (Daniel et al., 2023).

These mechanisms underlying cell cycle-dependent plasticity are complex and multifaceted (EL Kasmi and Stenmark 2015; Viola et al. 2019; Chambers et al. 2021; Daniel et al. 2023). As described above, cyclins and CDKs coordinate cell cycle progression and macrophage activation states, while transcription factors such as NF- κ B and STATs play crucial roles in macrophage activation and polarization, with their expression and activity varying across different cell cycle phases. These regulators drive dynamic changes in macrophage gene expression profiles, thus influencing their functional properties. Moreover, the cell cycle influences the metabolic and bioenergetic status of macrophages, which in turn affects their activation state (EL Kasmi and Stenmark 2015; Viola et al. 2019; Chambers et al. 2021; Daniel et al. 2023). Metabolic reprogramming is a hallmark of macrophage activation, with distinct metabolic pathways being associated with different activation states. The cell cycle regulates metabolic pathways such as glycolysis, oxidative phosphorylation, and fatty acid metabolism, which all are essential for macrophage function.

Epigenetic modifications affect the macrophage cell cycle and activation (Daniel et al. 2023). They include changes in chromatin structure and histones modifications that alter gene expression patterns in a cell cycle-dependent manner, thus influencing macrophage responses. For instance, during certain cell cycle phases, macrophages may go through chromatin remodeling that enhances or suppresses the expression of genes involved in inflammation or tissue repair. These epigenetic modifications permit macrophages to evolve their activation states to specific environmental cues, thus fine-tuning their responses to inflammatory stimuli and tissue-specific signals.

4. Novel techniques advancing macrophage regulation

Advancing our understanding of the regulatory processes and developing targeted therapies can be greatly aided by innovative techniques in macrophage research (Shimi et al. 2004; Ishikawa-Ankerhold et al. 2012; De Los Santos et al. 2015; Na et al. 2015; Wu et al. 2020; Zhang et al. 2021; Song et al. 2022; Fan et al. 2023; Miljkovic

et al. 2023) i) High-Throughput Screening (HTS) rapidly test thousands of conditions to identify modulators of macrophage function that are relevant to diseases ii) Single-Cell RNA Sequencing (scRNA-seq) generate new data about the individual cellular responses at the transcriptomic level, thus shedding light on eventual population heterogeneity iii) Live cell imaging techniques, including Fluorescence Recovery After Photobleaching (FRAP) and Fluorescence Resonance Energy Transfer (FRET), allow analyzing real-time dynamics of macrophage related proteins and the signaling pathway activation iv) Mass Cytometry (CyTOF) that uses metal-labeled antibodies for detailed cellular analysis and CRISPR-Cas9 gene editing enable precise manipulations of such genes to study their roles in response to cytokines and growth factors (Wu et al. 2020) v) proteomic screens like Tandem Mass Tag (TMT) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) can identify quantifying proteomic changes and discovering new signaling molecules involved in macrophage regulation. All these approaches have recently become pivotal for advancing our understanding of macrophage biology and developing targeted therapies.

5. Conclusions

The dynamic regulation of the macrophage cell cycle in response to different stimuli and circadian clock, and the mechanisms underlying cell cycle-dependent plasticity will have significant clinical implications. Dysregulation of macrophage activation states and cell cycle control is associated with various inflammatory diseases, autoimmune disorders, and cancer. Thus, targeting cell cycle regulators, transcription factors, or epigenetic modifiers in macrophages presents promising therapeutic opportunities for modulating immune responses and treating inflammatory disorders. By harnessing the dynamic nature of macrophage plasticity, the cell cycle, and circadian rhythm-regulated responses researchers can develop novel strategies for precision medicine and personalized immunotherapy.

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Conflict of Interest

The authors declare no conflict of interest.

References

- A-Gonzalez N, Guillen JA, Gallardo G, Diaz M, DeLaRosa JV., Hernandez IH, Casanova-Acebes M, Lopez F, Tabraue C, Beceiro S, Hong C, Lara PC, Andujar M, Arai S, Miyazaki T, Li S, Corbi AL, Tontonoz P, Hidalgo A, Castrillo A (2013) The nuclear receptor LXR α controls the functional specialization of splenic macrophages. *Nat Immunol* 14(8):831–839. <https://doi.org/10.1038/NI.2622>
- Antonucci JM, StGelais C, Wu L (2017) The Dynamic Interplay between HIV-1, SAMHD1, and the Innate Antiviral Response. *Front Immunol* 8(NOV):1541. <https://doi.org/10.3389/fimmu.2017.01541>
- Aravindaram K, Yang NS (2010) Anti-inflammatory plant natural products for cancer therapy. *Planta Med* 76(11):1103–1117. <https://doi.org/10.1055/s-0030-1249859>
- Ashcroft GS (1999) Bidirectional regulation of macrophage function by TGF- β . *Microbes Infect* 1(15):1275–1282. [https://doi.org/10.1016/S1286-4579\(99\)00257-9](https://doi.org/10.1016/S1286-4579(99)00257-9)
- Badia R, Pujantell M, Riveira-Muñoz E, Puig T, Torres-Torronteras J, Martí R, Clotet B, Ampudia RM, Vives-Pi M, Esté JA, Ballana E (2016) The G1/S Specific Cyclin D2 Is a Regulator of HIV-1 Restriction in Non-proliferating Cells. *PLoS Pathog* 12(8). <https://doi.org/10.1371/JOURNAL.PPAT.1005829>
- Chambers M, Rees A, Cronin JG, Nair M, Jones N, Thornton CA (2021) Macrophage Plasticity in Reproduction and Environmental Influences on Their Function. *Front Immunol* 11. <https://doi.org/10.3389/fimmu.2020.607328>
- Chen Q, Ross AC (2004) Retinoic acid regulates cell cycle progression and cell differentiation in human monocytic THP-1 cells. *Exp Cell Res* 297(1):68–81. <https://doi.org/10.1016/j.yexcr.2004.02.017>
- Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, Xiao GG, Rao L, Duo Y (2023) Macrophages in immunoregulation and therapeutics. *Signal Transduct Target Ther* 8(1):207. <https://doi.org/10.1038/s41392-023-01452-1>
- Daniel B, Belk JA, Meier SL, Chen AY, Sandor K, Czimmerer Z, Varga Z, Bene K, Buquicchio FA, Qi Y, Kitano H, Wheeler JR, Foster DS, Januszyk M, Longaker MT, Chang HY, Satpathy AT (2023) Macrophage inflammatory and regenerative response periodicity is programmed by cell cycle and chromatin state. *Mol Cell* 83(1):121-138.e7. <https://doi.org/10.1016/J.MOLCEL.2022.11.017>
- DeLosSantos C, Chang CW, Mycek MA, Cardullo RA (2015) FRAP, FLIM, and FRET: Detection and analysis of cellular dynamics on a molecular scale using fluorescence microscopy. *Mol Reprod Dev* 82(7–8):587–604. <https://doi.org/10.1002/mrd.22501>
- Derynck R (1994) TGF- β -receptor-mediated signaling. *Trends Biochem Sci* 19(12):548–553. [https://doi.org/10.1016/0968-0004\(94\)90059-0](https://doi.org/10.1016/0968-0004(94)90059-0)

- Dinasarapu AR, Gupta S, Maurya MR, Fahy E, Min J, Sud M, Gersten MJ, Glass CK, Subramaniam S (2013) A combined omics study on activated macrophages - Enhanced role of STATs in apoptosis, immunity and lipid metabolism. *Bioinformatics* 29(21):2735–2743. <https://doi.org/10.1093/bioinformatics/btt469>
- Dupont M, Sattentau QJ (2020) Macrophage cell-cell interactions promoting HIV-1 infection. *Viruses* 12(5). <https://doi.org/10.3390/v12050492>
- Edris NA, Aboulhoda BE, El-Din SS, Fouad AM, Albadawi E, Rashed LA, Elessawy KB (2022) Toll-Like Receptor Signaling in the Pathogenesis of Chronic Dacryocystitis: Implication of c-FOS Transcription Factor and its Downstream Ejector Chemokine Genes CCL2, CCL4, CXCL3, CXCR4 with a Shift of the M1/M2 Macrophage Phenotype. *Comb Chem High Throughput Screen* 26(3):489–497. <https://doi.org/10.2174/1386207325666220509150457>
- El Dika M (2013) Régulation de la phase M du cycle cellulaire par CDK1, PP2A et CDC6
- El Dika M, Fritz AJ, Toor RH, Rodriguez PD, Foley SJ, Ullah R, Nie D, Banerjee B, Lohese D, Tracy KM, Glass KC, Fritze S, Ghule PN, Heath JL, Imbalzano AN, van Wijnen A, Gordon J, Lian JB, Stein JL, Stein GS (2022) Epigenetic-Mediated Regulation of Gene Expression for Biological Control and Cancer: Fidelity of Mechanisms Governing the Cell Cycle. *Results Probl Cell Differ* 70:375–396. https://doi.org/10.1007/978-3-031-06573-6_13
- EL Kasmi KC, Stenmark KR (2015) Contribution of metabolic reprogramming to macrophage plasticity and function. *Semin Immunol* 27(4):267–275. <https://doi.org/10.1016/j.smim.2015.09.001>
- Fan P, Zhang Y, Ding S, Du Z, Zhou C, Du X (2023) Integrating RNA-seq and scRNA-seq to explore the mechanism of macrophage ferroptosis associated with COPD. *Front Pharmacol* 14:1139137. <https://doi.org/10.3389/fphar.2023.1139137>
- Ferreira IATM, Zachary Porterfield J, Gupta RK, Mlcochova P (2020) Cell cycle regulation in macrophages and susceptibility to HIV-1. *Viruses* 12(8). <https://doi.org/10.3390/v12080839>
- Gordon S, Plüddemann A (2017) Tissue macrophages: Heterogeneity and functions. *BMC Biol* 15(1). <https://doi.org/10.1186/s12915-017-0392-4>
- Gosselin D, Link VM, Romanoski CE, Fonseca GJ, Eichenfield DZ, Spann NJ, Stender JD, Chun HB, Garner H, Geissmann F, Glass CK (2014) Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. *Cell* 159(6):1327–1340. <https://doi.org/10.1016/J.CELL.2014.11.023>
- Gosselin D, Skola D, Coufal NG, Holtman IR, Schlachetzki JCM, Sajti E, Jaeger BN, O'Connor C, Fitzpatrick C, Pasillas MP, Pena M, Adair A, Gonda DD, Levy ML, Ransohok RM, Gage FH, Glass CK (2017) An environment-dependent transcriptional network specifies human microglia identity. *Science* 356(6344):1248–1259. <https://doi.org/10.1126/SCIENCE.AAL3222>
- Hinz M, Krappmann D, Eichten A, Heder A, Scheidereit C, Strauss M (1999) NF- κ B Function in Growth Control: Regulation of Cyclin D1 Expression and G0/G1-to-S-Phase Transition. *Mol Cell Biol* 19(4):2690–2698. <https://doi.org/10.1128/mcb.19.4.2690>
- Hocevar BA, Howe PH (1998) Mechanisms of TGF- β -induced cell cycle arrest. *Miner Electrolyte Metab* 24(2–3):131–135. <https://doi.org/10.1159/000057360>

- Hoekel G, Ginhoux F (2018) Fetal monocytes and the origins of tissue-resident macrophages. *Cell Immunol* 330:5–15. <https://doi.org/10.1016/j.cellimm.2018.01.001>
- Holden JA, O'Brien-Simpson NM, Lenzo JC, Orth RKH, Mansell A, Reynolds EC (2017) *Porphyromonas gulae* activates unprimed and gamma interferon-primed macrophages via the pattern recognition receptors Toll-like receptor 2 (TLR2), TLR4, and NOD2. *Infect Immun* 85(9). <https://doi.org/10.1128/IAI.00282-17>
- Hwang I, Choi YS, Jeon MY, Jeong S (2010) NF- κ B p65 represses β -catenin-activated transcription of cyclin D1. *Biochem Biophys Res Commun* 403(1):79–84. <https://doi.org/10.1016/j.bbrc.2010.10.118>
- Imperatore F, Maurizio J, Vargas Aguilar S, Busch CJ, Favret J, Kowenz-Leutz E, Cathou W, Gentek R, Perrin P, Leutz A, Berruyer C, Sieweke MH (2017) SIRT1 regulates macrophage self-renewal. *EMBO J* 36(16):2353–2372. <https://doi.org/10.15252/EMBJ.201695737>
- Ishikawa-Ankerhold HC, Ankerhold R, Drummen GPC (2012) Advanced fluorescence microscopy techniques-FRAP, FLIP, FLAP, FRET and FLIM. *Molecules* 17(4):4047–4132. <https://doi.org/10.3390/molecules17044047>
- Jiang X, Tian W, Sung YK, Qian J, Nicolls MR (2014) Macrophages in solid organ transplantation. *Vasc Cell* 6(1):5. <https://doi.org/10.1186/2045-824X-6-5>
- Joyce D, Albanese C, Steer J, Fu M, Bouzahzah B, Pestell RG (2001) NF- κ B and cell-cycle regulation: The cyclin connection. *Cytokine Growth Factor Rev* 12(1):73–90. [https://doi.org/10.1016/S1359-6101\(00\)00018-6](https://doi.org/10.1016/S1359-6101(00)00018-6)
- Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: Update on toll-like receptors. *Nat Immunol* 11(5):373–384. <https://doi.org/10.1038/ni.1863>
- Kim ET, White TE, Brandariz-Núñez A, Diaz-Grikeró F, Weitzman MD (2013) SAMHD1 Restricts Herpes Simplex Virus 1 in Macrophages by Limiting DNA Replication. *J Virol* 87(23):12949–12956. <https://doi.org/10.1128/jvi.02291-13>
- Laguet N, Sobhian B, Casartelli N, Ringeard M, Chable-Bessia C, Ségéral E, Yatim A, Emiliani S, Schwartz O, Benkirane M (2011) SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. *Nature* 474(7353):654–657. <https://doi.org/10.1038/NATURE10117>
- Lellupitiyage Don SS, Mas-Rosario JA, Lin HH, Nguyen EM, Taylor SR, Farkas ME (2022) Macrophage circadian rhythms are differentially affected based on stimuli. *Integr Biol (Camb)* 14(3):62–75. <https://doi.org/10.1093/INTBIO/ZYAC007>
- Liao X, Shen Y, Zhang R, Sugi K, Vasudevan NT, Amer Alaiti M, Sweet DR, Zhou L, Qing Y, Gerson SL, Fu C, Wynshaw-Boris A, Hu R, Schwartz MA, Fujioka H, Richardson B, Cameron MJ, Hayashi H, Stamler JS, Jain MK (2018) Distinct roles of resident and nonresident macrophages in nonischemic cardiomyopathy. *Proc Natl Acad Sci U S A* 115(20):E4661–E4669. <https://doi.org/10.1073/PNAS.1720065115>
- Liu L, Luc Y, Martinez J, Bi Y, Lian G, Wang T, Milasta S, Wang J, Yang M, Liu G, Green DR, Wang R (2016) Proinflammatory signal suppresses proliferation and shifts macrophage metabolism from Myc-dependent to HIF1 α -dependent. *Proc Natl Acad Sci U S A* 113(6):1564–1569. <https://doi.org/10.1073/PNAS.1518000113>

- Lucas T, Waisman A, Ranjan R, Roes J, Krieg T, Müller W, Roers A, Eming SA (2010) Diferential Roles of Macrophages in Diverse Phases of Skin Repair. *The Journal of Immunology* 184(7):3964–3977. <https://doi.org/10.4049/jimmunol.0903356>
- Malumbres M, Barbacid M (2009) Cell cycle, CDKs and cancer: a changing paradigm. *Nat Rev Cancer* 9(3):153–166. <https://doi.org/10.1038/NRC2602>
- Matsushime H (1995) Macrophage cell cycle control by M-CSF/CSF-1. *Rinsho Ketsueki* 36(5):406–409
- Mehta HM, Malandra M, Corey SJ (2015) G-CSF and GM-CSF in Neutropenia. *J Immunol* 195(4):1341–1349. <https://doi.org/10.4049/JIMMUNOL.1500861>
- Menéndez-Gutiérrez MP, Röszer T, Fuentes L, Núñez V, Escolano A, Redondo JM, De Clerck N, Metzger D, Villedor AF, Ricote M (2015) Retinoid X receptors orchestrate osteoclast differentiation and postnatal bone remodeling. *J Clin Invest* 125(2):809–823. <https://doi.org/10.1172/JCI77186>
- Metcalf S, Anselmi N, Escobar A, Visser MB, Kay JG (2022) Innate Phagocyte Polarization in the Oral Cavity. *Front Immunol* 12. <https://doi.org/10.3389/fimmu.2021.768479>
- Miljkovic M, Lozano S, Castellote I, de Cózar C, Villegas-Moreno AI, Gamallo P, Jimenez-Alfaro Martinez D, Fernández-Álvaro E, Ballell L, Garcia GA (2023) Novel inhibitors that target bacterial virulence identified via HTS against intra-macrophage survival of *Shigella flexneri*. *mSphere* 8(5). <https://doi.org/10.1128/msphere.00154-23>
- Mily A, Kalsum S, Loreti MG, Rekha RS, Muvva JR, Lourda M, Brighenti S (2020) Polarization of m1 and m2 human monocyte-derived cells and analysis with flow cytometry upon mycobacterium tuberculosis infection. *Journal of Visualized Experiments* 2020(163):1–20. <https://doi.org/10.3791/61807>
- Mlcochova P, Heilig R, Fischer R, Gupta RK (2024) CD4 T cell contact drives macrophage cell cycle progression and susceptibility to lentiviral transduction. *bioRxiv* :2024.01.15.575666. <https://doi.org/10.1101/2024.01.15.575666>
- Mlcochova P, Sutherland KA, Watters SA, Bertoli C, de Bruin RA, Rehwinkel J, Neil SJ, Lenzi GM, Kim B, Khwaja A, Gage MC, Georgiou C, Chittka A, Yona S, Noursadeghi M, Towers GJ, Gupta RK (2017) A G1-like state allows HIV -1 to bypass SAMHD 1 restriction in macrophages. *EMBO J* 36(5):604–616. <https://doi.org/10.15252/embj.201696025>
- Munsif M, Sweeney D, Leong TL, Stirling RG (2023) Nebulised granulocyte–macrophage colony-stimulating factor (GM-CSF) in autoimmune pulmonary alveolar proteinosis: a systematic review and meta-analysis. *European Respiratory Review* 32(170). <https://doi.org/10.1183/16000617.0080-2023>
- Na YR, Hong JH, Lee MY, Jung JH, Jung D, Kim YW, Son D, Choi M, Kim KP, Seok SH (2015) Proteomic analysis reveals distinct metabolic differences between granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF) grown macrophages derived from murine bone marrow cells. *Molecular and Cellular Proteomics* 14(10):2722–2732. <https://doi.org/10.1074/mcp.M115.048744>
- Nagahara H, Ezhevsky SA, Vocero-Akbani AM, Kaldis P, Solomon MJ, Dowdy SF (1999) Transforming growth factor beta targeted inactivation of cyclin E: cyclin-dependent kinase 2

- (Cdk2) complexes by inhibition of Cdk2 activating kinase activity. *Proc Natl Acad Sci U S A* 96(26):14961–14966. <https://doi.org/10.1073/PNAS.96.26.14961>
- Pascual-García M, Carbó JM, León T, Matalonga J, Out R, Van Berkel T, Sarrias M-R, Lozano F, Celada A, Valledor AF (2011) Liver X receptors inhibit macrophage proliferation through downregulation of cyclins D1 and B1 and cyclin-dependent kinases 2 and 4. *J Immunol* 186(8):4656–4667. <https://doi.org/10.4049/JIMMUNOL.1000585>
- Pearce EL, Pearce EJ (2013) Metabolic pathways in immune cell activation and quiescence. *Immunity* 38(4):633–643. <https://doi.org/10.1016/j.immuni.2013.04.005>
- Petritsch C, Beug H, Baimain A, Oft M (2000) TGF- β inhibits p70 S6 kinase via protein phosphatase 2A to induce G(1) arrest. *Genes Dev* 14(24):3093–3101. <https://doi.org/10.1101/GAD.854200>
- Pinheiro DML, de Oliveira AHS, Coutinho LG, Fontes FL, de Medeiros Oliveira RK, Oliveira TT, Faustino ALF, Lira da Silva V, de Melo Campos JTA, Lajus TBP, de Souza SJ, Agnez-Lima LF (2019) Resveratrol decreases the expression of genes involved in inflammation through transcriptional regulation. *Free Radic Biol Med* 130:8–22. <https://doi.org/10.1016/j.freeradbiomed.2018.10.432>
- Pugazhenth S, Zhang Y, Bouchard R, Mahakey G (2013) Induction of an Inflammatory Loop by Interleukin-1 β and Tumor Necrosis Factor- α Involves NF- κ B and STAT-1 in Differentiated Human Neuroprogenitor Cells. *PLoS One* 8(7). <https://doi.org/10.1371/journal.pone.0069585>
- Ravitz MJ, Wenner CE (1997) Cyclin-dependent kinase regulation during G1 phase and cell cycle regulation by TGF- β . *Adv Cancer Res* 71:165–207. [https://doi.org/10.1016/s0065-230x\(08\)60099-8](https://doi.org/10.1016/s0065-230x(08)60099-8)
- Röszer T (2018) Understanding the Biology of Self-Renewing Macrophages. *Cells* 7(8). <https://doi.org/10.3390/cells7080103>
- Ruscetti FW, Dubois C, Falk LA, Jacobsen SE, Sing G, Longo DL, Wiltrout RH, Keller JR (1991) In vivo and in vitro effects of TGF- β 1 on normal and neoplastic haemopoiesis. *Ciba Found Symp* 157. <https://doi.org/10.1002/9780470514061.ch14>
- Sai K, Wang S, Balasubramanian V, Conrad C, Lang FF, Aldape K, Szymanski S, Fokt I, Dasgupta A, Madden T, Guan S, Chen Z, Yung WKA, Priebe W, Colman H (2012) Induction of cell-cycle arrest and apoptosis in glioblastoma stem-like cells by WP1193, a novel small molecule inhibitor of the JAK2/STAT3 pathway. *J Neurooncol* 107(3):487–501. <https://doi.org/10.1007/s11060-011-0786-z>
- Schott K, Fuchs NV., Derua R, Mahboubi B, Schnellbacher E, Seifried J, Tondera C, Schmitz H, Shepard C, Brandariz-Nuñez A, Diaz-Grikeró F, Reuter A, Kim B, Janssens V, König R (2018) Dephosphorylation of the HIV-1 restriction factor SAMHD1 is mediated by PP2A-B55 α holoenzymes during mitotic exit. *Nat Commun* 9(1). <https://doi.org/10.1038/s41467-018-04671-1>
- Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT, Sahebkar A (2018) Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol* 233(9):6425–6440. <https://doi.org/10.1002/JCP.26429>

- Shimi T, Koujin T, Segura-Totten M, Wilson KL, Haraguchi T, Hiraoka Y (2004) Dynamic interaction between BAF and emerin revealed by FRAP, FLIP, and FRET analyses in living HeLa cells. *J Struct Biol* 147(1):31–41. <https://doi.org/10.1016/j.jsb.2003.11.013>
- Shirato K, Sato S (2022) Macrophage Meets the Circadian Clock: Implication of the Circadian Clock in the Role of Macrophages in Acute Lower Respiratory Tract Infection. *Front Cell Infect Microbiol* 12. <https://doi.org/10.3389/FCIMB.2022.826738>
- Sieweke MH, Allen JE (2013) Beyond stem cells: self-renewal of differentiated macrophages. *Science* 342(6161). <https://doi.org/10.1126/SCIENCE.1242974>
- Song J, Jiang J, Kuai L, Luo Y, Xing M, Luo Y, Ru Y, Sun X, Zhang H, Liu T, Li X, Li B (2022) TMT-based proteomics analysis reveals the protective effect of Jueyin granules on imiquimod-induced psoriasis mouse model by causing autophagy: Inducing autophagy for Jueyin granules treatment of psoriasis-like inflammation. *Phytomedicine* 96. <https://doi.org/10.1016/j.phymed.2021.153846>
- Syed V (2016) TGF- β Signaling in Cancer. *J Cell Biochem* 117(6):1279–1287. <https://doi.org/10.1002/jcb.25496>
- Timmons GA, O'Siorain JR, Kennedy OD, Curtis AM, Early JO (2020) Innate Rhythms: Clocks at the Center of Monocyte and Macrophage Function. *Front Immunol* 11:1743. <https://doi.org/10.3389/FIMMU.2020.01743>
- Ushach I, Zlotnik A (2016) Biological role of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) on cells of the myeloid lineage. *J Leukoc Biol* 100(3):481–489. <https://doi.org/10.1189/jlb.3ru0316-144r>
- Uzbekov R, Prigent C (2022) A Journey through Time on the Discovery of Cell Cycle Regulation. *Cells* 11(4). <https://doi.org/10.3390/CELLS11040704>
- Vannella KM, Wynn TA (2017) Mechanisms of Organ Injury and Repair by Macrophages*. *Annu Rev Physiol* 79:593–617. <https://doi.org/10.1146/annurev-physiol-022516-034356>
- Vico T, Youssif C, Zare F, Comalada M, Sebastian C, Lloberas J, Celada A (2022) GM-CSF Protects Macrophages from DNA Damage by Inducing Differentiation. *Cells* 11(6). <https://doi.org/10.3390/CELLS11060935>
- Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A (2019) The metabolic signature of macrophage responses. *Front Immunol* 10(JULY). <https://doi.org/10.3389/fimmu.2019.01462>
- Wang L, Hong W, Zhu H, He Q, Yang B, Wang J, Weng Q (2024) Macrophage senescence in health and diseases. *Acta Pharm Sin B* 14(4):1508–1524. <https://doi.org/10.1016/J.APSB.2024.01.008>
- Weiss G, Schaible UE (2015) Macrophage defense mechanisms against intracellular bacteria. *Immunol Rev* 264(1):182–203. <https://doi.org/10.1111/IMR.12266>
- Witzell I, Koh LF, Perkins ND (2010) Regulation of cyclin D1 gene expression. *Biochem Soc Trans* 38(1):217–222. <https://doi.org/10.1042/BST0380217>
- Wolf G (2000) Cell cycle regulation in diabetic nephropathy. *Kidney Int Suppl* 58(77). <https://doi.org/10.1046/j.1523-1755.2000.07710.x>

- Wu K, Lin K, Li X, Yuan X, Xu P, Ni P, Xu D (2020) Redefining Tumor-Associated Macrophage Subpopulations and Functions in the Tumor Microenvironment. *Front Immunol* 11:1731. <https://doi.org/10.3389/fimmu.2020.01731>
- Wynn TA, Chawla A, Pollard JW (2013) Macrophage biology in development, homeostasis and disease. *Nature* 496(7446):445–455. <https://doi.org/10.1038/NATURE12034>
- Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, Strauss-Ayali D, Viukov S, Guilliams M, Misharin A, Hume DA, Perlman H, Malissen B, Zelzer E, Jung S (2013) Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity* 38(1):79–91. <https://doi.org/10.1016/J.IMMUNI.2012.12.001>
- Yu D, Qi S, Guan X, Yu W, Yu X, Cai M, Li Q, Wang W, Zhang W, Qin J-J (2022) Inhibition of STAT3 Signaling Pathway by Terphenyllin Suppresses Growth and Metastasis of Gastric Cancer. *Front Pharmacol* 13:870367. <https://doi.org/10.3389/fphar.2022.870367>
- Zhang L, Jiang X, Pfau D, Ling Y, Nathan CF (2021) Type I interferon signaling mediates Mycobacterium tuberculosis-induced macrophage death. *J Exp Med* 218(2). <https://doi.org/10.1084/JEM.20200887>
- Zhou C, Ma J, Su M, Shao D, Zhao J, Zhao T, Song Z, Meng Y, Jiao P (2018) Down-regulation of STAT3 induces the apoptosis and G1 cell cycle arrest in esophageal carcinoma ECA109 cells. *Cancer Cell Int* 18(1):53. <https://doi.org/10.1186/s12935-018-0549-4>

Figure Legends

Fig. 1. Macrophage functions and processes depend on the phase of the cell cycle.

The phases of the cell cycle are: G1, S, G2, M. The cell cycle is also affected by the circadian clock that regulates the expression of cyclins and CDKs. Under the effect of growth factors, nutrients, cytokines, and microbes, G1 can reversibly transit to the resting phase G0. The macrophages in G0 are more resistant, and in G1, more permissive to HIV-1 infection. G1 and probably also G2 macrophages can enter senescence, a durable cell cycle arrest accompanied by the production of inflammatory factors.

Fig. 2. Circadian rhythm regulation of macrophage functions.

Macrophage/monocyte migratory behavior, phagocytosis, metabolism, pro- and anti-inflammatory cytokine production, and sepsis mortality (in the mouse model) oscillate within 24 hours.



