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Macrophages and stem/progenitor cells interplay in adipose tissue and skeletal muscle: a review

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Abstract: Like all immune cells, macrophages do not act autonomously but in unison with other immune cells, surrounding tissues, and the niche they occupy. Constant exchange of information between cellular and noncellular participants within a tissue allows for preserving homeostasis and defining responses in a pathologic environment. Although molecular mechanisms and pathways involved in reciprocal signaling between macrophages and other immune cells have been known for decades, much less is known about interactions between macrophages and stem/progenitor cells. Based on the time when stem cells form, there are two stem cell types: embryonic stem cells existing only in an early embryo, which are pluripotent and can differentiate into any cell type present in an adult, and somatic (adult) stem cells formed in fetus and persisting for whole adult life. Tissues and organs have their own (tissue-specific and organ-specific) adult stem cells, which serve as a reserve for tissue homeostasis and regeneration after injury. It is still uncertain whether organ- and tissue-specific stem cells are actual stem cells or just progenitor cells. The important question is how stem/progenitor cells can sculpt macrophage phenotype and functions. Even less is known if or how macrophages can shape stem/progenitor cell functions, their divisions, and fate. We describe here examples from recent studies of how stem/progenitor cells can affect macrophages and how macrophages can influence stem/progenitor cell properties, functions, and destiny.

Keywords: Macrophage; stem cell; asymmetric division; immortal DNA

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Introduction

Cell-to-cell communications and interactions may occur through cell-cell contact, secretion and receiving soluble factors, extracellular vesicles (exosomes/microvesicles), and organelle transfer (1-3). Intercellular signaling is categorized into paracrine, autocrine, endocrine, and direct contact signaling based on the distance traveled by a signal to reach its target. In paracrine signaling, cells

in close vicinity release the signaling molecule (ligand), which binds the appropriate receptor on the surface of the acceptor cell. Autocrine signaling occurs when the signal released from the cell binds to the receptor of the very same cell. Endocrine signaling allows the transmission of signaling molecules (hormones) over long distances using body fluids and the circulatory system. In direct contact signaling, small molecules and ions diffuse through cell

junctions connecting neighboring cells. Another mechanism of intercellular communication occurs via exosomes and/or tunneling nanotubes (TNTs), long cellular processes which temporarily connect partner cells and allow an exchange of organelles (2,4-8). Although potentially all these intercellular communication mechanisms can be used for interaction between macrophages and stem cells, usually, under given circumstances and depending on a particular need and microenvironment, some are preferred over others. In this review we describe the examples of macrophage-stem cell crosstalk in health and disease and indicate how the intercellular communication routes and components, can be used therapeutically.

Types of stem and progenitor cells

Stem cells have two basic properties: self-renewal and the ability to differentiate into different cell types. Stem cells can divide asymmetrically or symmetrically (9,10). To achieve self-renewal, each asymmetric division of stem cell creates two daughter cells of different fates; one remains an undifferentiated stem cell, and another differentiates into a specialized cell. The symmetric division produces two identical stem cells, or two cells which enter a differentiation pathway. In contrast to progenitor cells, which also self-renew but only for a short time, stem cells self-renew throughout a lifetime of an organism. Depending on the applied criterium stem cells are divided into several categories. Based on the ability to develop into different cell types, stem cells are categorized into totipotent (can form all embryonic and adult cell lineages) (11), pluripotent (can differentiate into all cell types in an adult) (12), multipotent (give rise to multiple cell types within a given cell lineage) (13), and unipotent, (can self-renew but give rise to only one cell type) (14,15). Based on the time when stem cells form, there are two stem cell types: embryonic stem cells existing only in an early embryo, which are pluripotent and can differentiate into any cell type present in an adult, and somatic (adult) stem cells formed in fetus and persisting for whole adult life (16-19). Tissues and organs have their own (tissue-specific and organ-specific) cache of adult stem cells, which serve as a reserve for tissue homeostasis and regeneration after injury (20). Depending on location, adult stem cells are divided into mesenchymal, epithelial, skin, neural, and blood (hematopoietic) stem cells, plus resident stem cells characteristic of a given organ. For example, resident liver stem cells are in fetal and neonatal ductal plates, and intrahepatic biliary tree of an adult (21). Resident pancreatic

stem cells are in pancreatic ducts (22), and resident neural stem cells are in the hippocampus, basal ganglia of cerebral hemispheres, neocortex, and spinal cord (23). Resident stem cells of skeletal muscle are the subpopulation of the satellite cells located between the plasma membrane (sarcolemma, myolemma) and basement membrane of muscle fibers. It is still disputed whether organ- and tissue-specific stem cells are actual stem cells or just progenitor cells.

A somewhat distinct category is mesenchymal stem cells (MSC, stromal cells) situated within connective tissue surrounding different organs (24). Interestingly, the properties of MSCs differ depending on their location within body. In addition to these naturally occurring stem or progenitor cells, there are also artificially created (induced) pluripotent stem cells (iPSCs) (25). Those are various types of somatic cells reprogrammed *in vitro* into an embryonic-like state, which can differentiate into neurons, skin, blood, and liver cells, and precursors of egg, sperm, and bone (26-28).

Types of macrophages

Macrophages are immune cells of an innate branch of the immune system. Key activities of macrophages are phagocytosis of pathogens, dead cells, and debris, and signaling and stimulation of other immune cells. The main criteria for categorizing macrophages are their functional program and location within the body and tissues.

Although the exact functions of macrophages will differ depending on location and task at hand, based on their functional program, macrophages are divided into pro-inflammatory [M1, classically activated (AM)], mainly involved in anti-pathogen and anti-tumor responses, and clearing debris, and the anti-inflammatory [M2a-d, alternatively activated (AAM)] macrophages, responsible for tissue repair and regeneration, angiogenesis, and parasite containment (29,30,31). M1 are induced by T helper cells type 1 (TH1) cytokines, such as interferon gamma (IFN γ), interleukin (IL)-2, IL-10, and tumor necrosis factor (TNF)- α/β , and produce proinflammatory cytokines, reactive oxygen species (ROS), and inducible nitric oxide synthase (iNOS). M2a are induced by TH2 cytokines such as IL-4 and secrete a chitinase-like protein (YM1), acidic mammalian chitinase (AMCase), and arginase 1 (Arg1). M2b [regulatory macrophages (Mregs)] are induced by a combination of immune complexes (antibodies bound to different antigens) and Toll-like receptor (TLR) ligands. Mregs secrete large amounts of IL-10 and small amounts of IL-12, inhibit proliferation of activated T cells, and,

thus, have immunosuppressive role in inflammation and transplantation, and promote cancer progression (32,33). M2c (inactivated macrophages) are induced by anti-inflammatory factors, such as glucocorticoids, IL-10, and TGF- β . They produce IL-10, TGF- β , chemokine (C-C motif) ligand 16 (CCL16), and chemokine (C-C motif) ligand 18 (CCL18), and phagocytose apoptotic cells. M2d are pro-angiogenic; they are induced by IL-6 and A2 adenosine receptor agonist (A2R), and produce vascular endothelial growth factor (VEGF), IL-10, and TGF- β (34,35). An additional category recently identified is memory macrophages, which can remember antigens they had contact with and mount faster and enhanced response during subsequent encounter. Until recently, such memory ability was believed to be restricted to adaptive immune cells (36,37). Based on their location, macrophages are differently named. For example, bone macrophages are called osteal macrophages (38); alveolar macrophages are in the lungs, microglial cells in the brain, Langerhans cells (LC) in the skin, Kupffer cells in the liver, histiocytes in connective tissue, etc. (39). A separate category is tumor-associated macrophages (TAMs), which populate many types of tumors and, depending on the cancer type and tumor environment, fight or promote cancer development and metastasis (40-43). Another distinct category, described as a mononuclear phagocytic system (MPS), includes all types of macrophages and their bone marrow (BM) progenitors (44).

Origin of macrophages

During mammalian embryogenesis, macrophages develop directly (without a monocytic progenitor) from the ectoderm of the yolk sac (45,46). Subsequently, the fetal liver acquires hematopoietic progenitors from the yolk sac and hematogenic endothelium of embryonic mesoderm (aorta-gonad-mesonephros region). From this point on, the fetal liver produces circulating macrophage precursors (monocytes) (47). Subsequently, hematopoiesis switches from fetal liver to thymus and BM, which become a main source of all blood cell lineages, including circulating monocytes (46). However, most types of tissue-resident macrophages in adults do not derive from circulating monocytes but originate from the yolk sac or fetal liver and colonize tissues/organs during embryonic and fetal development. For example, microglia derive mainly from yolk sac progenitors; Langerhans cells have chimeric origin from the yolk sac and fetal liver, while kidney and lung macrophages derive from the yolk sac and hematopoietic

precursors (48-50). These resident macrophages self-maintain locally throughout adult life without (or minimal) input from circulating monocytes. In contrast, during disease and inflammation, most macrophages infiltrating tissues/organs derive from circulating monocytes.

Macrophage interactions with stem/progenitor cells

Macrophages affect stem cells already during embryogenesis when they regulate hematopoietic stem cells (HSCs) and hematopoietic stem progenitor cells (HSPCs) homing and retention in BM or extramedullary hematopoietic sites (e.g., spleen). Loss- and gain-of-function experiments in zebrafish (a vertebrate hematopoietic model) showed that vascular cell adhesion molecule-1 (VCAM-1)⁺ macrophages (named the usher cells) located in the vicinity of HSPCs are necessary for their retention and homing to the vascular niche (46,51). VCAM-1, through interaction with $\alpha 4\beta 1$ integrins, is necessary for HSC rolling and adhesion to blood vessel endothelium (52). Another study showed that VCAM-1⁺ macrophages, which reside in the red pulp of the spleen, control HSCs retention in the spleen. Inhibition of VCAM-1 or depletion of splenic macrophages releases HSCs from the spleen to peripheral blood (46,53).

Among many examples of the interplay between macrophages and stem or progenitor cells in the adult organism, best described are those in adipose tissue and muscle.

Adipose tissue stem cells and macrophages

Adipose tissue (fat or fatty tissue) is composed of fat cells (adipocytes), stromal cells, endothelial cells, and infiltrating leukocytes and macrophages called adipose tissue macrophages (ATMs). Adipose tissue serves as energy storage, regulates metabolism through endocrine signaling, and cushions organs. There are three main types of adipocytes: white, beige, and brown, which differ in abundance, phenotype, and function (54). The most abundant are white adipocytes [white adipocyte tissue (WAT)], which contain a single, large lipid droplet and a reduced number of cellular organelles. White fat is located under the skin, around internal organs, and inside the bones (BM fat). White adipocytes store energy and act as endocrine and secretory organs. They secrete molecules regulating lipid metabolism, vascular homeostasis, and inflammation, such as leptin (food intake/energy use

balance), angiotensinogen (blood pressure and fluid balance), adiponectin (increases insulin secretion), acylation-stimulating protein (triglyceride synthesis and storage, fatty-acid esterification, increases glucose uptake), adiponectin (lipid metabolism, glucose levels, and insulin sensitivity), retinol-binding protein (transport of retinol), TNF- α (an inflammatory cytokine), IL-6 (anti-inflammatory cytokine), plasminogen activator inhibitor-1, fasting-induced adipose factor (lipid and glucose metabolism, angiogenesis), a fibrinogen-angiopoietin-related protein (lipid and glucose metabolism, insulin sensitivity), metallothionein (metal binding and stress response protein), and resistin (induce insulin resistance) (55,56). Beige adipocytes have multiple lipid droplets and many mitochondria. They are scattered among white adipocytes and generate heat under cold exposure. Brown adipocytes [brown adipocyte tissue (BAT)] exist only in mammals, and their main function is thermogenesis, i.e., the transfer of energy from food into heat. They have many lipid droplets and iron-containing mitochondria, which give them a characteristic dark color. In an adult human, brown fat is in the neck, chest, around kidneys, adrenal glands, and aorta.

Adipose stromal cells include adipose progenitor cells (APCs), fibro-inflammatory precursors, and cells supporting the vasculature. Because APCs are multipotent (can differentiate into many cell lineages including adipocytes, chondrocytes, and osteoblasts), they were renamed into adipose stem/stromal cells (ADSCs). ADSCs differ from MSCs, which are mainly committed to osteoblastic and chondrogenic fates. ADSCs secrete various cytokines and growth factors and have immunomodulatory functions (57,58). In mice there are two main types of self-renewing APCs in the WAT: CD24⁺ and CD24⁻, which give rise to several subpopulations of committed preadipocytes that differentiate into white or beige adipocytes (59).

ATMs originate from the yolk sack, self-proliferation *in situ* driven by monocyte chemoattractant protein 1 (MCP-1), and BM precursors (60). They regulate adipose tissue homeostasis, lipid and energy metabolism, mitochondrial function, and inflammatory processes in obesity. Recent single-cell mass cytometry and genetic lineage tracking studies of non-obese mice identified ten functionally different subsets of resident ATMs within the WAT (61). Eight subsets consisted of mannose receptor CD206⁺ macrophages, which differed in the expression of TIM4 (T-cell immunoglobulin and mucin domain containing protein 4), scavenger receptor CD163, and major histocompatibility complex major histocompatibility

complex II (MHC II), and two subsets of CD206⁻ macrophages. These studies also showed that the TIM4⁺CD163⁺ subset has an embryonic origin, while TIM4⁺CD163⁻, TIM4⁻CD163⁺ and CD206⁻ subsets derive from the BM precursors. All these subsets of macrophages are involved in phagocytosis, endocytosis, and antigen processing. High-fat diet induces infiltration of CD206⁻ macrophages and downregulates MHC II in TIM4⁺ macrophages (61). In lean humans and mice, macrophages constitute around 5% of adipose tissue but dramatically increase, up to 50%, in obese individuals. In addition to the expansion of ATM number, there is also a shift in macrophage phenotype from M2 to M1 macrophages, and shift from the CD206, IL-10, Mrc2, Ym1/Chi3L3, and Mgl1/2 expression to the IL-6, Nos2, and CD11c expression. This phenotypic switch of ATMs promotes the pro-inflammatory environment in obese adipose tissue, which in turn, affects insulin sensitivity (62). Also, the location of macrophages changes; in lean individuals, macrophages are dispersed among adipocytes, while in obesity, they are mainly located within crown-like structures (CLS) (62,63). CLS are formed by macrophages surrounding dead adipocytes and engulfing cell debris and lipids (*Figure 1*). Studies showed that in obesity, saturated fatty acids derived from adipocytes activate TLR4 signaling pathway and macrophage-inducible Ca²⁺-dependent lectin receptor (Mincle) of cell death response, inducing inflammatory responses (63). Although in sustained obesity, macrophages in adipose tissue are the main source of inflammatory factors such as MCP-1 that promotes chronic inflammation, the question was which cells are the source of initial inflammation occurring during the first few days of high-fat diet and long before massive infiltration of macrophages. Studies addressing this question showed that adipocyte progenitor cells (AdPCs) are the initial source of MCP-1 that mediates chronic inflammation. They showed that one week of a high-fat diet increases proliferation, via transcription factor inhibitor of differentiation 3 (Id3) of AdPCs and MCP-1 production. This, in turn, recruits additional macrophages to adipose tissue (*Figure 1*) (64).

Little is known how macrophages regulate preadipocyte maintenance, survival, proliferation, and the exit from the cell cycle that is a prerequisite for differentiation into adipocyte. M2 macrophages activated by IL-4 promote preadipocyte survival through activation of the phosphoinositide 3-kinase (PI3K)-Akt and mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase 1/2 (ERK1/2) pathways (*Figure 2*)

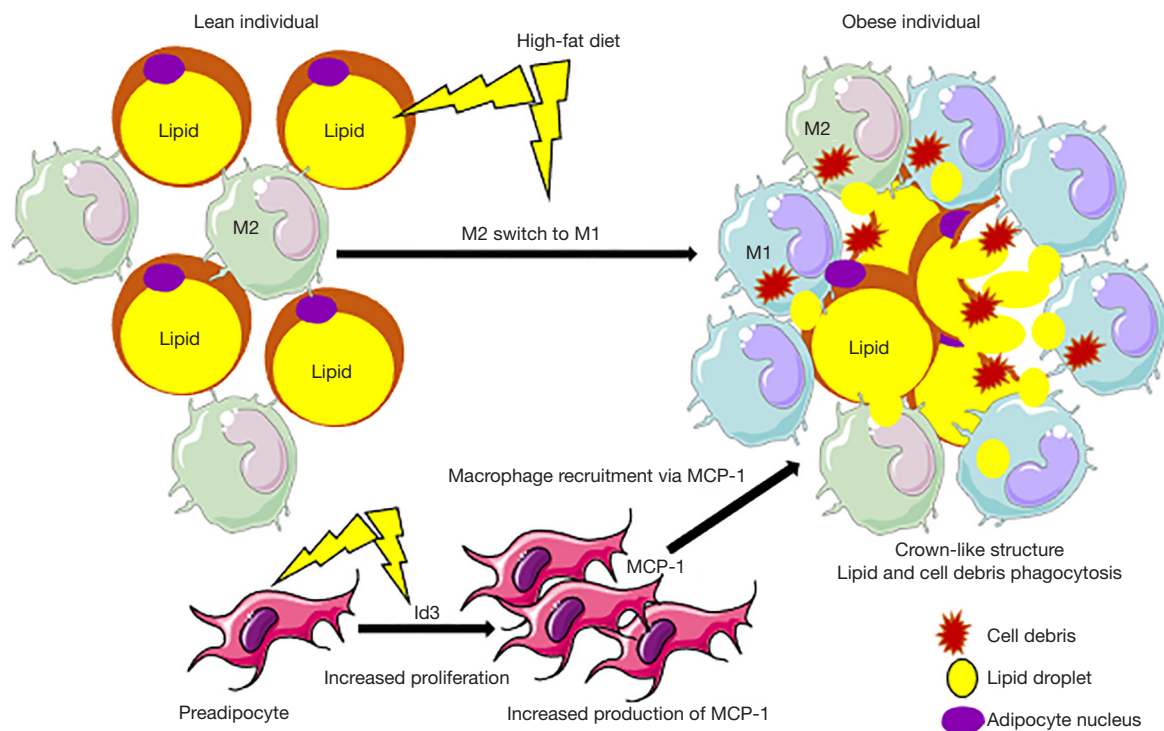


Figure 1 Interactions between macrophages and preadipocytes/adipocytes in the adipose tissue. In the lean individual, the M2 (anti-inflammatory) macrophages are dispersed between the adipocytes. They keep adipose tissue homeostasis. The influx of lipids in a high-fat diet induces a switch of macrophages phenotype from M2 to the pro-inflammatory M1. In high-fat condition, macrophages form the crown-like structure, which surrounds adipocytes. Macrophages phagocytose dead cells and debris. A high-fat diet also induces the proliferation of pre-adipocytes through the activation of the Id3 factor and activates the synthesis of MCP-1. MCP-1 mediates chronic inflammation and recruits additional monocytes/macrophages to the adipose tissue. Id3, inhibitor of differentiation 3; MCP-1, monocyte chemoattractant protein-1.

(59,65,66). Human and mouse M1 macrophages inhibit the expression of cell cycle proteins [cyclin A, cyclin-dependent kinase 2 (CDK2)] in preadipocytes, which, in turn, inhibits their clonal expansion and differentiation (67,68) (Figure 2). Additionally, $\text{TNF-}\alpha$, IL-6, IL-1 β , and nitric oxide (NO) produced by M1 macrophages push preadipocytes toward fibrotic phenotype (Figure 2) (59,69,70).

Recent studies showed that *in vitro*, differentiation of adipose tissue-derived mesenchymal stem/stromal cells into adipocytes was inhibited by macrophage-derived supernatants, especially M1-derived supernatant. The inhibitory effect of M1 macrophages depended on $\text{TNF-}\alpha$ and IL-1 β , and antibodies blocking these cytokines reduced inhibition (71).

Skeletal muscle stem cells and macrophages

Skeletal muscles consist of long contractile multinuclear

muscle cells (myofibers). Between the cell membrane (sarcolemma, myolemma) and extracellular matrix (basement membrane, basal lamina) of muscle fibers, there is a population of mononuclear myogenic cells called satellite cells. During embryogenesis, the fusion of mesoderm-derived progenitors (myoblasts) creates myofibers. In the adult, fusion is only sporadic to replace fibers dying from use, injury, or hypertrophic muscle growth (72-74). Under homeostatic conditions, satellite cells are quiescent, but after injury, they proliferate and differentiate into new muscle and satellite cells. Clonal analysis showed that satellite cells differ in function. Some proliferate extensively and give rise to differentiated and self-renewed progeny, while others have limited divisions before differentiation (75). Within a population of satellite cells, there is a small subpopulation of satellite stem cells. When activated by trauma or injury, these cells divide both symmetrically and

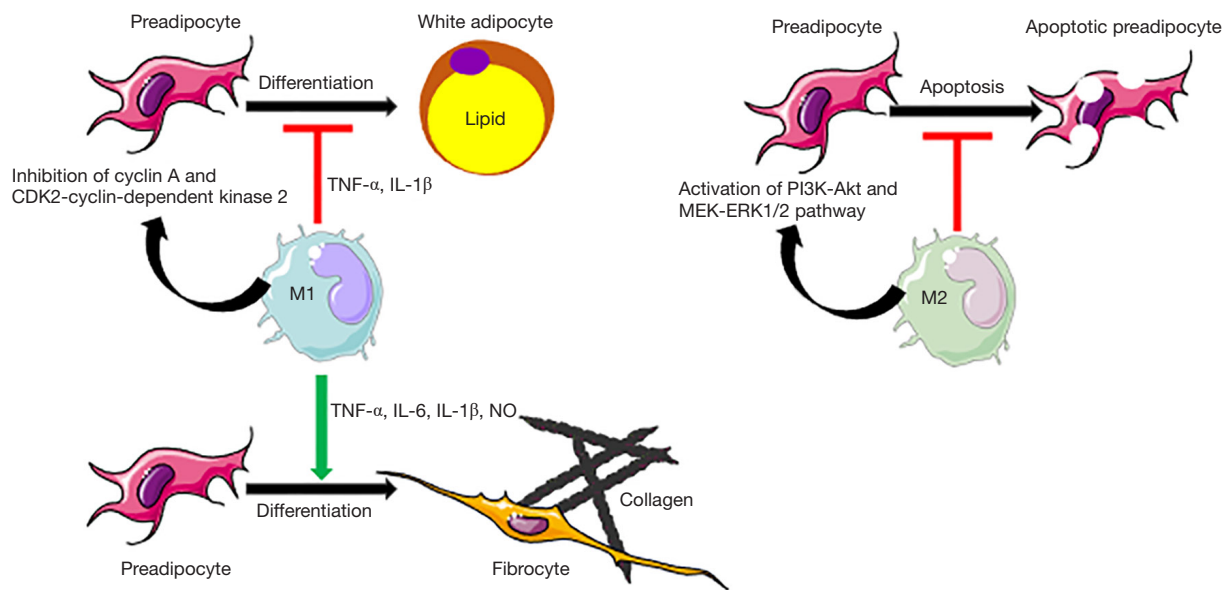


Figure 2 Effect of macrophages on preadipocyte fate. M1 macrophages inhibit the expression of the cell cycle proteins (cyclin A, CDK2) in preadipocytes, which, in turn, inhibits their clonal expansion and differentiation. TNF- α and IL-1 β produced by M1 macrophages inhibit preadipocyte differentiation, and TNF- α , IL-6, IL-1 β , and NO push preadipocyte differentiation toward the fibrotic phenotype. The M2 macrophages inhibit preadipocyte apoptosis and promote their survival by activating the PI3K-Akt and MEK-ERK1/2 pathways. CDK2, cyclin-dependent kinase 2; ERK1/2, extracellular signal-regulated kinase 1/2; IL, interleukin; MEK, mitogen-activated protein kinase kinase; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; TNF, tumor necrosis factor.

asymmetrically. Symmetrical divisions expand their number, while asymmetric divisions produce satellite stem cells and myogenic progenitors. Myogenic progenitors proliferate and differentiate into new muscle fibers by fusing with themselves or with the existing fibers (76-78). One must be aware that the cells that repair skeletal muscle are not the satellite stem cells (which do not fuse) but the myogenically committed daughters of those stem cells. The satellite stem cell population must asymmetrically divide and differentiate into myogenically committed cells, expressing myogenin and myoD, which are no longer satellite stem cells but the myogenic progeny. These myogenically committed cells proliferate, differentiate, migrate, and only after they exit the cell cycle, they turn on a required machinery for fusion. The universal marker for satellite cells from various animal species (human, monkey, pig, mouse, chick, frog, salamander, and zebrafish) is the paired domain transcription factor paired box 7 (Pax7). While myogenic progenitors also express myogenic regulatory factor myogenic factor 5 (Myf5), the Myf5 negative satellite cells represent a stem cell population (78,79). Quiescent satellite cells express Pax7 and forehead box (FOXO) transcription

factor (79,80). Chromosome and DNA labeling studies showed that during asymmetric divisions of muscle stem cells, the original chromatids (DNA strands), which are templates for DNA replication during the mitotic S phase, are inherited by a stem-like daughter cell, while newly replicated chromatids (DNA) segregate to the myogenic progenitor (81,82). These observations support the hypothesis of “immortal DNA” (83-86), postulating that preferential retention of immortal (template) DNA prevents the accumulation of mutations (occurring during DNA replication) in stem cells (Figure 3). Another theory assumes that asymmetric segregation of chromatids relates to their different epigenetic state, which determines gene expression patterns and cell fate (87). Finding that asymmetric cell-fate determinant Numb (88) co-segregates with original DNA templates to daughter cell, expressing the self-renewal marker Pax7, also support the immortal DNA hypothesis (Figure 3) (80).

Resident and infiltrating macrophages in muscles are crucial for muscle homeostasis, regeneration, and repair. Resident macrophages of skeletal muscle originate from the yolk sac, fetal liver, and blood monocytes, which

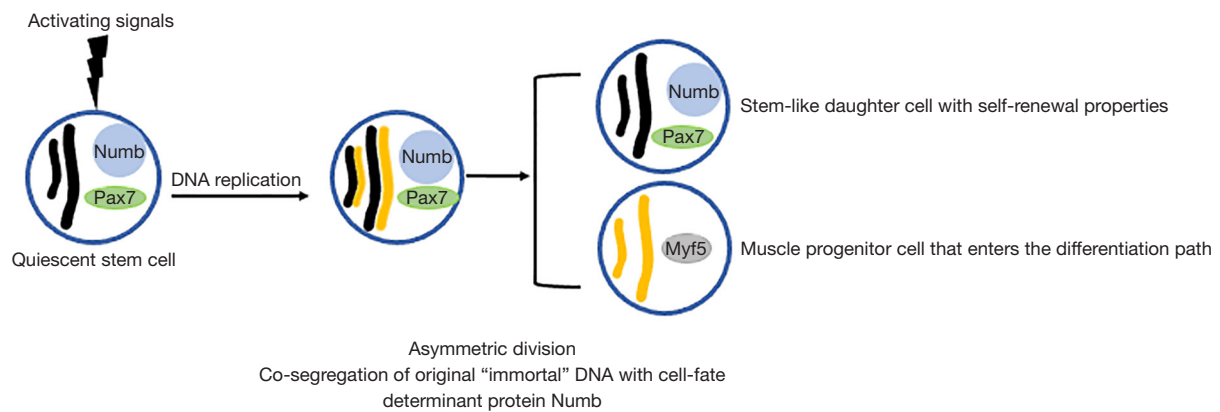


Figure 3 Asymmetric division of myogenic stem cell according to the immortal DNA hypothesis. Quiescent stem cell expresses stemness markers Numb and Pax7. Activated (by developmental or injury signals) stem cell enters division and replicates DNA during the mitotic S phase. The "old" chromosome (chromatid/DNA) is colored black, and the newly synthesized chromatid is yellow. The division of the stem cell and segregation of Numb, Pax7, and old and new chromatids (DNA) are asymmetrical. The daughter cell inheriting Numb, Pax7, and old (original) DNA becomes the stem cell with cell-renewal properties, and the sibling lacking stemness markers becomes the muscle progenitor cell, which expresses myogenic factor Myf5 and enters the muscle differentiation pathway. Inheritance of the old (original copy) of the DNA assures that the stem cells' DNA does not contain mutations possibly created during DNA replication. Myf5, myogenic factor 5; Pax7, paired box 7.

derive from adult BM (89,90). Resident macrophages are $CD45^+F4/80^+CD64^+$, and they express transcription factors Maf, Mef2c, and Tcf4, and a low level of glycosylphosphatidylinositol (GPI)-anchored protein Ly6C, and a high level of CD163, and CD206 (Figure 4) (91,92). Resident macrophages seem to be muscle-type specific; limb muscle macrophages have lower expression of stress-related proteins than those of respiratory muscle. Based on their function, there are two subtypes of muscle resident macrophages: $CCR2^+/MHC\ II^{high}/Lyve1^{low}$ macrophages are more active in antigen presentation, while $CCR2^-/MHC\ II^{low}/Lyve1^{high}$ macrophages are more active in phagocytosis (92). During injury, muscle is infiltrated with $Ly6C^{high}$ monocytes. The resulting $Ly6C^{high}$ macrophages release pro-inflammatory cytokines [TNF- α , IL-6, and prostaglandin E synthase 2 (PGE2)], which promote proliferation and inhibit myoblasts/satellite cells differentiation and fusion (Figure 4). In contrast, during healing and muscle regeneration, anti-inflammatory cytokines (IL-4 and IL-13) released by $Ly6C^{low}$ macrophages promote differentiation and fusion and inhibit myoblasts/satellite cell proliferation (Figure 4) (93,94). Macrophages affect myoblast precursors not

only through paracrine signaling but also through direct physical contact involving adhesion molecules VCAM-1, intercellular adhesion molecule 1 (ICAM-1), and platelet endothelial cell adhesion molecule 1 (PECAM-1). Such direct interaction inhibits apoptosis of myogenic precursors (Figure 4) (94-96). Transfer of mitochondria between macrophages and stem cells via TNTs or vesicles can improve metabolism, muscle progenitors' proliferation, and stem cell differentiation potential (Figure 4) (97-99).

Conclusions

Reciprocal interactions between stem/progenitor cells and macrophages and the effect of macrophage polarization status on stem/progenitor cell fate open new therapeutic possibilities for many diseases. For example, manipulation of macrophage polarization and/or accumulation may activate or inhibit stem cell proliferation or differentiation and benefit a treatment. Further studies of tissue-resident and infiltrating macrophages using modern techniques of single-cell transcriptome and lineage tracing are necessary to gain insight into the identity and origin of macrophages and stem cells within different tissues and organs.

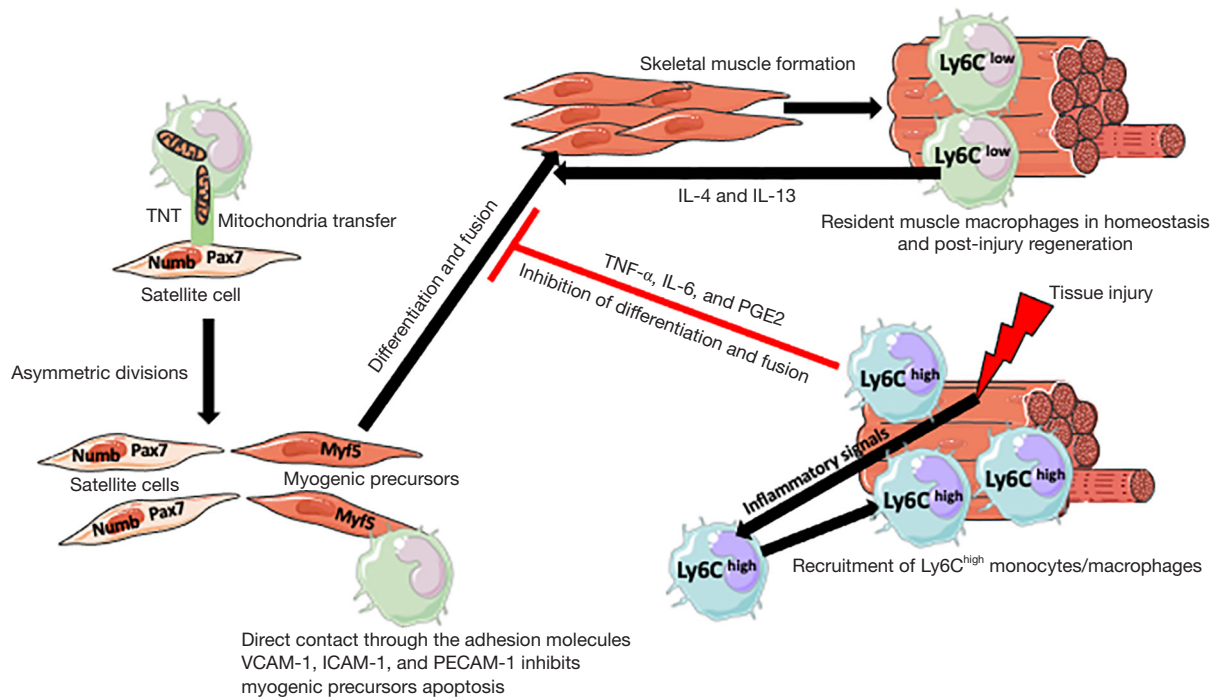


Figure 4 Interactions between macrophages and satellite/myogenic precursor cells in the skeletal muscle. Satellite cells express stemness markers Numb and Pax7. Macrophages improve satellite cells' metabolism and survival by delivering, via TNTs, metabolically fit mitochondria, and by inhibiting apoptosis through direct cell-cell contact mediated by the adhesion molecules VCAM-1, ICAM-1, and PECAM-1. The asymmetric divisions of stem cells produce new stem cells, which inherit stemness markers, and the myogenic precursors, which express myogenic factor Myf5 and differentiate, and fuse to form differentiated muscle cells. Differentiated skeletal muscle contains resident macrophages that express low levels of Ly6C and promote via secretion of IL-4 and IL-13, the differentiation and fusion of myogenic precursors. Ly6C^{low} resident macrophages retain muscle homeostasis and promote muscle regeneration. Muscle injury produces inflammatory signals, which recruit Ly6C^{high} monocytes/macrophages to the muscle. Ly6C^{high} macrophages secrete TNF- α , IL-6, and PGE2, which inhibit differentiation and fusion of myogenic precursors. ICAM-1, intercellular adhesion molecule 1; IL, interleukin; Ly6C, lymphocyte antigen 6C; Myf5, myogenic factor 5; Pax7, paired box 7; PECAM-1, platelet endothelial cell adhesion molecule 1; PGE2, prostaglandin E synthase 2; TNF, tumor necrosis factor; TNT, tunneling nanotube; VCAM-1, vascular cell adhesion molecule-1.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://sci.amegroups.com/article/view/10.21037/sci-2023-009/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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