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ORIGINAL ARTICLE

Molecular Process of Stem Cells in Modern Biology

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ABSTRACT

Stem cells have a wide range of traits, including the ability to self-renewal and differential interactions between various cell types that vary with their location within tissue and their immediate surroundings. Inhibitors of both are influenced by the cell cycle, genes involved in chromosomal rearrangements, critical developmental proteins, and signaling pathways. Wnt, Notch, Hedgehog Pathways, BMI-1, OCT3/4, ARF, NANOG, p16Ink4a, and this includes HOXB4, SOX2, and their homologous paralog, govern self-renewal. Stem cells and their molecular pathways that regulate self-renewal and differentiation hold great promise for theoretical and practical studies.

Keyword: gene regulation of stem cell self-renewal and differentiation genes for BMI-1, NANOG, OCT3, OCT4, p16Ink4a, SOX2, microenvironment, ARF protein proteins 1 (hedgehog), proteins 2 (Wnt.), and receptors 3 (notch).

INTRODUCTION

Danchakoff's (1916) described the precursor cells in the bone marrow, which gave birth to the field of stem cell biology; Maximow's confirmation of this result established its credibility (1). Stem cells are defined as cells with the potential to self-replicate indefinitely by cell division (self-renewal) and differentiate into other cell types specialized, not only morphologically but also functionally; this is how a small population of stem cells can increase in just a few months to give rise to millions of copies with the same features as its original (2).

Trans-differentiation, also known as plasticity, is a unique property of these cells, making them a beautiful resource for scientific and clinical study in recent years. "Plasticity" is a phrase that combines relates to the fact that these cells can form cell groups outside of their tissue of origin; this is the case with Hematopoietic Stem Cells (HSC) and mesenchyme cells, both of which can develop into diverse cell lineages in the lab and living organisms (3).

Mesenchymal cells demonstrated the ability to trans-differentiate into osteoblasts and adipocytes when subjected to the right stimuli, while HSCs could give rise to the liver, nerve, and muscle cells. There are three or four distinct kinds of stem cells (4). Two broad categories can be used to describe stem cells: First, they can be classified as either (1) multi-potent cells, (2) pluripotent cells or (3) potential to-type cells, (4) embryonic and adult mother cells depend on the tissue of origin (5).

Totipotent cells are those that have the potential to generate even more totipotent cells, as seen in the case of fertilization, in which a single cell, the zygote, serves as the paradigm for the generation of all the cells that will comprise the embryo and, later, the adult because totipotent cells can only be obtained in the earliest stages of embryo development, it's crucial to understand how and why these cells eventually become specialized and differentiate into the many different cell types found in an adult. Differentiation occurs as a result of changes in gene expression. Suppose the extracted cells are grown between 7 and 14 days post-fertilization when the embryo is in the blastocyst stage. In that case, it will never give rise to a complete seed but rather a specific cell line determined by currently expressed genes (6).

As the embryo grows and develops inside the mother's uterus, its cells become increasingly specialized, eventually differentiating into the many types of cells that make up an adult organism. HSCs are an excellent example of a committed, multi-potent mother with a higher degree of differentiation because they are branded by a specific fabric and can only give rise to cell types of the tissue to which they belong. These HSCs are the precursors to all blood cell types (red blood cells, white blood cells, and platelets). Stem cells get their name because they can originate in either embryonic or adult tissue. Cells are derived from embryos, adults, ESCs and ASCs (7).

The former is equivalent to totipotent precursors that can divide indefinitely in vitro; thus, a great deal of attention has been paid to the development of various types of even superficial tissues and organs using them, as well as the incorporation of foreign genes; thus, they are a fantastic vehicle for the palliative gene therapy and show great promise for the future of medicine. On the other hand, adult stem cells (ASCs) are multipotential progenitors that can renew themselves and give rise to specialized cells that can repair lesions tissue and restore senile cells; likewise, they exhibit great biological versatility based on their ability to drastically alter phenotype in response to changes in the microenvironment in which they develop. There are seven types of stem cells in the bone marrow (8).

Hematopoietic stem cells (HSCs), which are found in the bone marrow (1–3% of mononuclear cells), umbilical cord blood (0.2–1%), and peripheral blood (0.001–0.025%), stand out among the most studied because of their ability to of proliferation and differentiation in progenitors impaired hematopoietic (9).

It is important to note that the percentage of stem cells among umbilical cord mononuclear cells decrease as the pregnancy progresses, from 11% at week 17 to 1% at week 38; however, these cells have a distinct advantage over bone marrow HSCs because they graft 10 to 50 times better on hosts xenogenesis (10).

According to studies of HSC ontogeny, these cells first appear in the embryo between the third and fourth weeks of development and then travel through the fetal circulation, first to the yolk sac, then to the spleen and liver, and finally to the bone marrow, the organ par excellence of adult hematopoietic cells (11). The bone marrow contains two distinct populations of cells (9).

Because of their role in lifelong Hematopoietic System Maintenance, HSC-LPs from murine models are crucial to the success of hematopoietic transplantation. CMH: primarily long-term (CMH-LP) (long-term hematopoietic stem cells, LT-HSC). Short-term (CMH-CP) (short-term hematopoietic stem cells, ST HSC) are derived from compromised progenitors during

hematopoiesis; together, the HSCs have become the biological basis for bone marrow transplants for people with leukemia or bone marrow aplasia; I know too used therapeutically in patients with non-hematological diseases like myocardial infarctions and ischemia (12).

Besides embryonic stem cells, mesenchyme stem cells, adult multipotential progenitor cells (AMPC) (multi-potent adult progenitor cells, MAPCs), and SP stem cells have been identified in bone marrow (lateral population cells) (13).

Osteoblasts, chondroblasts, adipocytes, and myoblasts, all mesodermal cell types, can develop from the first type of cells, also called stromal cells. An excellent example of a committed, multi-potent mother with a high degree of differentiation is a Hematopoietic Stem Cell (HSC), which can only give rise to cell types of the tissue to which it belongs and is, therefore, the source of all three types of blood cells (red blood cells, white blood cells, and platelets (14). The term “stem ce” refers to the fact that these cells can originate either in embryonic or adult tissue (15).

The former is equivalent to totipotent precursors that can divide indefinitely in vitro; hence, a great deal of attention has been paid to their ability to generate complex tissues and organs and to incorporate foreign genes, making them a promising platform for future medical applications such as palliative gene therapy. On the other hand, adult stem cells (ASCs) are multipotential progenitors that can renew themselves and give rise to specialized cells that can repair lesions tissue and restore senile cells; likewise, they display great biological versatility based on their ability to radically alter phenotype in response to changes in the microenvironment in which they develop (8).

Different Types of Stem Cells in Bone Marrow: Hematopoietic stem cells (HSCs) are found in a variety of adult tissues, including the bone marrow (1–3% of mononuclear cells), umbilical cord blood (0.2–1%), and peripheral blood (0.001–0.025%). HSCs stand out because of their unique ability to proliferate and differentiate into functional hematopoietic progenitors with defects (8).

In addition, umbilical cord HSCs have a competitive advantage over bone marrow hematopoietic stem cells because they graft 10–50 times better on host xenogenic. Still, their percentage among mononuclear cells decreases with gestational age, from 11% at 17 weeks to 1% at 38 weeks (16).

Ontogenetic studies of HSCs show that they first appear in the embryo between the third and fourth weeks of development, traveling through the fetal circulation to the yolk sac, the spleen, the liver, and finally, the bone marrow, the organ par excellence of adult hematopoietic cells (17).

In murine models, HSC-LPs are crucial to the success of hematopoietic transplantation because they are the primary long-term hematopoietic stem cells (CMH-LP) (long-term hematopoietic stem cells, LT-HSC) that contribute to the maintenance of the hematopoietic system throughout life. Together, HSCs have become the biological basis for bone marrow transplants for people with leukemia or bone marrow aplasia; and are also used therapeutically in patients with non-hematological diseases such as myocardial infarction and ischemia (18).

Mesenchymal stem cells, adult multipotential progenitor cells (AMPC; multi-potent adult progenitor cells, MAPCs), and SP stem cells are also found in bone marrow (lateral population cells) (19). The first type, stromal cells, can become other types of functional mesodermal tissue cells like osteoblasts, chondroblasts, adipocytes, and myoblasts; this ability is what gives stromal cells their name depends on a set of markers that allow for recognizing them, looking for the surface antigens SH2, SH3, CD29, CD44, CD71, and CD90. However, these cells do not express the conventional HSC surface antigens CD34 and CD45 (20).

Because of their high telomerase activity during the culture period, AMPCs can divide more than 120 times without showing signs of aging. They also activate Oct-4, Nanog, and Rex-1, transcription factors essential for maintaining the undifferentiated state and promoting cell proliferation like embryonic stem cells. While AMPc lacks the stem cell marker CD34, they do express high levels of other markers, including CD13, SSEA-1 (mouse/rat), and SSEA-4, as well as low levels of Flk-1, Sca-1, and Thy-1 (human) (21).

SP stem cells are identified in mouse bone marrow via a novel method based on the flow cytometric analysis of double wavelength using the dye Hoechst, which emits blue fluorescence at 450 nm and red color at 650 nm; via this double technique, recognized a small subset of cells (less than 0.1%) revealing red and blue fluorescence low. Sca-1, an antigen found in CMH, was later shown to be expressed by these cells. Still, they failed to stain with an antibody cocktail targeting markers of Mature HSCs, which have been shown to have potent long-term hematopoietic repopulation activity in mouse bone marrow. We know that these cells can differentiate in MHC in humans and rodents; this is an underexplored but potentially fruitful field for many therapeutic applications (22).

Composition of the Microenvironment in the Spinal Cord: The microenvironment determines stem cell fate, which includes chemicals (such as hormones) and different types of cells (endothelium, adipocytes, T lymphocytes, macrophages, and fibroblasts) that provide the cells with physical support and the point of adhesion they need to survive (23).

Control was thought to arise from this central environment as the most critical factor for exchanging stem cells for the most differentiated cells in the case of HSCs, where this interaction includes growth factors and extracellular matrix (24).

Reproducing the microenvironment allowed for the cultivation of in vitro stem cells; using a cloak to suppress mitotic activity in fibroblasts made it possible to keep undifferentiated cell lines for study; however, spontaneous differentiation of these lineages, a situation that calls for an understanding of the biochemical and genetic mechanisms that regulate self-renewal and differentiation in that specific compartment (25).

Thus, the mysteries of stem cells can be broken down into two categories: those of the molecular events that define them and those of the signals that regulate their differentiation and reprogramming (26).

Regeneration and Individuality: Mother cells can either self-renew indefinitely or differentiate into a new type of cell based on their location and the surrounding tissue. Studies have attempted to explain why these cells behave a certain way, but many mysteries remain unsolved. The mechanisms of self-renewal, differentiation, and cell proliferation, as well as the underlying signaling pathways, have all been the subject of recent advances in our understanding of the basic biology of these processes (27).

In general terms, the different niches can modify their regulatory properties in response to the particular needs of the fabric; however, regardless of the place in question, there are common reporting mechanisms which is essential to know and which are best characterized in the hematopoietic system, but it wasn’t a simple study of molecular mechanisms that control hematopoiesis because HSCs cannot be maintained in vitro for extended periods; Furthermore, there is difficult to control the self-renewal versus differentiation, particularly in the process of self-renewal cell cycle inhibitors, genes involved in chromosomal rearrangements, proteins (28).

To successfully maintain the undifferentiated state, integrating the different intrinsic signaling pathways with extrinsic signals emitted by the microenvironment is necessary to move cells. It is essential to understand the mechanisms that regulate the state of undifferentiating due to its importance in understanding stem cell biology and the development of cancer (29).

Path without Wings (Wnt): This pathway is a cascade of signals that guides proliferative and differentiation events in embryonic and adult development. Its proteins are hydrophobic due to palmylate bound to cysteine in position C77, which is vital for its operation. This large family of proteins has been studied mainly in mouse models.

Bone marrow expression consisted of Wnt 2B, Wnt 3A, and Wnt 10B. While Wnt factor 5A is known for its role in bone marrow function, it also plays an essential role in stromal cell maintenance and, in conjunction with Wnt factor 10B, in fetal liver cells. These cell transcription factors work with niche cell-produced elements to determine whether stem cells will self-renew or die (29).

Differentiation: Wnt proteins are ligands that bind to specific receptors on the cell membranes of the cells that produce them and the cells immediately surrounding them. Frizzled family (Fz) receptors and proteins linked to low-density lipoprotein receptors (low-density lipoprotein receptor protein, LRP) are two receptors that can interact with these ligands; when a ligand binds to LRP, it can form a complex tetrameric with Fz. It has been hypothesized that Frizzled-related proteins (FRP) can counteract Wnts by binding and preventing them from exerting their effect (30).

Wnt has been studied extensively in the hematopoietic field due to its essential role in cell production and medullary stroma. Still, many different intracellular signaling pathways have been proposed for it. The ability of lethally irradiated mice to repopulate their hematopoietic systems was studied, and it was found that Wnt factor 5A, in conjunction with murine stroma and HSC, promotes the expansion of undifferentiated hematopoietic progenitors and indirectly participates in the regulation of the microenvironment by influencing the production of osteoblasts, which in turn are essential regulators of the niche of these cells (31).

The pathway of -catenin has been the focus of most research into HSC self-renewal; this pathway culminates in -catenin's nuclear translocation and physical binding to activate the transcription factor TCF / LEF (T-cell specific transcription factor / Lymphoid Enhancer binding factor-1) and suppress cell differentiation, thereby aiding in the preservation of pluripotency (32).

In the nucleus, -catenin displaces corepressors of the TCF/LEF family of genes by functioning as a transcriptional co-activator. These cell proliferation genes have promoter regions that are bound to by proteins like Groucho (GRG), CBP (Cyclic AMP binding protein), BRG1 (gene related to Brahma-1), and p300. Similarly, low concentration -catenin binds to the transcriptional corepressors of the same TCF / LEF complex to repress genes when this pathway is not activated. All of these interconnected mechanisms work together to promote the growth of stem cells, which includes HSCs (33).

Casein kinase 1 (CK1) and kinase axin glycogen synthase-3B (GSK3B) sequentially phosphorylate -catenin at the aminoterminal; in particular, CK1 phosphorylates al amino acid Ser 45, giving way to GSK3B phosphorylate to other three amino acids (Thr 41, Ser 37, and Ser 33), and finasteride is then added. In contrast to the previous steps, in which ruffled cytoplasmic protein is transferred (DVL) to the cell membrane when binding Wnt, they unite with their recipient, nuclear translocation occurs when -catenin accumulates and is translocated to the nucleus (34).

This occurs because the dissociation of the GSK3B complex and axin prevents the phosphorylation of -catenin and its subsequent degradation. 30,31Embryonic development, morphogenesis and migration, cell proliferation, and differentiation rely heavily on this signaling cascade. Recent research has also linked it to the expansion of HSCs in both ES and NS cells, and it was previously thought to play a role in both of these processes. Cell culture techniques could produce desirable results using the protein Wnt3a promotes the growth of epidermal stem cells (35).

Activation of receptors and associated signaling pathways: Nuclear localization signals and OPA sequences (opacity-associated adhesion proteins) rich in glutamine that function as activators of transcription are found in DICN, which is released after the ligand-receptor complex has been formed (36).

In the case of the HES gene (Hairy/enhancer of split), which negatively regulates the specific gene expression of lineage, the released DICN molecule is activated CSL (short for Chisel) to mediate signal transduction in the nucleus and, more generally, binds to promoter sequences in DNA for regulation of some target genes.

Notch 4 plays a crucial role in breast development and carcinogenesis in vivo, and its overexpression in vitro suppresses epithelial cell differentiation in the normal mammary gland (37).

Using the Notch gene, researchers have shown that this pathway is active in HSCs and that when hematopoietic cells differentiate, expression of the reporter gene is down-regulated. Only a tiny fraction of mature cells exhibit in vivo reporter activity, which points to this path's significance for maintaining the HSCs' undifferentiated state and, thus, their capacity to self-renew.

It is safe to say that Notch activation in any stem cell type results in the transcriptional suppression of lineage-specific genes, suppressing differentiation and promoting self-renewal. Transmembrane cleavage by -secretase or Presenilin, which in turn triggers nuclear translocation of Notch's intracellular domain, and separation by the ADAM family of proteases (A disintegrin and metalloproteinase) (DICN) (38).

Nuclear localization signals and OPA sequences (opacity-associated adhesion proteins) rich in glutamine that function as activators of transcription are found in DICN, which is released after the ligand-receptor complex has been formed. The HES gene (Hairy/enhancer of split) negatively regulates the expression of a specific lineage-specific gene after DICN is released, activating a molecule called CSL (short for Chisel) that binds to promoter sequences in DNA to regulate gene expression (39).

Overexpression of Notch 4 in the culture prevents mammary epithelial cells from differentiating into their normal phenotype. In vivo, this same protein is crucial for breast development and carcinogenesis (40). Using Notch gene reporters, researchers have shown that this pathway is active in HSCs and that as hematopoietic cells differentiate, expression of the reporter gene is downregulated. Only a tiny fraction of mature cells show in vivo reporter activity. This evidence suggests that this path is critical for maintaining HSCs in an undifferentiated state and provides further support for the role of Notch proteins in HSC self-renewal.

In conclusion, Notch activation in any stem cell type causes transcriptional suppression of lineage-specific genes, which blocks differentiation and encourages self-renewal of the neural or hematopoietic stem cells; moreover, increased cell growth and this pathway facilitates survival in living organisms.

The role of Hedgehog in the self-renewal of stem cells has also been suggested by studies looking at the effects of recombinant Shh on breast tissue formation and the consequences of cyclopamine, an inhibitor of Santo (41).

Similarly, mutations in some oncogenes involved in the waterfall, such as Smo, Shh, Gli 1, and Gli 2, have been linked to the development of cancers such as medulloblastoma, basal skin carcinomas, and breast cancer, suggesting that the signaling mediated by this pathway plays a role in carcinogenesis (42).

Third-Party Contributors to the Regeneration Process: BMI-1 is a transcription factor that controls the expression of p16Ink4a and ARF, two tumor suppressor genes identified as biomarkers of cellular aging; abnormal expression of both is associated with interference of self-renewal in murine HSC, as it prevents proliferation and leads to apoptosis (43).

However, stem cell type appears responsible for determining these two genes' role in cycle control. They generally regulate the retinoblastoma (Rb) and p53 proteins, which regulate differentiation, senescence, and survival. Recent research has shown that in mice lacking BMI-1.59.6, p16 Ink4a and ARF are upregulated in MHC and neural stem cells (CMN). This factor controls their expression via negative feedback (44).

Different Elements Involved in the Regeneration Process: ARF, BMI-1, and p16 Ink4a as biomarkers of cellular aging, p16Ink4a and ARF are tumor suppressor genes regulated by the BMI-1 factor; abnormal expression of both is associated with interference of self-renewal in murine HSC, as it stops proliferation and leads to apoptosis (45)

These two genes play a role in stem cell cycle regulation appear to be type-specific. They regulate the retinoblastoma (Rb) and p53 proteins, which regulate differentiation, senescence, and survival. Recent research indicates that in mice lacking BMI-1.59, MHC and CMN stem cell expression of p16 Ink4a and ARF is unregulated in similar proteins to HOXB4 (46).

Transcription factors encoded by Hox genes control embryonic development and blood cell production. A DNA-binding domain consisting of a sequence of 60 highly conserved amino acids is shared by 39 members of this large family of proteins. Overexpression of this factor in the bone marrow is related to the expansion of HSCs, in vivo and in vitro, demonstrating its role in the self-renewal of said cells; additionally, there is only one high expression in primitive hematopoietic cells, which decreases as specific differentiation occurs of lineage. Similarly, it is demonstrated that CD34+ cells express the transcription factor HoxC4 and that their overexpression induces the proliferation of multiline age progenitors; data presented to date indicate that the combination of HoxB4 and HoxC4 is associated with HSC expansion (47).

Trimeric nuclear transcription Y (NF-Y) is activated by HoxB4 working with USF1/2. Studies in HoxB4-deficient mice reveal normal hematopoietic development, suggesting that Hox4 gene paralogs can rescue the loss of HoxB4 function. Hox4 gene paralogs share the same protein structure as HoxB4 and include the NF-Y and USF1/2 binding sequences HxRE1 and HxRE2, respectively SOC3, SOC4, and NANOG (48).

Nanog is a homeobox-containing transcription factor whose activity is crucial for the in vitro and in vivo maintenance of HSCs and ESCs; additionally, there is a low regulation of this factor during differentiation; in the absence of which, in mice, results in a primitive differentiation of the endoderm (49).

In particular, embryonic stem cells (ESCs) rely on the factors Nanog, Oct3/4, and SOX2 to control their ability to self-renew and maintain their pluripotency. It's unclear how they control their expression; however, the Nanog gene is not the only one regulated by the Oct-Sox complex, and binding sites for these two factors have been identified in the promoter regions of the genes Fgf-4, Utf-1 (50).

Oct-3/4 plays an essential role in self-renewal and has high expression in most embryonic stem cell lines by binding to AGTCAAAT repetition sequences present in the promoter regions of some genes. This factor acts together with SOX 2, a member of the SOX family of HMG transcription factors box (51).

Loss of SOX2 also aids in the formation of extraembryonic endoderm, while up-regulation of Oct 3/4 is associated with mesoderm and endoderm formation and down-regulation with trophectoderm differentiation. Like other factors involved in self-renewal, Oct 3/4 contributes to tumorigenesis in adult germ cells; in mice, dysplastic lesions of the skin and intestine develop when this factor is expressed abnormally. These results provide a new perspective to the scientific community, and elucidating these regulatory mechanisms in the self-renewal process has become essential in comprehending carcinogenesis and therapeutic options for treating cancer (52).

Diversity: Like their self-renewing properties, stem cell differentiation has been studied extensively, mainly through hematopoietic assays. A group of factors controls the process of differentiation of transcription factors; these factors' signaling activates a set of predetermined lineage-specific director genes (53).

HSCs are an excellent example of this mechanism, and they fall into two distinct groups: (1) regulators of development that are not lineage-specific, such as GATA-1 (for the sequence guanine-adenine-thymine-adenine) and PU-1, and (2) regulators of development that directly influence the differentiation of all hematopoietic lineages fail if the lineage-specific stimulating factors and cytokines (which can differ for elytroid, myeloid, lymphoid, monocytes, and megakaryopoiesis differentiation) are absent (54).

Cell differentiation has been described as a non-adaptive phenomenon whose model involves changes in the expression of these cells' genes. Several theories have been proposed to explain this process. They've proven to be an invaluable resource for scientists.

The GATA 1 and PU-1 factors have been considered essential mediators in cell differentiation of hematopoietic mothers; similarly, it has been thought that the dynamic relationship between the genes OCT4, SOX2, and Nanog is of great relevance in the process of differentiation of embryonic stem cells (55).

Cell signaling pathways and the spinal cord microenvironment are essential in differentiating hematopoietic stem cells. Interleukins (IL), specifically IL-3, IL-6, and IL-11, have been the subject of extensive in vitro testing for their potential roles in this process. In conclusion, the unique properties of stem cells make them look very promising in the therapy of various diseases, and the knowledge gained from studying their biological behavior and the pathways involved in their self-renewal and differentiation paves the way for an optimistic panorama in both basic and applied research. While many in vitro findings have yet to be replicated in vivo, it is also worth noting that more in-depth experimental work is needed to understand the molecular mechanisms playfully (56).

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