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SHORT REVIEW ARTICLE

STEM CELLS NICHE- *A COMPLEX MOLECULAR MILIEU*

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ABSTRACT

Stem cells research have an interesting history that has been somewhat tainted with debate and controversy but has progressed dramatically with the countless research studies across the world and hold a great promise for regenerative medicine and cell-based therapies. The fate and function of stem cells are governed by a combination of intrinsic determinants and signals from the local microenvironment, or niche. The number of known interactions that regulate stem cell- niche has dramatically increased during the past few years. Further technological advancements and refined computational models will allow exploring the mechanisms for therapeutic purposes.

INTRODUCTION:

Stem cells have been defined as undifferentiated cells capable of proliferation, self-renewal, production of a large number of differentiated progeny and regeneration of tissues. Stem cells have been located in the early stages of development after egg fertilization, the umbilical cord, placenta and in several adult organs. Stem cells have varying abilities to differentiate into different cell types. The hallmark properties of stem cell self-renewal and differentiation are governed by a complex set of extrinsic cues in collaboration with intrinsic gene regulatory machinery- niche. A niche is considered to be a subset of tissue cells and extracellular substrates that can indefinitely house one or more stem cells and control their self-renewal and progeny production *in vivo*. The extensive research work in this field have delineated that different micro-environmental cues such as soluble signaling protein factors (e.g. growth factors, small molecules), immobilized substrates (e.g. extracellular matrix proteins, proteoglycans), cell-cell interactions (e.g. cell adhesion molecules, cadherins, Notch ligands), and mechanical forces (e.g. substrate rigidity, flow, stretch) communicate in a complex manner to influence various signaling pathways, and ultimately affect cell fate and function. Accordingly, the identification of extrinsic factors and their downstream, intracellular signaling pathway targets has led to much progress in understanding how to control the expansion and directed differentiation of stem cells.

Table 1: Various growth factors regulating the stem cell fate & functions:

External factors		Internal factors (Transcription Factors)	
IGF	Growth promoting activity	Oct4	POU-type Homeodomain containing TF
FGF	Self-renewal	Sox2	HMG box containing DNA binding domain
Wnt	ESC Proliferation	Nanog	Homeobox TF
BMP	Trophoblast or extraembryonic endodermal differentiation	UTF1	Coactivator of ATF2
Notch	Promotes differentiation	ZFP42	Zn finger DNA binding domain
TGF-β	Proliferation, cellular differentiation, and other functions	FBXO15	Contain F-box motif, Component of SCF-type E3 ubiquitin ligase complex
Noggin	Self-renewal		

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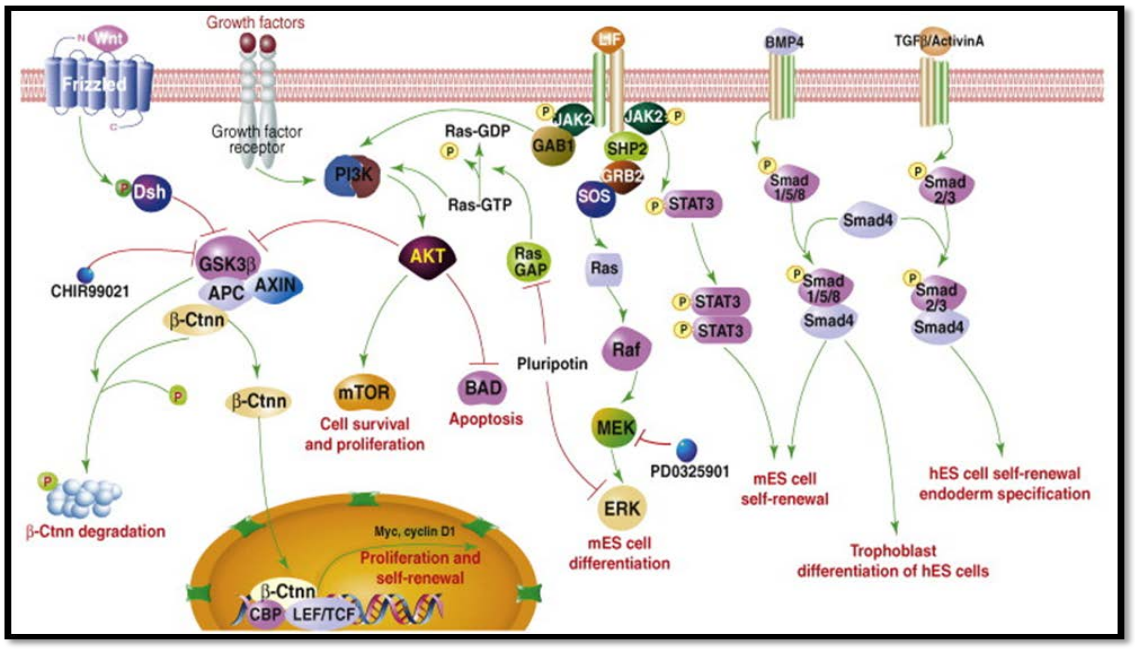

Figure 1: Source: Li and Ding, 2009

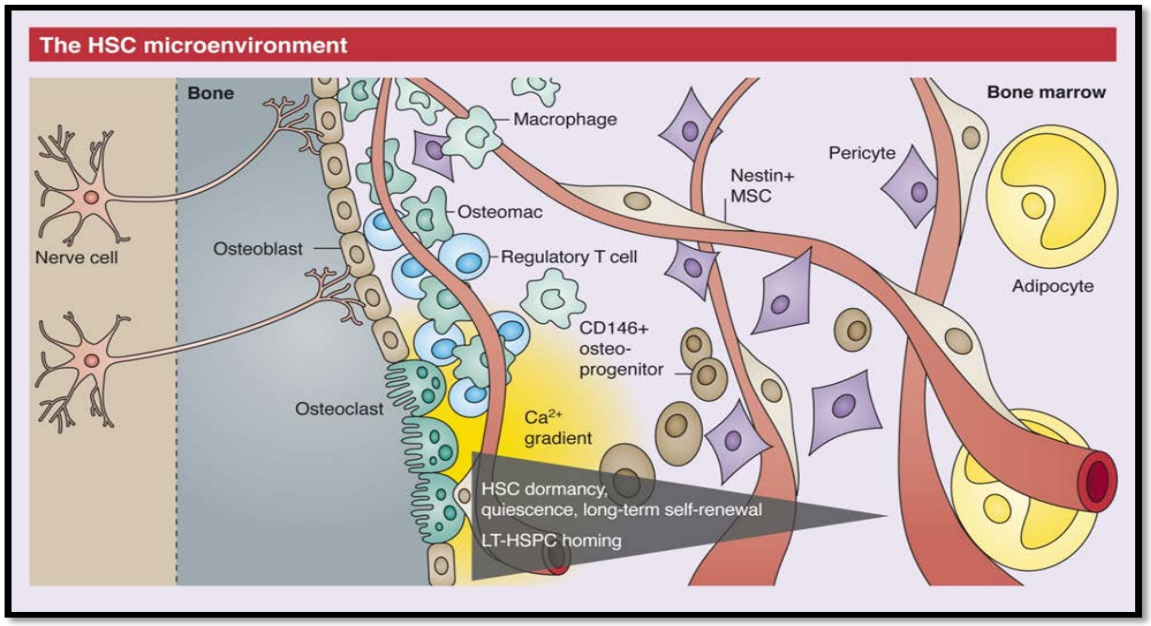

Figure 2: Source: Celso & Scadden, 2011

A glimpse of Hematopoietic Stem Cell niche:

The blood system serves as a paradigm for understanding tissue stem cells, their biology, and involvement in aging, disease, and oncogenesis. Because mature blood cells are predominantly short lived, stem cells are required throughout life to replenish multilineage progenitors and the precursors committed to individual hematopoietic lineages. Hematopoietic stem cells (HSCs) reside as rare cells in the bone marrow in adult mammals and sit atop a hierarchy of progenitors that become progressively restricted to several or single lineages (Orkin, 2000). These progenitors yield blood precursors devoted to unilineage differentiation and production of mature blood cells, including red blood cells, megakaryocytes, myeloid cells (monocyte/macrophage and neutrophil), and lymphocytes. As with all other stem cells, HSCs are capable of self renewal—the production of additional HSCs—and differentiation, specifically to all blood cell lineages. The hematopoietic microenvironment provides a complex molecular milieu that regulates the self-renewal and differentiation activities of stem cells.

Extracellular matrix (ECM) and growth factor signaling networks are known to interact in a complex manner. A reductionist approaches that test the cellular response to

individual ECM components and growth factors alone cannot be used to predict the response to more complex mixtures without knowledge of the underlying signaling network.

A way forward:

An emerging field of combinatorial chemistry in collaboration with chemical biology/ chemical genomics consisting of methodologies like chemical libraries with small molecules, high-throughput screenings and refined computational databases has came forward to address the challenge and enable the detailed elucidation of stem cell processes, and thus, greatly contribute to the development of stem cell based therapeutic approaches including transplantation and tissue engineering schemes, stem cell targeted pharmaceuticals and gene delivery strategies.

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