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The role of β-catenin in the hematopoietic stem cell niche

Ryan DA Thomas
McMaster University, rdathomas@hotmail.com

Neil D. Dattani
McMaster University, nddattani@gmail.com

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Abstract

Stem cells are undifferentiated cells which are maintained within a specific niche. A stem cell niche is a microenvironment of cells that maintain stem cell functionality, and one example is the hematopoietic stem cell (HSC) niche. This niche provides support for HSCs, which give rise to hematopoietic cells such as erythrocytes and leukocytes. β-catenin is one of several proteins involved in the functioning and maintenance of the HSC niche. This protein is an intrinsic factor of HSCs and a component of the Wnt signalling pathway, which is integral to differentiation and proliferation. Experiments investigating overactive β-catenin have shown expansion of the HSC niche, while other experiments blocking β-catenin activity have shown attenuated HSC niche capacity. The results suggest that β-catenin plays a crucial role in HSC proliferation and differentiation within the niche. In agreement with these results, improper regulation of β-catenin has been implicated in the development of leukemia.

The stem cell niche

Stem cells are unspecialized cells with two defining characteristics: the ability to renew almost indefinitely, and the potential to undergo differentiation to give rise to a variety of specialized cell types (Spradling et al., 2001). They exist in stem cell niches, which are defined as microenvironments of cells which support and allow stem cells to maintain tissue homeostasis (Moore & Lemischka, 2006). A niche allows stem cell numbers to be preserved by isolating them from various stimuli, such as differentiation and apoptotic factors, which would act to reduce stem cell numbers. Only under certain conditions will a niche direct stem cells to differentiate into specialized cell types. Additionally, the stem cell niche prevents cancerous growth by protecting against uncontrolled stem cell division. There are many different stem cell

niches serving various purposes throughout the body (Spradling et al., 2001; Moore & Lemischka, 2006).

The hematopoietic stem cell niche

One of many stem cell niches, the hematopoietic (blood-forming) stem cell niche is found in bones. Within the hematopoietic stem cell (HSC) niche HSCs are in close contact with bone and bone marrow, and cell to cell interaction is responsible for the inhibition of uncontrolled HSC differentiation (Moore & Lemischka, 2006). Studies have shown that osteoblasts and osteoclasts, the cells responsible for bone remodelling, are involved in the development and function of the HSC niche (Wilson & Trumpp, 2006), and osteoblasts are also known to produce a variety of hematopoietic growth factors.

HSCs exist proximal to the endosteal surface of trabecular bone (Moore & Lemischka, 2006; Yin & Li, 2006). They can differentiate into either lymphoid cell progenitors or myeloid cell progenitors (Figure 1). Lymphoid progenitors further specialize into T cells, B cells, natural killer cells, and dendritic cells. Myeloid progenitors further specialize into erythrocytes, platelets/megakaryocytes, granulocytes, and monocytes/macrophages. There are many intrinsic and extrinsic factors which control these processes (Nemeth & Bodine, 2007).

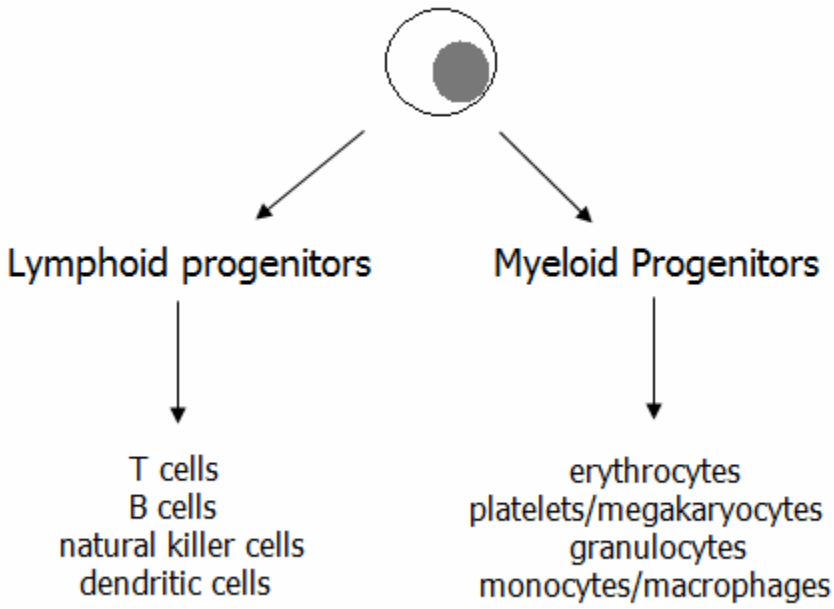

Figure 1. Differentiation pathways for hematopoietic stem cells (HSCs). Unspecialized HSCs first differentiate into either lymphoid progenitors or myeloid progenitors. Lymphoid progenitors further specialize into T cells, B cells, natural killer cells, and dendritic cells. Myeloid progenitors further specialize into erythrocytes, megakaryocytes/platelets, granulocytes, and monocytes/macrophages.

β-catenin and the Wnt signalling pathway in the hematopoietic stem cell niche

β-catenin (Beta-catenin) is a component of the wingless (Wnt) signalling pathway, an evolutionarily conserved signal transduction pathway which supports normal HSC niche function (Reya et al., 2003; Staal & Clevers 2005; Wilson & Trumpp, 2006; Malhotra & Kincade, 2009). β-catenin acts downstream of Wnt and mediates replication, differentiation, and apoptosis.

In the absence of Wnt signalling, β-catenin associates with a multi-protein destruction complex and is phosphorylated. This leads to its ubiquitination and consequent degradation by proteasomes (Staal & Clevers, 2005). However, when Wnt proteins secreted by osteoblast cells in the niche bind to receptors on the surface of HSCs, β-catenin degradation is inhibited. β-

catenin subsequently accumulates in the HSC and is translocated to the nucleus. In the nucleus, it associates with another multi-protein complex, and thereby regulates gene transcription (Moon et al., 2002; Staal & Clevers 2005; Moore & Lemischka, 2006). Increased or decreased amounts of β-catenin result in the loss of quiescence in HSCs, thus only a fine tuned activation of β-catenin allows for normal HSC function (Suda & Arai, 2008).

β-catenin is also required for the development of the mesoderm, one of three primary germ layers in developing embryos. The mesoderm gives rise to hematopoietic organs, vasculature, and long bones of the limbs. Experiments altering regular β-catenin activity will better elucidate its role in this process (Nemeth et al., 2009).

Role of constituently active β-catenin in the Wnt pathway

Reya et al. (2003) performed a study to determine how the activation of downstream elements of the Wnt pathway would affect HSC function. Wnt signalling was activated in HSCs, which were sorted by fluorescence-activated cell sorting (FACS). Retroviruses were used to introduce murine [constituently-active β-catenin]-IRES-GFP (β-catenin, green fluorescent protein, internal ribosome entry site) into HSCs (Reya et al., 2003). A control virus containing only IRES-GFP was also used. In non-control test cultures, it was observed that constituently active β-catenin expanded the pool of HSCs in terms of phenotype and function. Additionally, constituently active β-catenin allowed certain committed progenitor cells to reacquire undifferentiated properties (Reya et al., 2003; Moore & Lemischka, 2006).

It was also seen that β-catenin upregulated genes for HoxB4 and Notch1, two proteins which are candidates for therapeutic stem cell interventions (Entrez Gene: HOXB4; Entrez Gene: NOTCH1). In HSCs infected with the constituently active β-catenin, HoxB4 was upregulated 3.5-fold and Notch-1 was upregulated 2.5 fold compared to control HSCs (Reya et al., 2003).

Effects of β-catenin inactivation in the Wnt pathway

Nemeth et al. (2009) studied the effects of inactivating β-catenin in the hematopoietic stem cell niche. It was hypothesized that β-catenin is necessary to the hematopoietic stem cell niche to support normal haematopoiesis. Mice were bred to contain non-functional β-catenin, and their bone marrow was extracted for analysis. Mice without β-catenin inactivation were used as controls. Bone marrow extracts from the mice were cultured in vitro and analysed using flow cyclometry, histochemical staining, and histology (Nemeth et al., 2009). It was seen that a β-catenin deficiency resulted in a diminished ability to support early HSCs, lower osteoblast numbers, and a reduction in associated growth factors. These results suggest that β-catenin plays an important role in the niche for the generation of osteoblasts, as well as for the preservation and expansion of early hematopoietic cells in the hematopoietic stem cell niche (Nemeth et al., 2009). Fleming et al. (2008) reported similar findings.

Implications for Human Health

β-catenin and its role within the Wnt signalling pathway have been implicated in several serious diseases. For example, misexpression of β-catenin has been linked to several different types of cancers, including leukemia. Leukemia is a cancer originating in HSCs, resulting in altered production of specific hematopoietic cell types (Byrd et al., 2004). B cell chronic lymphocytic

leukemia (CLL) is the most prevalent form of leukemia. CLL is characterized by excessive proliferation of abnormal B cell lymphocytes, and it causes several adverse health effects including organ enlargement, rapid erythrocyte destruction, and immune system deficiency. Survival times range from months to decades after disease onset. (Byrd et al., 2004; Lu et al., 2004; Ysebaert et al., 2006). A better understanding of the role β-catenin plays in this and other diseases is needed to improve human health and survival.

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RDA Thomas

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To Maya - For always knowing, without ever being told, that I need someone like you in my life.