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Review

# BMP signaling and stem cell regulation

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**Abstract**

Stem cells play an essential role in cellular specialization and pattern formation during embryogenesis and in tissue regeneration in adults. This is mainly due to a stem cell's ability to replenish itself (self-renewal) and, at the same time, produce differentiated progeny. Realization of these special stem cell features has changed the prospective of the field. However, regulation of stem cell self-renewal and maintenance of its potentiality require a complicated regulatory network of both extracellular cues and intrinsic programs. Understanding how signaling regulates stem cell behavior will shed light on the molecular mechanisms underlying stem cell self-renewal. In this review, we focus on comparing the progress of recent research regarding the roles of the BMP signaling pathway in different stem cell systems, including embryonic stem cells, germline stem cells, hematopoietic stem cells, and intestinal stem cells. We hope this comparison, together with a brief look at other signaling pathways, will bring a more balanced view of BMP signaling in regulation of stem cell properties, and further point to a general principle that self-renewal of stem cells may require a combination of maintenance of proliferation potential, inhibition of apoptosis, and blocking of differentiation.


*Keywords:* BMP; Stem cell; Embryonic stem cell; Germline stem cell; Hematopoietic stem cell; Intestinal stem cell

## Introduction

Stem cells are the key subset of cells functioning as ancestor cells to produce a variety of types of functionally specialized mature cells in a given tissue, while at the same time undergoing self-renewal, a process of reproducing themselves without losing their developmental potentiality. This self-renewal process is controlled by intrinsic genetic pathways that are subject to regulation by extrinsic signals from the microenvironment (called niche) in which stem cells reside. Stem cells play essential roles ranging from embryonic development and organogenesis (embryonic/fetal stem cells) to tissue regeneration (adult stem cells) (Lin, 2003; Spradling et al., 2001; Watt and Hogan, 2000; Weissman, 2000). To maintain homeostasis, a precise balance between self-renewal and differentiation of stem cells is essential. Loss of this balance tends to lead to uncontrolled cell growth or pre-maturation and thus results in tumors, cancers, or tissue defects. Therefore, understanding the complex signal regulation of stem cell development is crucial for future therapeutic applications. In this review, we will focus on progress that has been made in research studying the *b*one *m*orphogenesis *p*rotein (BMP) signaling pathway in regulation of stem cell properties.

BMPs belong to the *t*ransformation *g*rowth *f*actor beta (TGFβ) superfamily. They are involved in regulation of cell proliferation, differentiation, and apoptosis and therefore play essential roles during embryonic development and pattern formation (Massague, 1998). To maintain homeostasis in adults, the BMP signal also participates in tissue remodeling and regeneration, in which regulation of stem cell behavior is prominent.

There are more than 20 BMPs. Some BMPs have a distinct function while others have overlapping functions, depending on the specificity of their interaction with different types of receptors and the tissues in which they

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are differentially expressed (Mishina, 2003). Accumulated evidence indicates that BMPs play an important role in regulation of stem cell properties; however, their functions are different in the different stem cell compartments. For instance, in *Drosophila* *g*ermline *s*tem *c*ells (GSCs), Dpp (homolog of BMP2/4) is essential for the maintenance of stem cells (Xie and Spradling, 1998); in *e*mbryonic *s*tem *c*ells (ESCs), BMP signaling appears to be required for ESC self-renewal but this is owing to its ability to block neural differentiation (Ying et al., 2003a) in addition to its ability to promote non-neural (mesoderm and trophoblast) differentiation (Xu et al., 2002; Ying et al., 2003a); in mesenchymal stem cells, the BMP signal induces osteoblastic differentiation through Bmpr1b but inhibits osteoblastic differentiation through Bmpr1a (Chen et al., 1998); in intestinal stem cells (ISCs), BMP signaling inhibits stem cell activation and expansion (He et al., 2004); and in hematopoietic stem cells (HSCs), BMP signaling through Bmpr1a restricts stem cell number by controlling the niche size (Zhang et al., 2003). A critical and comparative review of the roles of BMPs in different settings and in different stem cell compartments is necessary for a balanced view towards BMP function in the regulation of stem cell properties, and thus will provide important insight into understanding the complex signaling regulation of stem cell self-renewal and fate determination.

## Stem cell self-renewal—an event independent of other cellular events or the result of a combination of other cellular events?

The molecular mechanisms that control stem cell self-renewal remain largely unknown, albeit a large body of literature has been published with regard to stem cell self-renewal and the related signaling pathways. In the literature, self-renewal is generally described as a parallel cellular event of proliferation, differentiation, and apoptosis. However, accumulated evidence suggests that self-renewal of stem cells requires a combination of events: maintenance of their proliferation potential, inhibition of apoptosis, and blocking of differentiation.

Multiple signaling pathways have been reported to contribute to the regulation of stem cell self-renewal. However, different molecules and the underlying pathways may play different and overlapping roles in this regard. Maintaining proliferation potential is an obvious principle required for self-renewal of stem cells. However, it is worthwhile to point out that proliferation potential (defined as the capacity of stem cells to undergo continuous division) is different from proliferation per se in that the more the stem cells undergo active proliferation, the more they tend to lose their potential for proliferation. Therefore, stem cell proliferation potential is a functional property which can only be measured by continuous in vitro cell culture, or in vivo repopulation functional assay, rather than by measurement of the rate of proliferation. Recently, several lines of evidence have suggested that the Wnt signaling pathway through β-catenin is important for self-renewal of HSCs (Austin et al., 1997; Brandon et al., 2000; Murdoch et al., 2003; Reya et al., 2003; Van Den Berg et al., 1998; Willert et al., 2003), hair follicle stem cells (DasGupta and Fuchs, 1999; Gat et al., 1998; Huelsken et al., 2001), ISCs (He et al., 2004; Sancho et al., 2003; Sancho et al., 2004), and ESCs (Sato et al., 2004). In addition to its function in lineage fate determination, the prominent role of Wnt signaling favors cell proliferation and promotes cell growth. Abnormal activation of β-catenin leads to over-proliferation of stem cells and results in tumors in the intestines and in hair follicles (Gat et al., 1998; Sancho et al., 2004). In contrast, deletion of a Wnt downstream factor, Tcf4, leads to loss of stem cells in the intestines (Korinek et al., 1998). These observations suggest that Wnt/β-catenin signaling is important for the proliferation potential of stem cells as β-catenin may stimulate Tert (encoding the catalytic subunit of telomerase) expression via activation of Myc (He et al., 1998; Wang et al., 1998; Zou et al., 2005). The idea that limiting the proliferation potential affects stem cell self-renewal has been well demonstrated by studies of telomerase (Morrison et al., 1996), HoxB4 (Antonchuk et al., 2002; Helgason et al., 1996; Kyba et al., 2002; Sauvageau et al., 1995), p18 (Yuan et al., 2004), P21(Cheng et al., 2000), and Bmi (Lessard and Sauvageau, 2003; Molofsky et al., 2003; Park et al., 2003).

Recent reports indicate that suppression of apoptosis plays an essential role in stem cell self-renewal (Domen and Weissman, 2000; Domen et al., 2000; Opferman et al., 2005; Yamane et al., 2005). This idea is further enforced by the fact that the role of β-catenin in promoting HSC self-renewal is prominent in the Bcl2-transgenic mouse (Reya et al., 2003), indicating that a coordination between Bcl2, which inhibits apoptosis, and β-catenin, which is important for proliferation potential, is required for stem cell self-renewal. Likewise, transgenic expression of the activated form of β-catenin alone tends to lead to crypt cell apoptosis, as shown in the intestinal system (Wong et al., 1998). It is also reported that Akt is activated during intestinal stem cell activation and division (He et al., 2004), as well as during hair follicle stem cell activation (Zhang and Li manuscript, submitted). As Akt is a cell survival factor in general, activation of Akt during stem cell activation and division may be necessary to protect stem cells from apoptotic stress including that from partial anoikis, a phenomenon caused by detachment from the extracellular matrix during cell division (Khwaja et al., 1997). Consistent with this conclusion, activation of PI3K/Akt, as a consequence of the loss of PTEN-function, has been reported to result in expansion of embryonic and neural stem cell populations (Groszer et al., 2001; Kimura et al., 2003).

An important feature of stem cell self-renewal is to maintain the stem cell in an undifferentiated state. Inhibition of stem cell differentiation can lead to an accumulation of