

## RESEARCH HIGHLIGHT

# Bmi-1, stem cells and prostate carcinogenesis

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Malignant transformation is likely to arise in a subset of organ-specific primitive cells that are subverted to acquire the properties of uncontrolled self-renewal.<sup>1,2</sup> It is therefore likely that stem cells and tumor-initiating cells share many properties and that an understanding of the biology of normal stem cells and the identification of the pathways and molecules that regulate their self-renewal may result in our ability to design inhibitors that control the growth of tumor cells. In an interesting recent paper, Lukacs *et al.*<sup>3</sup> show that the polycomb group transcriptional repressor, Bmi-1, regulates the self-renewal of normal prostate stem cells and also contributes to the initiation of prostate cancer.

Stem cells in the prostate are localized in the proximal region of the gland near the urethra. The majority of prostate stem cells have a basal cell phenotype and express high levels of Sca-1 and CD49f. Lukacs *et al.*<sup>3</sup> found that Bmi-1 was expressed in the proximal region primarily in basal cells. Expression of Bmi-1 in the Sca-1-positive/CD49f<sup>high</sup> stem cell population was sevenfold higher than in luminal prostate cells. As the prostate primarily loses differentiated luminal cells after castration, stem cells become more concentrated in the castrated prostate. The percentage of Bmi-1 positive cells also increased in castrated prostate. These results suggested that Bmi-1 is localized to prostate stem cells.

To examine the function of Bmi-1 in stem cells, Lukacs *et al.*<sup>3</sup> knocked down its expression using small interfering RNAs or overexpressed it in prostate cells. Effects on stem cell properties were measured using an assay based on the fact that stem cells can grow in a

semisolid medium, forming a sphere of cells. The number of spheres generated gives a measure of stem cell number, while the size of the spheres reflects the proliferative potential of the stem cells. In these assays, decreased expression of Bmi-1 reduced both the number and size of spheres formed, while increased Bmi-1 expression enhanced both sphere formation and the size of spheres. These results suggested that Bmi-1 has a role in self-renewal of the stem cells. As Bmi-1 represses expression of the cell cycle inhibitors p16 and p19, Lukacs *et al.*<sup>3</sup> examined expression of these two proteins. As expected, knockdown of Bmi-1 increased expression of p16 and p19, whereas overexpression of Bmi-1 inhibited expression. Co-infection of prostate cells with p16 and p19 expression vectors caused inhibition of sphere-forming ability similar to that obtained with knockdown of Bmi-1, suggesting that Bmi-1 regulates stem cell renewal through its effects on these cell cycle inhibitors. Finally, the most rigorous test for stem cells is their ability to regenerate prostate tubules when co-implanted with urogenital sinus mesenchyme under the kidney capsule. Lukacs *et al.*<sup>3</sup> found that prostate cells with diminished expression of Bmi-1 had decreased ability to form tubules *in vivo*. Together these experiments provide convincing evidence that Bmi-1 is required for stem cell self-renewal and, consequently, the ability of stem cells to support the growth of prostate tissue.

To examine the role of Bmi-1 in the generation of tumors, Lukacs *et al.*<sup>3</sup> used two model systems that mimic steps in the evolution of human prostate tumors. In one model, prostate cells co-inoculated under the renal capsule with urogenital sinus mesenchyme overexpressing FGF10 form hyperplastic prostatic intraepithelial neoplasia (PIN)-like lesions in the regenerated tubules. Knockdown of Bmi-1 in the prostate cells greatly diminished the number of hyperplastic tubules obtained. In the second model,

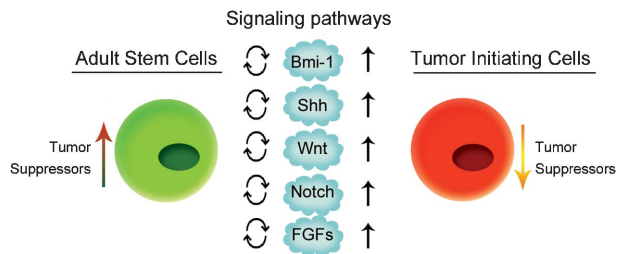
knockout of the tumor suppressor phosphatase and tensin homolog (PTEN) in prostate cells caused prostate tumor growths when these cells were co-inoculated with urogenital sinus mesenchyme under the renal capsule. Knockdown of Bmi-1 in the cells with ablated PTEN resulted in smaller, less cellular growths containing fewer proliferating and more apoptotic cells. These results demonstrate that Bmi-1 is required for uncontrolled growth of prostate tumor-initiating cells.

In addition to its role in prostate stem cell self-renewal and prostate tumor initiation, Bmi-1 regulates the self-renewal of other types of stem cells and is also implicated in the growth of other tumors.<sup>3</sup> It is also highly expressed in prostate tumors with more aggressive features.<sup>4</sup> There is evidence that pathways that regulate the self-renewal of normal stem cells are deregulated in cancer stem cells, resulting in the continuous expansion of tumor cells.<sup>5,6</sup> Expression of stem cell self-renewal genes may be part of a common signature that stem cells and tumor initiating cells share. A relationship between stem cell and cancer cell molecular signatures has been shown for human hepatocellular carcinoma where the rat fetal liver stem cell signature has prognostic significance for human hepatocellular carcinoma.<sup>7</sup> The molecular signature of prostate stem cells identifies many pathways in common with prostate tumors, suggesting that aberrant activation of prostate stem cell pathways may contribute to the development of prostate tumors.<sup>8</sup> In addition to Bmi-1, components of the Shh and Wnt signaling pathways are elevated in primitive prostate cells.<sup>8,9</sup> Elevated activity in the Bmi-1 and other signaling pathways, possibly in conjunction with diminished levels of tumor suppressor molecules,<sup>10</sup> may result in malignant transformation of normal stem cells into their tumorigenic counterparts (Figure 1).

To develop prostate tumor-specific therapies, targets such as Bmi-1 may not be ultimately useful as this molecule is involved in

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**Figure 1** Signaling pathways in prostate tumor-initiating cells may be perturbed counterparts of those expressed in normal prostate stem cells. The pathways involved in self-renewal of normal stem cells are tightly regulated (G). The balance between proliferation and differentiation is maintained by tumor suppressor molecules and molecules that cause self renewal. A decrease of suppressor molecules and/or an increase in molecules that promote self-renewal can result in tumor initiation and tumor progression.

stem cell self-renewal in other organs. For future studies, efforts should be addressed to the identification of prostate tumor-specific stem cell pathways. As the prostate is a non-essential organ, ablation of normal prostate stem cells by targeting these pathways will not have adverse consequences.

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