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BMP signaling alterations in stem cells and their niche fuel tumor emergence and expansion

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Understanding the mechanisms underlying the early steps of cancer development will help to prevent and manage the disease. In healthy tissue, the microenvironment (niche) governs the fate of stem cells (SC) by balancing their self-renewal and differentiation through the regulation of the availability of soluble molecules, cell-cell contact, cell-matrix interactions, and physical constraints. Understanding the biology of the normal and malignant SC microenvironments has become a major focus as accumulating evidence indicates that the tumor microenvironment plays an active role in tumor initiation and progression. This is remarkably illustrated in Chronic Myelogenous Leukemia (CP-CML) where clinical data suggest that Leukemic stem cells (LSC) are likely to survive, expand and be responsible for disease persistence and eventual drug resistance due to their sustained interactions with the microenvironment. However, the mechanism underlying the effects of the microenvironment in the regulation, transformation and drug sensitivity of SC is poorly understood. To address this question in a general way, we investigated the status and biological function of the Bone Morphogenetic Protein in the CML model as the gold standard of a true stem cell disease and in breast cancer as representative of a solid tumor with identified cancer stem cells. BMPs, members of the TGF superfamily, are key mediators of stem cell regulation in development, hematopoietic, neural and epithelial systems. In addition, BMP pathway directly affects the niche and the resident stem cells. Within the BMP family, BMP2 and BMP4 emerge as important regulators of both normal and cancer stem cells. Using CML and breast cancer systems, we revealed a profound alteration of the signaling pathway in immature cells highlighting an outstanding deregulation of the BMP receptor of Type 1B (BMPR1B). We also found a strong increase of soluble BMP2 in the mammary niche and of BMP2 and BMP4 in the CML bone marrow. Interestingly in both systems, endothelial cells within the tumoral niche seem to be the main provider of soluble BMPs. These changes are accompanied by altered functional responses of primitive transformed cells to BMP2. In an inflammatory context, chronic exposure of immature epithelial cells to high exogenous BMP2 levels initiates cellular transformation toward a luminal breast tumor phenotype through a BMPR1B mediated signal. For the first time, we identified environmental factors, such as radiation or estrogen-mimetic, as inducers of BMP2-synthesis by stromal cells to levels comparable to those measured in luminal breast tumors. These data uncover a role of BMPs in tumor initiation in addition to its known effects in later stages of transformation and progression. Furthermore, using primary cells and a cell line mimicking early steps of CML, we demonstrated that myeloid progenitor expansion is driven by BMP2/4 exposure of cancer stem cells overexpressing BMPR1b. Using this early CML model, we further showed that the oncogene expression, the fusion protein BCR-ABL, directly increased BMPR1b expression at the membrane and that BMPR1b overexpression is specifically involved in the survival and expansion of cancer stem cells as well as amplification of committed myeloid leukemia progenitors. We have then revealed a major role of the BMPs to fuel cell transformation and expansion by over-amplifying a natural SC response. Our data indicates that this mechanism is likely relevant to explain survival of cancer stem cell independently of the initial oncogenic event and therefore be involved in resistance processes. Altogether, our data provide insight into the etiology of breast cancer and CML by revealing a new mechanism through which the stem cell microenvironment can promote the malignant transformation, preserve and expand transformed stem cells. Our results suggest new possibilities for the development of novel therapeutic tools specifically targeting the tumoral niche.

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