Abstract

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Harnessing Bone Morphogenetic Protein (BMP) Signaling to Regulate Epithelial to Mesenchymal Transition: A Novel Therapeutic Approach for the Treatment of Metastatic Cancer

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Abstract

Cancer stem cells (CSCs) are the driving force behind metastasis and recurrence. CSCs and their chemo-resistance emerge through the induction of Epithelial to Mesenchymal Transition process (EMT). Dedifferentiation of CSCs to an epithelial phenotype by reversing the EMT process may recover chemo-sensitivity. Harnessing the Bone Morphogenetic Protein (BMP) pathway to carry out this novel therapeutic approach may be a viable drug development strategy for treatment of metastatic cancer. Targeting CSCs therapeutically is challenging, since both bulk tumor cells and CSCs must be eliminated. Previously, we showed that Peptide123 (P123), designed from BMP structure, inhibited bulk tumor cell growth by activating BMP signaling and blocking TGF-β induced EMT. We further investigated P123 effects on human breast cancer stem cell (BCSC) growth (self-renewal), differentiation (EMT-reversal), and apoptosis (chemo-sensitivity). P123 or BMP-7 markedly suppressed BCSC tumorsphere formation, suggesting that both P123 and BMP-7 may inhibit BCSC self-renewal. FACS analysis of BCSCs treated with P123 or BMP-7 showed a marked decrease in $CD44^+$ cells with a gain in E-cadherin$^+$ cells. BCSCs treated with P123 demonstrated loss of intracellular vimentin expression and increase in plasma membrane β-catenin expression. Unlike BMP, P123 does not induce osteogenic differentiation markers or bone formation and therefore is unlikely to induce bone metastasis. Together, these results suggest that both P123 and BMP-7 may reverse EMT in BCSCs. Finally, BCSCs co-treated with paclitaxel and P123 showed an increase in Annexin V^+ cells compared to BCSCs treated with paclitaxel alone, suggesting P123 potentiation of apoptosis. Our findings suggest that P123, a novel peptide agonist of BMP signaling, has the potential to suppress bulk tumor cells and eliminate CSCs by inhibition of self-renewal, reversal of EMT, and an increase in chemo-sensitivity. Ultimately, harnessing the BMP pathway may lead to a new class of drugs for the treatment of metastatic cancer and recurrence.

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Biography

Dr. Ashish Bosukonda began research in the area of BMPs (Bone Morphogenetic Protein) 10 years ago and has since focused on BMP signaling and its effects on cancer progression and metastasis. He has developed a novel approach for control of cancer stem cell growth, and reversal of the EMT (epithelial to mesenchymal transition) and it's contribution to tumor metastasis and relapse. His research has led to novel therapeutics for potential treatment of advanced breast and prostate cancers. Ashish's contributions to drug discovery has been well recognized through awards from American College of Physicians and the American Medical Association. Dr. Bosukonda is an Internal Medicine Resident with career aspirations in Clinical Oncology.

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