BMP6 and Tumour associated macrophages

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Abstract Bone Morphogenetic Protein 6 (BMP6), a transforming growth factor-beta (TGF-β) superfamily member, plays the core role in tumor microenvironment in relation to its action on tumor-associated macrophages (TAMs). BMP6 promotes tumor development through its action on macrophage polarization towards an M2-like state with concomitant immunosuppression and pro-tumorigenic activity. Recent evidence has focused on the molecular mechanisms that execute BMP6-induced TAM reprogramming through Smad5 and STAT3 pathways, and its clinical relevance in various cancers such as renal cell carcinoma and prostate cancer. This review pertains to the role of BMP6 in the regulation of TAMs, the molecular pathways behind it, and its potential for treatment in cancer.

Keywords: Bone Morphogenetic Protein 6 (BMP6), Tumor-Associated Macrophages (TAMs), TGF-β Superfamily, Immunosuppression, Cancer Therapy

Introduction

Bone morphogenetic protein 6 (BMP6), part of the transforming growth factor-beta (TGF-β) superfamily, plays multiple roles in regulating various cellular processes, including growth, differentiation, and immune response (Lee et al., 2013). In the tumor microenvironment, BMP6 is recognized as an important factor influencing the actions of tumor-associated macrophages (TAMs), a diverse set of immune cells that can either enhance (M2-like) or inhibit (M1-like) tumor growth(Kwon et al., 2014; Lee et al., 2013). TAM polarization is highly plastic and context-dependent BMP6 was an important signal to promote macrophages towards an M2-like state, thereby driving tumor growth, angiogenesis, and immune evasion or strengthen anti-tumor immunity by supporting M1 activation(Lee et al., 2011). Understanding BMP6's dual role in regulating TAMs is crucial for comprehending its influence on tumor growth and for exploring new therapeutic strategies aimed at tumor-immune interactions. Yet, in some contexts, BMP6 may be pro-anti-tumor in promoting M1 activation, reflecting its bimodal role in tumor-immune interaction. This review discusses the role of BMP6 in TAM polarization, the molecular pathways underlying its action, clinical significance, and potential therapeutic approaches against the BMP6/TAM axis.

The role of BMP6 and M2 Polarization:

BMP6 has been shown to trigger the production of interleukin-10 (IL-10) by macrophages, a hallmark cytokine of M2 polarization. M2-like TAMs maintain tumor growth by enhancing angiogenesis, suppressing adaptive immunity, and stimulating tumor cell invasion and metastasis (Lee et al., 2013). Through such reprogramming, BMP6 indirectly contributes towards the establishment of a tumor-permissive immune landscape.

Molecular Mechanisms of BMP6-Induced TAM Polarization

In renal cell carcinoma (RCC), BMP6 induced M2 polarization is mediated by the activation BMP receptors (e.g., ALK2, BMPR-II) and initiate Smad1/5/8 phosphorylation and activating STAT3 signaling pathways in macrophages, which then leads to increased IL-10 production (Katsuta et al., 2019; Lee et al., 2013). BMP6 derived from prostate cancer stimulates TAMs to produce IL-1a through Smad1 and NF-kB1 pathway. IL-1α production supports tumor angiogenesis and growth

(Kwon et al., 2014). Collectively, these findings establish BMP6 as a master regulator of TAM reprogramming in the context of different cancers.

Clinical Significance of the BMP6/IL-10/CD68 Axis

Clinical evidence has identified a three-marker signature consisting of BMP6, IL-10, and CD68 (a macrophage marker) as a prognostic marker in RCC. Patients who had high levels of BMP6 and IL-10 showed unfavourable outcomes, such as higher recurrence and metastasis following surgery (Lee et al., 2013) . TCGA dataset analysis also identified that high expression of BMP6, BMP8A, BMP8B, and BMPR1B was associated with shorter overall survival across various tumor types (Katsuta et al., 2019). Elevated BMP6 expression has also been reported in melanoma, prostate carcinoma, and breast carcinoma, suggesting its broad clinical significance (Tan et al., 2021).

Therapeutic Potential: Targeting the BMP6/TAM Axis

Given that it is at the center of controlling TAM function, BMP6 is a desirable drug target. The following strategies are being investigated: BMP6 inhibitors, inhibitory antibodies or small molecules to block BMP6 activity. TAM reprogramming, immunomodulators that reprogram TAMs from an M2-like to an M1-like phenotype (Vadevoo et al., 2022).Combination therapies, TAM-targeting therapies in combination with immune checkpoint inhibitors to enhance T-cell activation, and signaling pathway blockade, STAT3 or Smad signaling inhibitors to inhibit BMP6-induced immunosuppressive polarization (Riabov et al., 2014). These approaches have the promise not only to disrupt BMP6-mediated immunosuppression but also to complement existing cancer immunotherapies to help patients**.**

Conclusion

BMP6 emerges as a critical factor in shaping the tumor immune landscape via its regulation of macrophage polarization. By promoting an M2-like, immunosuppressive TAM phenotype, BMP6 facilitates tumor progression, particularly in renal cell carcinoma. Understanding the molecular mechanisms behind BMP6 signaling, especially the Smad5/STAT3/IL-10 axis, offers promising avenues for targeted intervention. Therapies aimed at disrupting this immunosuppressive signaling loop or reprogramming TAMs hold potential to enhance current cancer immunotherapy strategies.

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