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Targeting the Substance P/Neurokinin-1 Receptor Axis: A Novel Avenue in Overcoming Cancer Resistance

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The role of the Substance P (SP)/Neurokinin-1 Receptor (NK-1R) system in cancer biology has gained growing recognition. Recent literature consistently supports its implication in cancer promotion, progression, resistance, and inflammation [1]. SP is a peptide of the tachykinin family involved in multiple pathophysiological mechanisms, including nociception, inflammation, and immune modulation. However, its pathological role particularly through its preferred receptor, NK-1R has become increasingly evident in several malignancies [2].

Numerous studies have shown that SP and NK-1R is overexpressed in human cancer cells and NK-1R is essential for the viability of cancer cells. Activation of NK-1R, either constitutively or through SP binding, promotes cancer cell proliferation, antiapoptotic, survival, Warburg effect, angiogenesis, invasion and migration for metastasis [1]. Furthermore, this pathway contributes significantly to the establishment of a pro-inflammatory microenvironment, which sustains tumor progression. In head and neck cancers—especially laryngeal and oral squamous cell carcinomas the SP/NK-1R system has been implicated in the transition from chronic inflammation to preneoplastic and neoplastic lesions [3, 4]. Beyond its role in cancer progression, the SP/NK-1R axis is also associated with resistance to oncologic treatments. Overriding or malfunctioning NK-1R signaling appears to interfere with treatment response through modulation of signaling cascades and cross-talk with other receptor systems, potentially affecting immune escape and chemoresistance. This has opened the door to drug repurposing strategies involving NK-1R antagonists [5, 6].

Aprepitant, a well-known NK-1R antagonist currently approved for chemotherapy-induced nausea and vomiting, has shown potential in preclinical studies as an antitumor drug. It exhibits antiproliferative, pro-apoptotic, anti-Warburg effect, antiangiogenic, prevent invasion and migration, and has anti-inflammatory effects in cancer models [1, 6]. Importantly, aprepitant's established safety profile and widespread availability make it a promising candidate for repositioning in oncology [1, 6]. The current evidence suggests that combining NK-1R antagonists with existing therapies could improve treatment response and potentially overcome resistance in multiple cancer types [3, 6]. Despite this progress, more precise characterization of NK-1R's role across different tumors is needed. NK-1R signals through various pathways, and its full and truncated isoforms may exert distinct functions. Understanding these nuances will be critical for optimizing the clinical use of NK-1R-targeted therapies. Moreover, the availability of selective antagonists and the emerging potential for biased ligands based on receptor structural states present exciting research and therapeutic opportunities [6].

In conclusion, the SP/NK-1R system represents a multifaceted target in cancer biology. Its involvement in carcinogenesis, inflammation, and resistance mechanisms positions it as a valuable focus for novel cancer therapies. Future research should seek to translate these findings into clinical strategies, which could transform cancer care through these new drugs. In addition, the drug aprepitant and other similar drugs should be repurposed as antitumor drugs in cancer therapy.

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