Antitumor Strategies Targeting Peptidergic Systems

Subjects: Neurosciences

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Peptidergic systems show promise as targets for fighting tumors. While some peptides encourage the growth and spread of tumor cells and angiogenic mechanisms, others display antitumor properties. As such, peptide ligands and receptor antagonists could be used as antitumor agents alone or in conjunction with chemotherapy or radiotherapy. Peptide receptor antagonists can counteract the oncogenic effects of specific peptides by inducing apoptosis in various types of tumor cells, hindering cancer cell migration and inhibiting angiogenesis. Peptides and peptide receptor antagonists are not currently used in clinical practice as antitumor agents. Still, aprepitant, a neurokinin 1 receptor antagonist, is a promising candidate due to its ability to promote apoptosis in many cancer cells. However, to utilize aprepitant as an anticancer agent, the dosage must be increased and administered for a more extended period. Moving beyond current protocols for aprepitant's use as an antiemetic is essential. Additionally, a common anticancer strategy with aprepitant is possible regardless of cancer cell type. Finally, combining aprepitant with chemotherapy or radiotherapy is encouraged.

peptide | peptide receptor | antitumor drug | anticancer | substance P | neurokinin-1 receptor antagonist | aprepitant

Many in vitro and in vivo experiments have demonstrated the fundamental roles that peptides and their receptors play in cancer progression [1]. After binding to their respective receptors, peptides promote proliferative and antiproliferative effects in cancer cells: the same peptide (e.g., galanin, orexin) can exert both effects in tumor cells (the reason for this being the G protein type and the subtype of receptor involved, for example, galanin 1, 2, and 3 receptors), whereas other peptides (e.g., substance P, neurotensin) mainly induce a proliferative action (oncogenic effect) in many types of tumor cells [2][3]. Accordingly, peptides and receptor antagonists can be used as potential anticancer drugs, although the latter compounds show a higher therapeutic capacity than peptides [4]. This is because peptides generally show poor bioavailability and a short half-life. However, it is essential to emphasize that some strategies are being developed to increase the therapeutic effects of peptides as well as their stability and delivery (e.g., peptide-loaded nanoparticles, peptide cyclization, conjugation of peptide drugs to natural/synthetic polymers, manipulation of the amino acid sequence, cell-targeting peptides, and cell-penetrating peptides) [5][6]. Some cell-penetrating short peptides show an antitumor action, and, in addition, they can also be used to carry anticancer cargo into tumor cells [7]. Indeed, cell-penetrating peptides–cargo complexes (CPP) are valuable for intracellular drug delivery. Different strategies provide safe, effective, and targeted transport without altering the membrane's physicochemical properties [8].

Unfortunately, although large amounts of data support the previously mentioned promising antitumor strategies, no antitumor drug targeting peptidergic systems is currently available in clinical practice. It is inexplicable that the tremendous clinical potential of peptide receptor antagonists as antitumor drugs has been entirely forgotten by pharmaceutical companies. In preclinical studies, peptide receptor antagonists (e.g., neurokinin-1 receptor antagonists) have shown anti-inflammatory, antiviral, antipruritic, anticonvulsant, anxiolytic, and analgesic effects. Still, unfortunately, these positive effects have not been reported in clinical trials [9][10]. This could be one of the reasons why pharmaceutical companies have not shown much interest in studying the antitumor capacity of peptide receptor antagonists. However, many convincing data show that the use of these antagonists is an encouraging antitumor strategy and that these compounds can be used as broad antitumor drugs because tumor cells overexpress peptide receptors compared to normal cells [11][12] and because peptide receptor antagonists promote apoptotic mechanisms in many types of cancer cells.

The apoptotic capacity promoted by these antagonists also occurs in normal cells but in a significantly lesser proportion [13]. A crucial challenge is to confirm the antitumor effects mediated by peptide receptor antagonists in clinical trials. Hence, repurposing these compounds as anticancer agents is urgently needed since some peptide receptor antagonists are currently used in clinical practice to fight other pathologies but not as antitumor drugs [11][13]. Thus, the repurposing of peptide receptor antagonists as anticancer agents must be developed and potentiated by researchers and clinicians. The beneficial effects of these antagonists would be enormous since tumor cells overexpress peptide receptors and the same antagonist promotes apoptosis in many types of tumors overexpressing the same peptide receptors. In addition, these antagonists could be administered alone or in combination with chemotherapy or radiotherapy [4].

The primary objective of this paper is to explore the various discoveries that have highlighted the role of peptides in the formation and progression of tumors. Additionally, this article aims to shed light on the vast therapeutic possibilities of peptide receptor antagonists as effective and comprehensive antitumor agents. Specifically, the focus is on antagonists that hinder peptides, such as undecapeptide substance P [10], responsible for promoting cell growth in different types of cancers.

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