Editorial Commentary

Importance of semaphorins in cancer immunity

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The semaphorin family is characterized by the presence of a sema domain and plexin-semaphorin integrin domains. Although, when they were first discovered, semaphorins were reported for their axon-guidance ability (1), recent studies indicate that semaphorins regulate several hallmarks of cancer (2-4). For example, semaphorin 3A (SEMA3A) reduced tumor growth and angiogenesis through upregulating the forkhead box O3a (FOXO3a) dependent, melanoma cell adhesion molecule (MelCAM) in breast cancer in xenograft NOD-SCID mouse model (5). SEMA3B was found to inhibit tumor growth, while increasing metastatic dissemination by activating the p38-MAPK-p21 pathway in immunocompromised $CD1^{-/-}$ nude athymic female mice (6). SEMA6A employed the FAS-associated death domain protein (FADD) and heme oxygenase 1 (HMOX1) to suppress survival and migration, respectively, in lung cancer cells (7,8). Moreover, the high expression of SEMA6D in the Tie-2 expressing monocyte subset within the tumor suggests that SEMA6D might induce angiogenesis by PlexinB1 or vascular endothelial growth factor receptor (VEGFR) signalling (9).

Researchers have recently recognized semaphorins' ability to influence immune responses in cancer, in addition to their effects on survival, metastasis, and angiogenesis in cancer cells. It is not surprising that semaphorins modulate immunity in cancer, since several members of the semaphorin family demonstrate a regulatory function in the immune system. SEMA3A, SEMA3B, and SEMA4D demonstrate the potential to induce tumor-associated macrophages that reduce anti-cancer immunity (10-14). SEMA3E, SEMA6D, and SEMA7A enhance the activities of T cells, monocytes, dendritic cells, or B cells (10,15). On the other hand, SEMA3A is one of the well-known immune suppressors, which has been reported to inhibit T cell proliferation (16) and to maintain the activity of T regulatory (Treg) cells by binding to the neuropilin 1 (NRP1) receptor (13). SEMA4A also supported survival of Treg cells via NRP1 binding (14).

Genes, such as cytotoxic T lymphocyte-associated antigen-4 (CTLA4), programmed cell death-1 (PD-1), and PD-1 ligand-1 (PD-L1), have been used for immunotherapy in cancer; however, their efficacy is not ideal, and the efficacy varies for different types of cancer. Semaphorins' extensive functions in immune regulation make them potential candidates for use in immunotherapy treatment for cancer. An anti-SEMA3A antibody was patented for the treatment of Alzheimer's disease and immune dysfunction, including lowering the immune suppression caused by tumor-secreted SEMA3A (US9879075B2). Also patented is a SEMA4D inhibitor to increase the frequency of a tumor-infiltrating leukocyte by blocking the binding of SEMA4D and its receptor (US9243068B2). Moreover, a phase 1b/2 study reported that Pepinemab (VX15/2503), a humanized IgG4 monoclonal antibody against SEMA4D, showed initial signals of antitumor activity in combination with avelumab in advanced non-small cell lung cancer (17). Furthermore, some patents focus on the receptors of semaphorins, such as PlexinD1 (US9422358B2) and NRP1 (US9540439B2), to promote anti-cancer immunity. Thus, semaphorins seem to be a rising star in immunotherapy treatment of cancer.

Currently, only a few semaphorins show promise in regulating anti-cancer immunity. However, the immune regulatory effects of most semaphorins are demonstrated in other diseases. For example, SEMA5A and SEMA7A are involved in the pathogenesis of rheumatoid arthritis by promoting activities of T cells (18). Research suggests that SEMA3E plays an important role in modulating immune responses to prevent allergic asthma (19). Furthermore, some semaphorins, whose receptors have the ability to regulate immunity when binding with other semaphorins, have not been investigated for their function in the immune system. Therefore, the knowledge of semaphorins in anti-cancer immunity is in its infancy, and more effort should be invested to understand utilizing semaphorins in cancer immunotherapy in the future.

In conclusion, evidence that semaphorins play important roles in immune regulation is increasing; however, there is still very little knowledge of the use of semaphorins in cancer immunity. The valuable study of the function of semaphorins in cancer immunity and immunotherapy should be expanded.

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Footnote

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