Reduction of tumor growth by an antibody to SEMA4D/MAb67, a murine version of humanized MAb VX15/2503


Abstract

Semaphorin 4D (SEMA4D; CD105) has been implicated in several key mechanisms of tumor progression, including vascularization, metastasis, immune evasion, and tumor invasion. Evaluation of SEMA4D in a wide array of tumor types and a study produced by inflammatory cells recruited to the tumor microenvironment. SEMA4D binding to plexin-B1 (PLXNB1) on endothelial cells promotes angiogenesis through regulation of cell behaviors such as migration, proliferation, and differentiation. Blockade of the SEMA4D/PLXNB1 interaction with an antibody to SEMA4D has been shown to reduce tumor growth in several preclinical models. In some tumor models the interaction is up-regulated by inhibition of anti-tumor immune response pathways. We demonstrated here that SEMA4D also regulates the balance and location of activated and alternatively activated macrophages in the tumor and that modulation of the anti-tumor immune microenvironment can result in anti-SEMA4D antibody-mediated tumor growth delay. In summary, blockade of SEMA4D induced tumor growth through effects on tumor microenvironment, angiogenesis, and vascular permeability, and, possibly, direct effects on tumor. Anti-SEMA4D treatment of SEMA4D mouse may represent a new therapeutic strategy for cancer treatment. We also studied antibody purified from several hybridomas. The antibodies are highly potent and selective for SEMA4D. Our understanding of the role of SEMA4D in this process is evolving.

Introduction

• SEMA4D binds PLXNB1 with 1 nM affinity and CD72 with 300 nM affinity
• Expresses receptor domains in the surface of a tumor and blood vessels as a B
• Activates T lymphocytes and induces dendritic cell maturation for antigen presentation to T lymphocytes
• Binds to PLXNB1 transactivates NET promoting angiogenesis and stimulating inflammatory growth of tumors
• In overexpressed in a variety of human tumors including head and neck prostate, pancreatic neuroendocrine tumors due to expression of the oncogene SV40 T antigen in adult patients with advanced solid tumors.

Treatment with anti-SEMA4D MAb 67-2 delays growth of Colon26 tumors in Balb/c Mice. Anti-tumor effect is dependent on competent immune system

Anti-SEMA4D antibody allows penetration of CD8+ T cells and M1 macrophage into areas of actively proliferating tumor

Anti-SEMA4D antibody increases tumor infiltration of tumor-specific cytotoxic CD8+ T cells

Summary

• We have generated a highly affinity mouse MAb 67-2 that significantly reduces tumor growth in vivo.
• The antibody has demonstrated anti-angiogenic activity in a highly vascularized neuroendocrine tumor model.
• The antibody also offers the number and location of infiltrating macrophage and lymphocytes, promoting an anti-tumor immune microenvironment and resulting in delayed tumor growth in an immunogenic tumor model.
• SEMA4D was first described as a regulatory axis guidance molecule during development. It is shown here to also inhibit immune infiltration of tumor stromal. Antibody blockade of SEMA4D increases this effect.
• Three studies, in conjunction with immunophenotyping, PHD, and toxicology studies on B and cytotoxic lymphocytes maintained support a clinical evaluation of the safety and tolerability of MAb VX15/2503 to inhibit tumor growth.