Semaphorins in Lung Cancer

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The secreted class 3 semaphorins, which include SEMA3F, a tumor-suppressor gene in lung cancer, were initially identified as molecules involved in the repulsion of developing nerve growth cones. These molecules are part of a larger family that includes transmembrane and membrane-associated proteins, some of which are expressed widely and implicated in other functions such as development and immune response.[1] SEMA3B and SEMA3F are both encoded in 3p21.3,[2–4] a region of frequent loss of heterozygosity in lung cancer,[5] which initially suggested that one or both of these genes might have tumor-suppressor activity. Since this hypothesis in 1996, several semaphorins have been implicated in cancer.[6–9] In this review, we focus on the function and signaling of semaphorins involved in lung cancer.

SEMAPHORIN SIGNALING

The neuropilins (NRP) NRP1 and NRP2 are high-affinity receptors for the class 3 semaphorins. However, in the absence of plexin co-receptors, they are insufficient to propagate a signal. Intracellular semaphorin signaling (Figure 1) involves small-GTPases, collapsin response-mediated protein, pERK1/2, and integrins, which result in the reorganization of tubulin and actin leading to modification of the cytoskeleton and changes in cell adhesion and migration.[10–12] Importantly, both NRP1 and NRP2 were also identified as vascular endothelial growth factor $(VEGF)_{165}$ co-receptors and are required for vasculature development. Several reports have indicated that class 3 semaphorins and $VEGF_{165}$ compete for NRP binding.[6–9] Although semaphorin activity is likely greater than just a VEGF antagonist, at least part of the antitumor activity appears to stem from this function.

SEMAPHORIN ANTITUMOR ACTIVITY IN LUNG CANCER

Initial expression studies demonstrated that levels of SEMA3F mRNA were reduced in a majority of lung cancer cell lines. In patient samples, protein levels of SEMA3F were often reduced and its subcellular localization was shifted from the plasma membrane to the cytoplasm.[13] In non–small-cell lung cancer, low SEMA3F levels were significantly correlated with advanced stage disease. In addition, the presence of an exclusive cytoplasmic localization was significantly correlated with high levels of $VEGF_{165}$, increased tumor grade, and aggressive disease.

In preneoplastic lesions, loss of SEMA3F protein staining was frequently observed.[14] Similarly, $VEGF_{165}$ immunostaining increased from low- to high-grade dysplasia and NRP levels increased between dysplastic and microinvasive lesions. Thus, deregulation of the $VEGF_{165}$/SEMA3F/NRP pathway is a frequent and early event in lung cancer pathogenesis. Subsequent in vivo studies using immunodeficient mice or rats have confirmed the capacity of SEMA3F to reduce or inhibit tumor development.[15–18] In these model systems, SEMA3F effects were both antiangiogenic[16,17] and antimetastatic.[16] In the report of Kusy et al.[18] using a lung cancer orthotopic model, the antitumor effects of SEMA3F were dramatic, with additional potential mechanisms involving reduced adhesion to extracellular matrix substrates and impaired signaling through the ERK pathway.

SEMA3B also has potent antitumor activity, as demonstrated in nude mice where an ovarian adenocarcinoma cell line transfected with SEMA3B showed reduced tumorigenicity and cell proliferation.[19] These in vivo results were confirmed in cell culture by SEMA3B transfection into the non–small-cell lung cancer cell line, H1299, which resulted in a greater than 90% reduction of colony formation.[20] Furthermore, in this cell line, SEMA3B overexpression induced apoptosis, whereas $VEGF_{165}$ led to cell proliferation.[21]

In summary, both SEMA3F and SEMA3B exhibit tumor-suppressor activity in lung cancer and other tumor types. Also of interest is the reported correlation between low levels of collapsin response mediator protein 1 and increasing tumor grade, invasion, and metastasis.[22] Together with deregulation of $VEGF_{165}$ and NRP receptors, it is apparent that the overall pathway(s) is affected in many, if not most, lung cancers. Potential therapeutic approaches include up-regulation of SEMA3F and SEMA3B expression by agents that target chromatin reorganization and DNA methylation.[6]

The semaphorin molecule itself may prove useful as a therapeutic agent.[23] In addition, we suggest that a combined approach involving VEGF inhibition and up-regulation of SEMA3F/SEMA3B might be even more effective.

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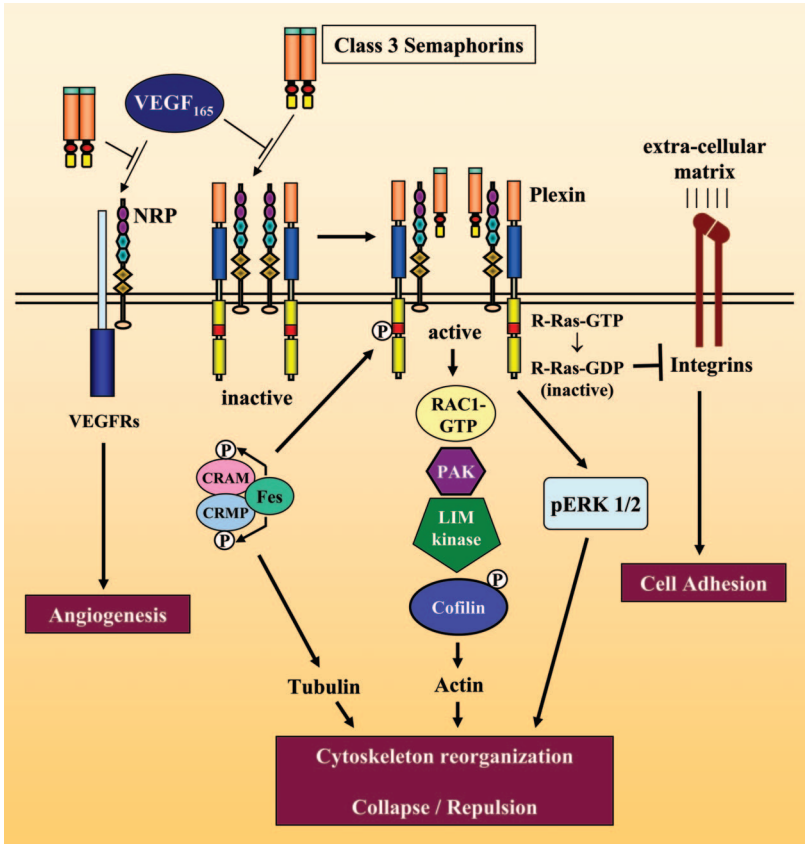

FIGURE 1. Class 3 semaphorin signaling. Binding of class 3 semaphorins to neuropilin and plexin leads to cytoskeleton reorganization, collapse, cell repulsion, and changes in cell adhesion. By competing with $VEGF_{165}$ for binding to neuropilin, they inhibit angiogenesis.

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