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To Die or Not to Die: Sema3E Rules the Game

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Refers To:
Jonathan Luchino, Mélanie Hocine, Marie-Claude Amoureux, Benjamin Gibert, Agnès Bernet, Amélie Royet, Isabelle Treilleux, Patrick Lécine, Jean-Paul Borg, Patrick Mehlen, Sophie Chauvet, Fanny Mann
Semaphorin 3E Suppresses Tumor Cell Death Triggered by the Plexin D1 Dependence Receptor in Metastatic Breast Cancers
Cancer Cell, *Volume 24, Issue 5*, *11 November 2013*, *Pages 673-685*

Sema3E, a ligand for PlexinD1, controls angiogenesis and promotes cancer invasion and metastasis. In this issue of *Cancer Cell*, Luchino and colleagues report that Sema3E also ensures breast cancer cell viability by blocking a previously unknown proapoptotic signaling cascade elicited by unliganded PlexinD1, thus behaving as a “dependence receptor.”

Main Text

Semaphorins are a large family of extracellular signals implicated in a range of developmental and physiological processes and also in cancer (Tamagnone, 2012). Semaphorin 3E (Sema3E) is a secreted member whose recognized receptor is PlexinD1. In addition to providing restrictive cues for angiogenesis, Sema3E-PlexinD1 signaling can regulate other cell types. However, there is not a unique intracellular pathway involved, and multiple effectors have been proposed, depending on cell context (Gay et al., 2011). Various reports implicate PlexinD1-dependent regulation of monomeric GTPases, leading to the inhibition of integrin-mediated cell-substrate adhesion; this is thought to regulate directional cell migration and, possibly, consensus signals for cell viability (e.g., in the endothelial lining of blood vessels). Additional studies have demonstrated that Sema3E-PlexinD1 signaling may mediate opposite functions in other contexts due to the involvement of PlexinD1-associated tyrosine kinases. This was shown by the Mann group in distinct populations of CNS neurons, which responded to Sema3E by either attraction or repulsion, depending on Nrp1 expression and VEGFR2 tyrosine kinase activation in association with PlexinD1 (Bellon et al., 2010). Notably, Sema3E does not activate VEGFR2 in endothelial cells, suggesting that functional coupling between plexins and tyrosine kinase receptors is ruled by mechanisms awaiting clarification. Furthermore, it was shown that Sema3E can induce the invasive and metastatic behavior of tumor cells by coupling PlexinD1 with the oncogenic tyrosine kinases ErbB2 and EGFR (Casazza et al., 2010).

In this issue of *Cancer Cell*, Luchino et al. (2013) report a novel function of Sema3E in cancer cells in preventing apoptotic cell death, potentially providing an alternative mechanism to account for its tumor- and metastasis-promoting function. The authors find increased Sema3E expression in advanced and metastatic human breast tumors, consistent with reports in colorectal carcinoma, melanoma, and ovarian cancer (Casazza et al., 2010 and Tseng et al., 2011). Interestingly, in this and other studies, PlexinD1 expression was also found to be consistently high in human tumors compared to normal tissues (Roodink et al., 2009), potentially supporting the relevance of an autocrine/paracrine Sema3E circuit in tumor progression.

The work of Luchino et al. (2013) is particularly exciting, because it proposes a new mechanism responsible for these functions. The authors found that ectopic PlexinD1 overexpression in nonmalignant HEK293T cells induced a significant increase in apoptosis, which was abrogated upon addition of Sema3E. The effect is mediated by the cytoplasmic domain of PlexinD1, but seems to be independent from the above-mentioned integrin regulatory activity. This paradigm fits with that of so-called “dependence receptors,” such as DCC, which mediate cell death signals basally that are blocked when ligand is present (Goldschneider and Mehlen, 2010). According to this paradigm, cells expressing dependence receptors either establish an autocrine ligand loop or become dependent on paracrine signals in the microenvironment for survival. For PlexinD1, the paradigm was validated by finding increased (PlexinD1-dependent) apoptosis in breast carcinoma cells subjected to Sema3E downregulation. Notably, Sema3E deficiency does not prevent cancer cell proliferation. The authors report unpublished data in agreement with previous studies showing that Sema3E-depleted cells grow in vitro and are equally tumorigenic in mice, although their invasive and metastatic behavior is impaired

(Casazza et al., 2010 and Tseng et al., 2011). Luchino and coworkers explain this apparent contradiction by postulating that a subpopulation of Sema3E-deficient cells capable of escaping PlexinD1-mediated death signals could emerge and be positively selected in culture (Luchino et al., 2013). Indeed, while PlexinD1 expression is quite widespread in tumor cells, Sema3E levels are much more discordant; thus, future studies may reveal mechanisms conferring independence from Sema3E survival signals. Of note, another putative ligand binding PlexinD1 with lower affinity, Sema4A, did not prove particularly active as an alternative blocker of PlexinD1-induced death signals.

To elucidate the pathway eliciting cell death downstream of PlexinD1, the authors identified an interactor of PlexinD1's cytoplasmic domain NR4A1/Nur77 and showed that this association is abrogated in the presence of Sema3E. The role of NR4A1 in the apoptotic response was confirmed by gene silencing, but the implicated molecular mechanisms are only partly understood. In presence of PlexinD1, NR4A1 may act at the mitochondria to promote apoptosis; however, it remains unclear how Sema3E can regulate this pathway. Unliganded "dependence receptors" are known to undergo proteolytic cleavage releasing an intracellular portion implicated in the death signaling cascade (Goldschneider and Mehlen, 2010). However, this is not shown for PlexinD1. Instead, full-length PlexinD1 interacts with NR4A1, suggesting its recruitment at the cell surface. Future studies could analyze potential correlations between PlexinD1, Sema3E, and NR4A1/Nur77 expression in human tumors. NR4A1/Nur77 was previously found downregulated in metastatic breast cancer, and this could account for a loss of Sema3E dependence in PlexinD1-overexpressing tumors (Figure 1A). Moreover, endothelial cells also express high levels of PlexinD1; thus, it will be interesting to study the relevance of this pathway in endothelial cells and other stromal cells in the tumor microenvironment.

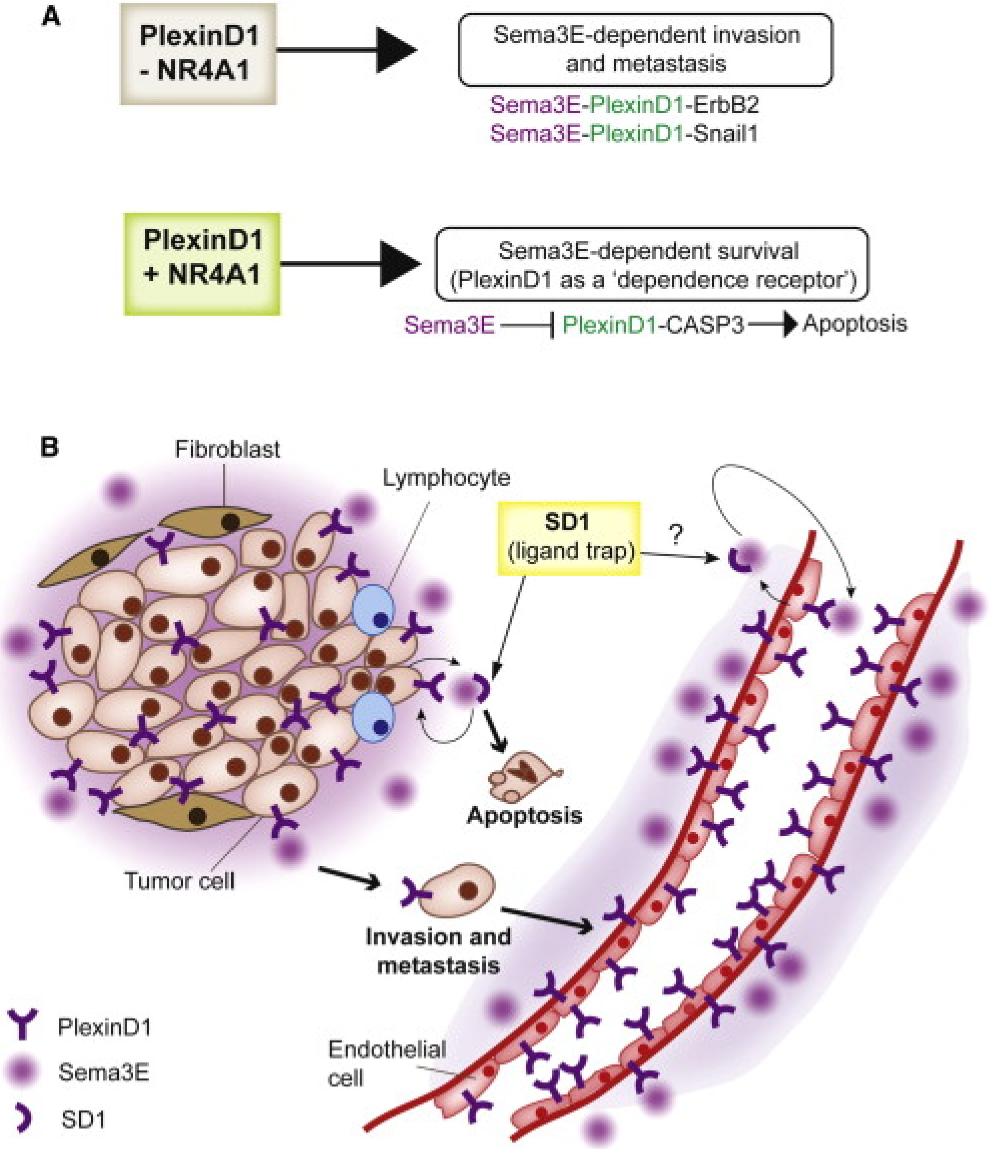
A
PlexinD1 - NR4A1
Sema3E-dependent invasion and metastasis
Sema3E-PlexinD1-ErbB2
Sema3E-PlexinD1-Snail1
PlexinD1 + NR4A1
Sema3E-dependent survival (PlexinD1 as a 'dependence receptor')
Sema3E —| PlexinD1-CASP3 → Apoptosis
B
Fibroblast
Lymphocyte
SD1 (ligand trap)
?
Apoptosis
Tumor cell
Invasion and metastasis
Endothelial cell
PlexinD1
Sema3E
SD1

Figure 1.
Sema3E-PlexinD1 Interactions Have Context-Dependent Consequences
(A) Sema3E binding to PlexinD1 can promote cancer invasion and metastasis. However, Sema3E becomes essential for cell viability when NR4A1 is associated with PlexinD1. Thus, in the presence of NR4A1, PlexinD1 acts as a "dependence receptor."
(B) The soluble extracellular portion of PlexinD1 (called SD1) was used as a Sema3E ligand trap. SD1 competes against transmembrane PlexinD1 for Sema3E binding, leaving this "dependence receptor" unliganded, which results in the apoptosis of cancer cells expressing high level of PlexinD1.

It was reported previously that interference with Sema3E signaling in preclinical mouse models can achieve a remarkable reduction of tumor growth and metastatic spreading by combined inhibition of cancer cells and tumor vasculature (Casazza et al., 2012 and Sabag et al., 2012). Here, Luchino et al. (2013) targeted tumor development by blocking survival signals mediated by Sema3E in breast cancer cells. This was achieved by overexpressing in tumor cells a soluble portion of the extracellular domain of PlexinD1, called SD1, capable of sequestering Sema3E and preventing receptor binding (Figure 1B). The affinity of this decoy receptor for Sema3E is low compared to full-length PlexinD1; however, on treatment with concentrated SD1, cancer cells underwent apoptosis, an effect that was specifically prevented by little amounts of Sema3E. Upon stable transfection of SD1, the growth of 4T1 cancer cells was inhibited due to the accumulation of the ligand trap in the conditioned medium. The authors do not provide evidence in vitro that SD1 activity is due to unleashing PlexinD1-dependent cell death signals. However, whereas SD1 overexpression in tumor cells strongly inhibited their growth in mice, tumors formed by PlexinD1-deficient cells were not affected by SD1. Thus, according to this model, downregulating PlexinD1 expression seems to be ideally suited to make tumor cells independent of Sema3E. Actually, PlexinD1 expression is rarely low in tumors and immortalized cancer cells, which supports the view that PlexinD1 can also independently elicit tumor-promoting signaling cascades in presence of the ligand. Moreover, although tumor vessels are known to express high levels of PlexinD1, they did not seem to be affected by SD1, which suggests that PlexinD1-induced death signaling is possibly a cancer cell-selective mechanism.

In a final set of experiments, Luchino et al. (2013) administered purified SD1 protein systemically to tumor-bearing mice. Consistent with applying a competitor mutated isoform of Sema3E (Casazza et al., 2012 and Sabag et al., 2012), this approach led to significant reduction of tumor growth and metastatic dissemination, confirming that Sema3E signaling in the tumor microenvironment is a relevant therapeutic target to inhibit tumor progression. In perspective, further improved molecular tools might be developed for this purpose. For instance, function-blocking antibodies are broadly applied in anticancer targeted therapy, and the potential efficacy of Sema3E- or PlexinD1-targeted antibodies will hopefully be tested in the future. Importantly, this new study expands the functions and signaling mechanisms potentially mediated by Sema3E in different tumor types; hence, efforts should be put into identifying the best applicable interfering tools in diverse characterized preclinical settings.

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