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THE ROLES AND MECHANISMS OF SEMAPHORINS ACTIVITY IN CANCER

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Abstract: Throughout embryonic and fetal development, semaphorins communicate via Plexin receptors to serve as directional cues. Their modulation of tumor angiogenesis, tumor development, cancer cell invasiveness, and metastasis is a relatively new discovery in the context of cancer. It is intriguing that activated plexins may Trans activate receptor tyrosine kinases including MET, ERBB2, FGFR2, and VEGFR2, resulting in different consequences depending on the cellular environment. In addition, several semaphorins simultaneously target endothelial and cancer cells, resulting in impressive suppression of angiogenesis and tumor development and anti-metastatic action. Taken together, these results support the idea that semaphorin signals are a viable therapeutic target for cancer treatment.

Keywords: Cell proliferation, Angiogenesis, Semaphorin, Cancer, Metasis

Introduction

The control of semaphorins has been linked to a wide variety of cancer processes, including angiogenesis, the invasiveness and metastasis of cancer cells, the growth of tumors, and the survival of cancer cells. The role of semaphorin, also known as SEMA, is contingent on the particulars of the many different histotypes of cancer. When SEMAs bind to certain receptors or co-receptors, such as Plexins, Neuropilins, and Integrins, they cause downstream effectors (such as PI3K/AKT, MAPK/ERK) to take action. For example, when SEMAs bind to Integrins, they cause the activation of MAPK/ERK [1]. This review article is intended to be read as an integrated whole, covering a wide range of topics related to semaphorins and cancer. These topics include the roles that semaphorins play in cell proliferation and survival, angiogenesis, invasion, metastasis, stemness, and chemo-resistance and response, respectively. In this article, we focused on the function that semaphorins play in the advancement of cancer by

analyzing the ways in which these proteins interact with other components of the tumor microenvironment [2]. SEMAs like SEMA3A and SEMA3B play a key part in inhibiting the growth of tumors, whereas SEMAs like SEMA3C play a role in encouraging the development of tumors. Because SEMAs all have somewhat different biological structures and each cancer histotype has its own unique features, it is necessary to examine each semaphorin as an independent entity and analyze its actions in a manner that is distinct from the other semaphorins'. It is of the utmost importance to have a more in-depth understanding of the molecular pathways that promote and sustain the malignant activity of cancer cells.

Research Methodology

Two forms of semaphorins, sema3F and sema3B, were formerly thought to work as axon guidance factors, but recent research suggests they instead act as tumor suppressors. It is not surprising that cells of tumors express high levels of semaphorin receptors, as this would explain how semaphorins might inhibit tumor cell growth and metastasis [3]. In addition, several semaphorins have been identified that inhibit tumor growth by modifying the tumor microenvironment.

Most studies have focused on how certain semaphorins affect tumor angiogenesis, but these molecules can also affect processes including the recruitment of other stromal cells like macrophages to the tumor microenvironment. Extensive studies had shown vascular endothelial growth factor A (VEGF-A) as a key mediator of angiogenesis (angiogenesis). Thanks to alternative splicing, there exists a plethora of its varieties. All splice variants of VEGF-A are bound and their signals transduced by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2 [4]. Here, this research study hypothesized that there could be receptors in endothelial cells that can discriminate between splice variants of VEGF-A, and we found that this was indeed the case. The proteins neuropilin and neuropilin-2 were identified. Our findings suggest that class-3 semaphorins, which have been implicated in axon guidance through binding to neuropilins, may also govern angiogenesis by influencing the activity of endothelial cells.

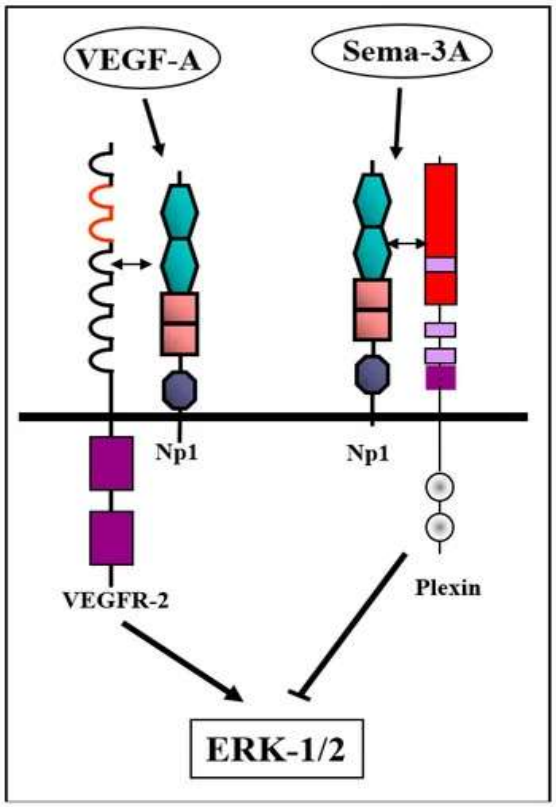

Figure 1: The pro-angiogenic signaling mediated by vascular endothelial growth factor receptor-2 is suppressed by Sema3A

(Source: [4])

Given the importance of angiogenesis to tumor growth, it seemed sense that semaphorins may affect tumor development if they controlled angiogenesis. Sema3F is one of several class-3 semaphorins that have been studied as potential cancer therapeutics due to evidence showing they suppress tumor angiogenesis and tumor growth [5].
The majority of class-3 semaphorins have been labeled as antitumorigenic and anti-angiogenic factors; nevertheless, semaphorins such as sema5A, sema4D, sema6A, sema7A and sema4A have been identified as promoters of angiogenesis and as promoters of tumor formation [6]. To that end, researchers are looking at these semaphorins as potential drug targets in the war against cancer. Many semaphorins, including Sema3C, Sema3A, and Sema3E, have been demonstrated to have opposing roles in the scientific literature, with some studies classifying them as tumor growth inducers and others as tumor growth inhibitors. It is unclear what molecular processes are at play here, but it is thought that semaphorin receptors develop complicated relationships with other kinds of membrane-bound receptors, such as tyrosine kinase receptors and adhesion receptors, among others. Sema3A, Sema3C, Sema3B, Sema3D, Sema3F and Sema3E have been covered in this study [6].

Result and discussion

Many semaphorins, including sema3A, sema3F, sema3B, and sema3E, have been the subject of extensive research into their potential implications on tumor growth. It is thought that additional, less-studied semaphorins promote tumor growth in a manner similar to that of plexins since they transduce their signal via plexin receptors. The best studied semaphorins' effects on tumor growth are described here.

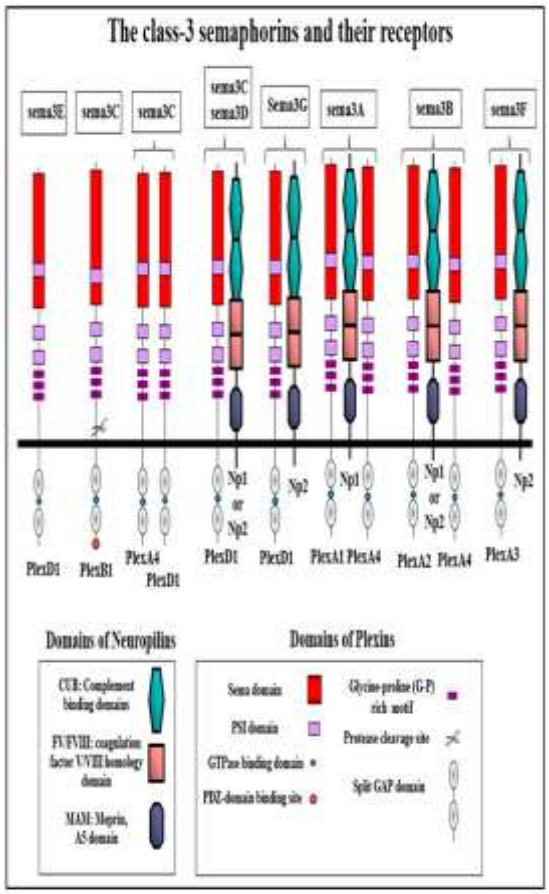

Figure 2: Class-3 Semaphorins
(Source: [7])

Sema3A:

Although other class-3 semaphorins may also transduce impulses through the neuropilin-1 receptor, Sema3A is unique in this regard. While plexin-A4 and –A1 are crucial for transduction of signal in endothelial cells and other

cell types, it seems that loss of plexin-A1 may be compensated for if enough additional plexins of A-type, such as plexin-A2, are produced.

It has been shown that Sema3A suppresses the formation of blood arteries during embryonic development. It cuts off blood flow to the developing chick's brain and limbs. In addition to acting as a vascular permeability factor, sema3A is also an anti-angiogenic semaphorin [6]. In addition, Sema3A effectively suppresses angiogenesis and tumor growth in a wide variety of solid tumors. Evidence suggests that sema3A acts as an ***"endogenous negative regulator of the angiogenic switch"*** since downregulating its expression in cells of tumor that promotes angiogenesis and progression of tumor across a range of solid tumor types. Scientists hypothesize that sema3A inhibits angiogenesis by hastening the demise of endothelial cells during prolonged activation. Inhibition of angiogenesis in vivo and tumor growth may also be achieved by over-expressing sema3A in tumor cells or by administering exogenous sema3A [7].

Sema3B:

In small cell lung cancer cells, the tumor suppressor gene sema3F is rendered inactive as a result of a combination of promoter methylation and loss of expression. So people end up taking on qualities that are shared by both sets of their parents. This protein functions as a natural defensive mechanism against endometrial cancer, despite the fact that methylation of the promoter causes Sema3B expression to be suppressed in oral squamous cell carcinoma. These data provide credence to the theory that polymorphisms in the sema3B gene are associated with a more dire outcome in prostate cancer patients [7].

As a result, the consequences of even a single nucleotide that is located in the wrong spot might be catastrophic. Those of African heritage and Hispanic descent who have a particular mutation in the sema3B gene were found to be at an increased risk of developing lung cancer. This risk was shown to be exacerbated by smoking (T415I). In addition, the expression of sema3B is reduced in stage 3 ovarian tumors and breast cancer tumors, which points to a possible role for this protein in the development of both illnesses. SEMA3A has only been shown to interact with neuropilin-1, but SEMA3B has been shown to interact with both types of neuropilin. For instance, sema3B-mediated signal transduction in endothelial cells requires both the plexin-A2 and plexin-A4 receptors; this is true for both normal endothelial cell progenitors and malignant U87MG glioma cells. Similarly, plexin-A1 receptors are required for sema3B-mediated signal transduction in vascular smooth muscle cells [8]. Direct inhibitory effects on tumor cells have been demonstrated for VEGF165, which blocks sema3B's proapoptotic actions, and VEGF121, which has no effect, both of which are involved in the aforementioned anchorage-independent development of responsive evidence that it kills lung cancer cells and causes apoptosis. The two neuropilins are selective for VEGF165 because they bind this splice variant but not the other, VEGF121. These results point to neuropilins as a potential mediator of sema3B's pro-apoptotic effects.

Sema3C:

In humans, non-MDR drug resistance has been related to a protein called Sema3C, which is created when the SEMA3C gene is expressed. Plexin-A1, -A2, and -D1 mediate the transduction of signals from np1 and np2 receptors. Its production in tumor cells is linked to tumor growth in a number of tumor types, in contrast to other class-3 semaphorins, which are related with tumor suppression. Class-3 semaphorins, including sema3C, were formerly thought to trigger angiogenesis; however, new research shows that sema3C acts as an inhibitor [9]. Sema3C is cleaved by furin-like pro-protein convertases and ADAMTS1 at conserved locations, much like the other proteins in its family.

Sema3D:

In contrast to sema3C, which conducts signal transduction through the plexin-D1 receptor, sema3D is capable of binding to both neuropilins. Over-expression of sema3D in breast cancer cells and glioblastoma cells both resulted in a decrease in the growth of tumors, an effect which was followed by a reduction in the creation of blood vessels. Although it was previously determined that sema3C and sema3E play important roles in the progression of tumors, it was just recently found that sema3D plays a role in the development of metastasis in pancreatic cancer. This finding suggests that the effects on tumor advancement may involve multiple pathways, each of which affects the progression of tumors in a different way [9].

Sema3E:

Once upon a time, scientists considered sema3E to be a metastasis-inducing semaphorin. Plexin-D1, unlike the other class-3 semaphorins, connects to and transmits signals through the plexin-D1 receptor in a very specific way. While plexin-D1 may interact with neuropilins to transduce the signals of other class-3 semaphorins like sema3A and sema3C49, it is vital to remember that this interaction may alter the cell's responses to sema3E. Sema3E, a member of the class-3 semaphorin family, acts as an endothelial cell repellent and inhibits angiogenesis [10]. During embryonic development, sema3E gradients control the formation of the dorsal aorta. The notochord and lateral plate mesoderm are the original sources of these gradients. As Sema3E is highly expressed in somites throughout embryonic development, it is possible that it inhibits vessel migration and hence limits blood vessel creation. The fact that Sema3E expression is mostly confined to the somites lends credence to this theory.

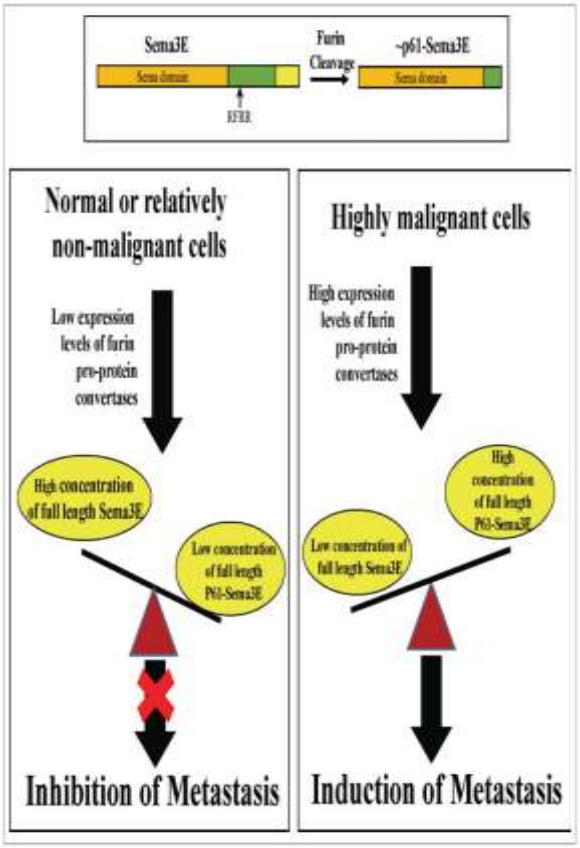

Figure 3: Duel role of Sema3E in tumor progression

(Source: [10])

In the human body, enzymes called furin like pro-protein convertases (FPPC) cleave sema3E into the active N-terminal fragment called p61-Sema3E. (Upper Panel). P61-Sema3E, in contrast to uncleaved full-length sema3E, may enhance tumor spread by boosting "in-trans" ErbB2-mediated signal transduction. This may be the case because P61-Sema3E is shorter [11]. Long-form sema3E has been shown to be beneficial against angiogenesis as well as metastasis. In contrast, malignant tumor cells have significantly elevated levels of FPPC expression. As a result, the overwhelming majority of the sema3E generated by tumor cells is cleaved to p61-Sema3E, which promotes rather than inhibits the formation of tumors.

Sema3F:

The tumor-suppressing gene sema3F was first identified in lung cancer. Recombinant sema3F, when expressed ectopically in lung cancer cells that express the sema3F receptor, inhibits the proliferation and invasion of these cells without requiring them to adhere to a particular matrix. In addition to suppressing the growth and invasion of both colon and breast cancer cells, it has also been shown to reduce the cancerous stemness of colorectal cancer cells

[11]. Similarly, sema3F SNPs were associated with an increased risk of getting prostate cancer and a worse prognosis for those who already had it. Overall, the data shows that sema3F has an inhibitory function in a broad range of malignancies by preventing the migration and proliferation of tumor cells that are sensitive to it.

Conclusion and future direction

In conclusion, at first, it was believed that semaphorins played a pivotal role in preventing tumor development and angiogenesis. Yet, evidence suggests otherwise, since various semaphorins have been shown to promote tumor development and angiogenesis.

Researchers have discovered that several semaphorins may either promote or suppress tumor development. As Sema3E demonstrates, semaphorins and their receptors may undergo major post-translational modifications that drastically alter their biological function. Recent evidence suggests that semaphorin receptors, as well as seemingly unrelated receptors like tyrosine-kinase receptors, may impact one another [12]. Understanding these interactions and post-translational alterations is crucial for creating therapeutic drugs to combat cancer and angiogenesis. Future research is expected to focus heavily on semaphorins, their receptors, and the interplay between these two systems and other signal transduction pathways. Semaphorins are expected to be the focus of a great deal of research in the not-too-distant future because of the possible role they may play in the onset of vascular illnesses including diabetic retinopathy and diabetic nephropathy. Certain semaphorins, such those found in the retina and kidney, have been demonstrated to play important regulatory roles in the development and maintenance of vascular and neuronal networks in many tissues.

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