CANCER RESEARCH

Tumor Biology

Abstract 3372: Semaphorin 3A normalizes the tumor vasculature and impairs tumor progression in a Nrp-1-independent manner

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Abstract

It is widely described that tumor vessel normalization, occurring in response to certain anti-angiogenic therapies, represents a remarkably advantageous anti-cancer strategy (1). We have demonstrated that Semaphorin 3A (Sema3A), an axon guidance cue part of class 3 semaphorins family, is an endogenous angiogenic inhibitor able to efficiently impair tumor progression, prolong the survival and normalize the tumor vasculature in different mouse models of spontaneous tumorigenesis (2). Moreover, we recently showed that Sema3A, by extending the normalization window and abrogating tumor hypoxia, overcame the resistance to the anti-angiogenic therapy inhibiting metastasis dissemination (3).

Stemming from these findings we sought to investigate the molecular mechanisms of vessel normalization and metastasis inhibition induced by Sema3A. Interestingly, by confocal microscope and western blot analysis, in a co-culture systems of human endothelial cells (ECs) and pericytes grown in contact, we observed that Sema3A dramatically down-modulated its receptor Nrp-1 in both cell types, with the consequent over-expression of PDGF-B and Ang-1, known to promote vessel maturation. Moreover, a wide screening of different genes and pathways modulated in the ECs/pericyte co-cultures revealed that the most modulated was the HGF/Met pathway. In fact, we observed that c-Met phosphorylation was impaired in FACS-sorted ECs co-cultured with human pericytes, compared to ECs grown as single layer. To better investigate the specific role of Sema3A in modulating HGF/Met activation in vessels, we detected a strong inhibition of HGF-induced Met phosphorylation in Nrp-1 silenced ECs induced by Sema3A, suggesting that this semaphorin could directly interfere with Met signaling. Notably, Sema3A impaired HGF-induced Met phosphorylation, not only in ECs, but also in several Nrp-1-silenced gastric, lung and pancreatic tumor cell lines, inducing apoptosis and blocking the invasiveness. Finally, treating an orthotopic mouse model of pancreatic ductal adenocarcinoma (PDAC) with adeno-associate virus (AAV)-8 expressing Sema3A, we observed a strong inhibition of tumor growth, a dramatic reduction of liver metastasis and a normalized and perfused tumor vessels phenotype. Remarkably, we found that Sema3A strongly and specifically inhibited Met activation in both tumor cells and vessels, in parallel to a down-modulation of Nrp-1.

We conclude that Sema3A normalizes the tumor vasculature and blocks cancer progression in a Nrp-1-independent manner, in part by inhibiting HGF/Met pathway.

References

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Previous

Back to top

July 2016
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Table of Contents

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