NATURAL BEVACIZUMAB RESISTANCE IS ASSOCIATED WITH HYPOXIA TOLERANCE AND PROLONGED ACTIVATION OF AUTOCRINE VEGF SIGNALING IN COLORECTAL CANCER CELLS AND CAN BE OVERCOME BY NINTEDANIB, A TRIPLE ANGIOKINASE INHIBITOR

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Aim: Colorectal cancer (CRC) is a common tumor type with a high mortality rate, in part due to intrinsic drug resistance. Although bevacizumab, a VEGF-directed neutralizing antibody, is particularly active in this pathology, some patients never respond for reasons not well understood. We here wish to clarify the role of autocrine VEGF signaling in the response of CRC cells to angiogenesis inhibition.

Methods: Mice with bevacizumab-sensitive or -resistant human CRC xenografts were treated with bevacizumab or nintedanib and the influence on tumor growth, viability and the expression of HIF-1alpha, HIF-2alpha, VEGF, pVEGFR1, pVEGFR2 and pS6 was determined. The influence of nintedanib and bevacizumab on HIF-VEGF signaling and viability was further characterized in CRC cells under normoxia and hypoxia.

Results: Our results show that CRC cells with intrinsic bevacizumab-resistance displayed pronounced upregulation of autocrine HIF-VEGF-VEGFR signaling in response to prolonged bevacizumab exposure whereas the same signaling pathway was downregulated in bevacizumab-sensitive xenografts. Importantly, both bevacizumab-sensitive and -resistant CRC xenografts were sensitive to nintedanib, a small molecule angiokinase inhibitor, which was associated with inhibition of mTORC1. In vitro studies revealed that bevacizumab-resistant cells displayed intrinsically higher HIF-VEGF signaling intensity and hypoxia tolerance compared to their bevacizumab-sensitive counterparts. Interestingly, although nintedanib showed comparable activity toward bevacizumab-sensitive cells under normoxia and hypoxia, the drug was three-fold more toxic to the resistant cells under hypoxia, suggesting that nintedanib attenuated the survival signaling that usually protects these cells from hypoxia-mediated cell death.

Conclusions: Our findings support a role for autocrine VEGF signaling in the survival of CRC cells to hypoxia and thus to angiogenesis inhibition. We further show that nintedanib, a small molecule angiokinase inhibitor, is active toward CRC models with intrinsic bevacizumab resistance supporting clinical trials of nintedanib in patients that do not respond to bevacizumab, alone or in combination with bevacizumab to increase angiogenesis inhibition.

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