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Chemorepulsion as a novel therapeutic concept to inhibit pancreatic cancer metastasis

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Pancreatic ductal adenocarcinoma (PDAC) has a high mortality rate primarily due to the absence of effective pharmacologic treatments and the limited effects of surgical resection in the early stages of the disease. The most frequent cause of death from the disease is due to its tendency to metastasize to the liver, at which point the chances of long-term survival drop significantly. Therefore, there is an urgent need to find a drug therapy that not only affects the primary tumor, but perhaps more importantly, prevents the formation of metastases in the liver. Neuropilin 2 (Nrp2) is a transmembrane co-receptor protein that binds a secreted protein called semaphorin 3F (S3F). Nrp2 is not expressed in the liver but is highly overexpressed in PDAC cells and PDAC-associated endothelial cells. Based on these observations, we hypothesized that S3F expression in the liver could repel metastasizing PDAC cells. As part of a series of prevention trials, we performed an IV injection of S3F expressing adenovirus in mice and thereby induced the expression of the protein in the liver. Three days later we performed an orthotopic injection of syngeneic PDAC cells. For our intervention trials, we inverted the sequence of tumor and virus injections. Our results showed a significant reduction in tumor metastases in the experimental SEMA3F-treated group compared to control virus treated mice. But the actions of Nrp2 are not limited to its ability to mediate repulsion. The tumor microvessel density and hence the overall PDAC tumor size was also reduced, thereby illustrating the systemic anti-angiogenic effects of S3F-mediated signaling via Nrp2. The action of Nrp2 on tumor growth was further elucidated by repeating the same experimental procedure in Nrp2-deficient mice. Again, we saw a reduction in size and microvessel density within the primary tumor, which validates our initial hypothesis that Nrp2 is necessary for tumor growth and angiogenesis in PDAC. In summary the therapeutic effects of inhibiting Nrp2 are twofold: First and foremost, we have shown that S3F expression in the liver will repel Nrp2-positive PDAC cells, as well as reduce tumor growth in the pancreas compared to the control. Finally, we have also demonstrated the anti-angiogenic effects of S3F.