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A sympathetic role for the pancreas in tumor progression?

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Recent reports suggest a neuro-psychological connection that increases aggressiveness of pancreatic ductal adenocarcinoma and the grim prognosis for its patients (Schuller, 2009; Schuller et al., 2012). How can stimulation of the nervous system affect pancreatic cancer, one may ask? The sympathetic nervous system (SNS) directly innervates organs such as eyes, the heart, lungs, blood vessels and digestive organs like the stomach and pancreas. Activation of the SNS and the hypothalamic–pituitary–adrenal (HPA) axis in response to a stressor causes release of the catecholamines norepinephrine and epinephrine. These two substances bind and activate α - and β -adrenergic receptors (AR) expressed on cells in these organs. Activation of AR triggers an orchestrated stimulatory and inhibitory G protein cascade resulting in downstream signaling cassettes and transcription factors that regulate cell proliferation and death (Lefkowitz, 2007; Zheng et al., 2005).

There is an extensive literature on the proliferation of pancreatic tumor cell lines in response to catecholamines and β -AR agonists *in vitro*. A number of reports exist on the use of subcutaneous xenograft models subjected to psychological stressors *in vivo*, as exquisitely reviewed by Schuller (2013). But, what is lacking in the field is an orthotopic model that has the capability of defining a specific role for SNS-innervated pancreatic stroma in stress-induced tumor progression and metastases.

In this issue of *Brain, Behavior, and Immunity*, Kim-Fuchs et al. (2014) set out to demonstrate β -AR involvement in pancreatic tumor growth and metastasis *in vivo*. Using poorly-differentiated Panc-1 human ductal adenocarcinoma cells transfected with luciferase, they implanted these cells into the tail of the pancreas of athymic nude mice and subjected them to 28 days of restraint stress (RST). Using IVIS bioluminescence analyses, the authors longitudinally tracked tumor growth in this orthotopic tumor model *in vivo*. They also evaluated local tumor cell dissemination into adjacent normal pancreas as well as distant metastases into the liver *ex vivo*. The authors found tumors in mice subjected to RST grew significantly faster (~11% per day) and presented a 10-fold increase in local tumor cell dissemination into adjacent normal pancreas. Importantly, 50% of mice subjected to RST presented with distant metastases to the liver compared to 0% in unstressed mice. To demonstrate β -AR activation was sufficient to induce pancreatic tumor progression, these observations were recapitulated in unstressed mice receiving the β -agonist isoproterenol. As further confirmation, the β -blocker propranolol suppressed these effects in mice subjected to RST. Interestingly, propranolol did not have an inhibitory effect on distant metastases in

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mice subjected to RST. This result suggested an alternate mechanism or synergy with other stress-induced pathways.

To learn if pancreatic tumor growth and metastasis were a direct result of catecholamines stimulating β_1 - and β_2 -AR-expressing Panc-1 tumor cells, or on the SNS-innervated pancreas itself, the authors analyzed Panc-1 tumor cells *in vitro* following isoproterenol stimulation. They observed cAMP accumulation – meaning β -AR *activation* – with no difference in cell proliferation. These results suggested that paracrine factors from the pancreas tumor microenvironment, or other pancreatic stromal cells, may be essential for promoting tumor cell proliferation *in vivo*. These data contradict studies demonstrating Panc-1 cell proliferation in response to both norepinephrine (Huang et al., 2012) and isoproterenol (Lin et al., 2012) *in vitro*, a phenomenon that may be explained by the level of β -AR stimulation (Wang et al., 2012). However, similar to both these reports, the authors did find that isoproterenol induced tumor cell migration. Panc-1 cells expressed modest levels of MMP2 and MMP9 (2- to 4-fold mRNA increases) in response to isoproterenol *in vitro*. In contrast, species-specific qRT-PCR from Panc-1 tumor xenografts showed tumor cell MMP9 mRNA was up-regulated 54-fold and pancreatic stromal cell MMP2 mRNA was increased 100-fold compared to unstressed mice. This finding, which is analogous to pancreatic tumors from patients (Määttä et al., 2000), highlights the importance of β -AR activation in the pancreatic tissue environment in promoting tumor cell dissemination.

These data represent a significant step forward in the field because the authors utilized an orthotopic mouse model of human pancreatic cancer. Because of the location of organs such as the pancreas, orthotopic implantation using laparoscopic techniques is not a trivial issue. Since previous *in vivo* studies were non-orthotopic in nature, any contribution of the tumor microenvironment or pancreas tissue itself toward tumor growth or cell dissemination cannot be conclusive. It must be considered, however, that the authors did not address any contribution of stress-mediated glucocorticoid signaling. Further, these results should be verified in other models of stress, like social disruption/reorganization, which better emulate the complications and stressors we face in daily life (Avitsur et al., 2009). Nevertheless, the significance of this report by Kim-Fuchs and colleagues include the first use of an orthotopic model of pancreatic cancer that is able to conclusively demonstrate a role for β -AR activation in tumor progression and tumor cell dissemination into adjacent normal pancreas *in vivo*. Additionally, these data offer support for new hypotheses to understand how pancreatic stromal cells contribute to tumor progression and spread that may be responsible for recurrence following primary tumor resection.

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References

- Avitsur R, Powell N, Padgett DA, Sheridan JF, 2009 Social interactions, stress, and immunity. Immunol. Allergy Clin. North Am. 29 (2), 285–293. [PubMed: 19389582]

- Huang XY, Wang HC, Yuan Z, Huang J, Zheng Q, 2012 Norepinephrine stimulates pancreatic cancer cell proliferation, migration and invasion via β -adrenergic receptor-dependent activation of P38/MAPK pathway. *Hepatogastroenterology* 59, 889–893. [PubMed: 22020907]
- Kim-Fuchs C, Le CP, Pimentel MA, Shackelford D, Ferrari D, et al., 2014 Chronic stress accelerates pancreatic cancer growth and invasion: a critical role for beta-adrenergic signaling in the pancreatic microenvironment. *Brain Behav. Immun.* 40, 40–47. [PubMed: 24650449]
- Lefkowitz RJ, 2007 Seven transmembrane receptors: something old, something new. *Acta Physiol. (Oxf.)* 190, 9–19. [PubMed: 17428228]
- Lin X, Luo K, Lv Z, Huang J, 2012 Beta-adrenoceptor action on pancreatic cancer cell proliferation and tumor growth in mice. *Hepatogastroenterology* 59, 584–588. [PubMed: 22353526]
- Määttä M, Soini Y, Liakka A, Autio-Harmainen H, 2000 Differential expression of matrix metalloproteinase (MMP)-2, MMP-9, and membrane type 1-MMP in hepatocellular and pancreatic adenocarcinoma: implications for tumor progression and clinical prognosis. *Clin. Cancer Res.* 6 (7), 2726–2734. [PubMed: 10914717]
- Schuller HM, 2009 Is cancer triggered by altered signalling of nicotinic acetylcholine receptors? *Nat. Rev. Cancer* 9, 195–205. [PubMed: 19194381]
- Schuller HM, 2013 The neuro-psychological axis of pancreatic cancer as a novel target for intervention. *Pancreat. Disord. Ther.* 3, 124.
- Schuller HM, Al-Wadei HA, Ullah MF, Plummer HK 3rd, 2012 Regulation of pancreatic cancer by neuropsychological stress responses: a novel target for intervention. *Carcinogenesis* 33, 191–196. [PubMed: 22072614]
- Wang L, Liu H, Chen X, Zhang M, Xie K, et al., 2012 Immune sculpting of norepinephrine on MHC-I, B7–1, IDO and B7-H1 expression and regulation of proliferation and invasion in pancreatic carcinoma cells. *PLoS One* 7, e45491.
- Zheng M, Zhu W, Han Q, Xiao RP, 2005 Emerging concepts and therapeutic implications of beta-adrenergic receptor subtype signaling. *Pharmacol. Ther.* 108 (257), 268.