

# Increased neutrophil infiltration as a body-wide effect in pancreatic cancer development



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Cancer has long been considered a systemic disease that can actively perturb normal host organs even from distant anatomic sites.<sup>1</sup> Such perturbations will likely induce alterations in gene expression and protein networks within those organs that could ultimately affect the organism's physiology<sup>1</sup> and may cause tissue damage beyond the tumor itself.<sup>2</sup> We now know a great deal of gene expression landscapes in tumor tissues and the adjacent normal tissues. However, our knowledge of other body-wide non-tumor organs is still limited. An earlier study provided some clues of the tumor effects on body-wide transcriptomes in a subcutaneous brain cancer model.<sup>3</sup> In a recent issue of *eBioMedicine*, Jiang and colleagues provided new insights into the body-wide molecular alterations in early pancreatic intraepithelial neoplasia, (PanIN) and late stage pancreatic ductal adenocarcinoma (PDAC) of mouse models of pancreatic cancer.<sup>4</sup> The study found that the number of DEGs (differentially expressed gene) in the non-tumor organs was generally several-fold higher in mice with PDAC than with PanIN. This is not surprising as the degree of tumor-driven systemic perturbations is expected to increase with tumor progression.

Comparing the transcriptomes of seven mouse organs: liver, lung, colon, stomach, kidney, heart, and brain, from animals with and without PanIN or PDAC, the number of DEGs varied greatly at the different organs, with the colon having the highest and the brain having the lowest levels affected by cancer or precursors in the pancreas compared to controls. Interestingly, the numbers of DEGs in liver and lung increased substantially from early stage to late stage, and liver and lung showed the highest number of upregulated genes among all seven mouse organs in late stage disease. It is tempting to speculate that the high burden of gene

perturbations in the liver and lung in PDAC-bearing animals may in part suggest why liver and lung are the two most common sites of metastasis of pancreatic cancer.

In recent years, mounting evidence indicates that neutrophils participate in each step of carcinogenesis, from tumor initiation to growth and metastasis.<sup>5</sup> In pancreatic cancer, neutrophils infiltrate pancreatic tumors at higher levels compared to normal pancreas; PDAC patients with high neutrophil infiltration have a worse prognosis.<sup>6,7</sup> Interestingly, the study by Jiang and colleagues found increased neutrophil infiltration in multiple organs at early stage of PDAC. The neutrophil infiltration was most prominent in the liver and lung, again the two most common metastatic sites of PDAC. Neutrophils are thought to be recruited to the pancreatic tumors by chemokines and other signaling molecules released from tumor cells.<sup>8</sup> But how do neutrophils accumulate in non-tumor organs? Studies have shown that tumor-derived factors released from primary tumor site could systemically condition distant sites for potential metastases.<sup>5</sup> In fact, early neutrophil accumulation at distant sites may be an indication for future metastasis.<sup>5</sup> The study by Jiang and colleagues provides further evidence of neutrophils filtration in non-tumor organs of PDAC mouse models. Just as macrophages could be characterized by several functional subtypes, neutrophils could also have different subtypes with opposing functions. Neutrophils at the PanIN stage are found to have greater migratory capacity but not immunosuppressive qualities.<sup>9</sup> In contrast, the neutrophils are less migratory and more immunosuppressive at later stages of PDAC.<sup>9</sup> In this context, more work is needed to characterize and understand the factors leading to neutrophil accumulation and activation in the non-tumor sites.

The study by Jiang and colleagues further explored a neutrophil-derived metabolite, LTB<sub>4</sub>, as a PDAC biomarker. From the study, it is clear that a subset of PDAC patients have elevated blood LTB<sub>4</sub> levels in comparison to both healthy controls and chronic pancreatitis. Combination of CA 19-9 and LTB<sub>4</sub> resulted in an impressive high area under the curve (AUC) value in distinguishing PDAC from healthy and chronic pancreatitis controls. Apparently, this is a single study with

**eBioMedicine 2022;81: 104089**

Published online xxx

<https://doi.org/10.1016/j.ebiom.2022.104089>

<https://doi.org/10.1016/j.ebiom.2022.104089>

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2022.104050>

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relatively small sample size. Expanding this study with larger patient cohorts and samples collected from multiple institutions would be required to validate these findings.

By investigating the body-wide gene expression landscapes influenced by the tumor-driven systemic perturbations, the study by Jiang and colleagues provides new evidence supporting the concept that cancer is a systemic disease. The findings that neutrophils accumulate in non-tumor organs at early stage of cancer is intriguing. Are the neutrophil infiltration in non-tumor organs simply an inflammatory response or early pre-metastatic niche? Can the neutrophil infiltration in the early stage of PDAC be exploited as an imaging marker for early detection? Future research is required to study the mechanisms of neutrophil infiltration and potential clinical implications.

#### Contributors

RC and SP wrote and edit the commentary. All authors have approved the final version.

#### Declaration of interests

The authors declare no conflicts of interest related to this work.

#### Acknowledgements

The authors thank Lisa A Lai (University of Washington, Seattle, WA) for her editorial assistance. The authors of this commentary are supported by grant funding from National Institutes of Health (NIH) under grant R01CA211892 and R01CA180949.

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