Editorial

Killer on the road?—cells from pancreatic preneoplastic lesions disseminate through pancreatic ducts on their way to cancer

Heiner Schäfer[1], Arne Traulsen[2], Susanne Sebens[1]

[1]Institute for Experimental Cancer Research, Kiel University & University Hospital Schleswig-Holstein Campus Kiel, Kiel, Germany; [2]Max Planck Institute for Evolutionary Biology, Plön, Germany

Correspondence to: Susanne Sebens, PhD. Group Inflammatory Carcinogenesis, Institute for Experimental Cancer Research, Christian-Albrechts-University Kiel and UKSH Campus Kiel, Arnold-Heller-Str. 3, Haus 17, 24105 Kiel, Germany. Email: susanne.sebens@email.uni-kiel.de.

Comment on: Makohon-Moore AP, Matsukuma K, Zhang M, *et al.* Precancerous neoplastic cells can move through the pancreatic ductal system. Nature 2018;561:201-5.

Submitted Feb 22, 2019. Accepted for publication Mar 05, 2019.
doi: 10.21037/hbsn.2019.06.03
View this article at: http://dx.doi.org/10.21037/hbsn.2019.06.03

Pancreatic ductal adenocarcinoma (PDAC) is ranked the fourth most common cause of cancer related deaths in western countries with a 5-year survival rate of less than 8% (1). It is estimated to be even the second most common cause by 2030 as there are no successful treatment options (2). Due to the lack of early and specific symptoms as well as non-invasive biomarkers, the majority of patients is diagnosed at an advanced and already metastasized disease stage, where palliative treatment remains the only option (3). Thus, in order to improve the dismal prognosis of PDAC patients, a much better understanding of PDAC evolution is urgently needed allowing earlier detection of the disease and providing novel therapeutic modalities. It is well appreciated that the most common precursor lesion of PDAC is the pancreatic intraepithelial neoplasia (PanIN) (4). According to the progression model (5,6) and supported by genetic studies, PanINs develop from low-grade to high-grade lesions finally leading to an invasive carcinoma. This progression is characterized and driven by the acquisition of genetic (and epigenetic) alterations. In fact, mutations in the oncogene *kras*, being one of the earliest genetic alterations, are present in 99% of even early low-grade PanINs (PanIN1) (5,6). In resected PDAC tissues, PanINs are often found in and around the tumor mass (7). Genetic analysis revealed that PanINs and adjacent carcinoma tissues share many common mutations albeit some mutations are apparently acquired not until the carcinoma stage (8,9). These data indicate that PDAC may origin from neighboring PanINs. However, the biology and genetic relationship between PanINs and PDAC and thereby PDAC evolution is still poorly understood.

Murphy *et al.* showed that pancreatic ductal epithelial cells at the PanIN stage already acquire a pronounced mutational burden, but still remain non-invasive, indicating that a long preneoplastic/premalignant stage precedes the onset of an invasive PDAC which requires further genetic and chromosomal abberations (8). In contrast, Notta *et al.* provide experimental evidence that some PDACs do not progress from PanINs in a linear and slow manner. They demonstrated in a certain number of PDACs complex rearrangement alterations presumably leading to simultaneous rather than sequential acquisition of malignant traits including invasive abilities (10). In light of these findings, the recently published study by Makohon-Moore *et al.* provides further insights into the understanding of how PDACs may evolve from PanINs (11). In their study, the authors envisioned three distinct scenarios for the evolution of PDAC from PanINs: (I) PanINs and PDAC do not have any somatic gene mutations in common and thus develop independently from each other; (II) certain mutations (passenger as well as driver mutations) are found in both PanINs and PDAC, however, PDAC contains additional alterations which are not found in PanINs, implying the existence of a common ancestral cell of PanINs and PDAC but the common ancestral as well as the founding PanIN cell yet lack genetic hits which are required to form a

malignant PDAC; (III) PanINs and PDAC share all driver mutations and some passenger mutations implying that the common ancestral cell has acquired all alterations required for malignant PDAC including invasive capabilities.

To distinguish between these three scenarios, whole-exome sequencing with subsequent phylogenetic analysis was performed of laser-capture microdissected PanINs and PDAC isolated each from 8 PDAC patients. In each of them, PanINs (PanIN2 or PanIN3) were determined in an anatomically region distinct from PDAC. Analysis of this cohort revealed that in 2 patients PanINs and PDAC display a *KRAS*^{G12D} missense mutation but did not share any passenger mutations. These findings point towards scenario 1 that PanIN and PDAC have evolved independently and both lesions accidentally acquired the *kras* mutation (considering the high frequency of *kras* mutations in more than 90% of PDAC). In 4 patients, certain driver mutations and various passenger mutations identified in the PDAC lesions were already found in PanINs of the same pancreas, too, but PDAC tissues exhibited additional driver mutations and other genetic alterations pointing towards scenario 2. Finally, analysis of PanINs and PDAC lesions from 2 patients revealed that PanINs and PDAC share several passenger mutations and all driver mutations, supporting the view that a single common ancestral cell has already acquired invasive abilities leading to its spreading in the ductal system, thus pointing towards scenario 3.

Since PanIN and PDAC lesions were dissected from anatomically different sites in the same pancreas, the cases pointing towards scenario 2 and 3 support the view that single cells—after having acquired distinct genetic alterations—are able to disseminate through the ductal system to initiate another coevolving neoplasm. Hence, PanINs and PDAC lesions in one patient may originate from a common ancestral cell involving intraductal spreading already at the precursor stage. Certainly, further studies on larger patient cohorts are needed to further substantiate our understanding according to which evolutionary scenario PDAC lesions and spatially divergent PanINs develop. In addition to new insights on the tumor evolution, these findings also provide further evidence for an early dissemination of pancreatic ductal epithelial cells already at PanIN stages (12). Studies using cell tracking in an endogenous PDAC mouse model system already demonstrated that pancreatic ductal epithelial cells in PanINs harboring a *kras* mutation undergo Epithelial-Mesenchymal-Transition by which they become enabled to enter the circulation and seed to the liver. However, outgrowth of these early disseminated pancreatic ductal epithelial cells to overt metastases requires (genetic/epigenetic) acquisition of further pro-metastatic traits (12-14). Even though it is still not clear whether intraductal spreading of pancreatic ductal epithelial cells relies on the same mechanisms and invasive traits as systemic dissemination, these findings greatly challenge the current view that PanINs are regarded as still benign (= non-invasive) precursor lesions. Accordingly, Notta *et al.* also conclude from their analysis that a single genetic hit might provide both invasive and metastatic properties to pancreatic ductal epithelial cells additionally implying a short latency period between the evolution of an invasive clone and its ability to systemically disseminate (10,12). Additionally, assuming that acquisition of invasive abilities is an early event in PDAC evolution, the question arises what might be the potential fitness advantage of this genotypic and phenotypic alteration? One explanation might be that by early spreading to different sites newly evolved clones enhance the probability to encounter environmental conditions in which these cells harboring a particular genotype are (concomitantly or later) selected, leading to clonal expansion and thereby tumor outgrowth. This applies to systemic but also intrapancreatic spreading of cell clones, because even within one organ microenvironmental conditions may vary, e.g., due to the availability of growth factors, inflammatory mediators, oxygen or metabolites. Accordingly, it could be shown that chronic inflammatory microenvironments due to aging reduce the fitness of B cell progenitor cells. However, mutations in the oncogene *NRAS*^{V12} or *Myc* confer a fitness advantage to the cells because they become enabled to better cope with aging-associated functional cellular defects so that these cells experience selection by the changed microenvironment (15). Hence, further studies are required that unravel which genetic and epigenetic alterations provide invasive and metastatic abilities (and other phenotypes) already to precursor cells. Furthermore, we need to better understand whether every PanIN acquires the ability to disseminate (intrapancreatically and systemically) or whether non-invasive and invasive PanINs may exist and, finally, which microenvironmental changes are required to select distinct geno- and phenotypes in PDAC evolution. Understanding the evolutionary aspects of PDAC initiation may then pave

the way for novel treatment strategies.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Schäfer H, Traulsen A, Sebens S. Killer on the road?—cells from pancreatic preneoplastic lesions disseminate through pancreatic ducts on their way to cancer. HepatoBiliary Surg Nutr 2019;8(4):392-394. doi: 10.21037/hbsn.2019.06.03

