Editorial

The contributions of hypoxia to poor outcomes in pancreatic cancer

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Cells need oxygen to efficiently synthesize energy carriers through the electron transport chain. In the absence of oxygen, this occurs much less efficiently and is not preferred in normal cells. In fact, a lack of oxygen (hypoxia) is a danger to most tissue types, and cells are endowed with robust response mechanisms to cope with this austerity. Hypoxia-inducible factor 1-alpha (HIF1α) is central in the signaling cascade that senses hypoxia and mounts the appropriate responses (1). HIF1α levels and activity are post-translationally rather than transcriptionally regulated: in the presence of oxygen, HIF1α levels are kept low by ubiquitylation and subsequent degradation. In the absence of oxygen, this degradation is prevented and HIF1α accumulates. Together with its beta subunit, the transcription of target genes is then initiated. These genes are involved in for instance angiogenesis [vascular endothelial growth factor (VEGF) (2)], and tissue homeostasis [Sonic Hedgehog (3,4)].

Tumor cells utilize metabolic routes not favored by normal cells (5). For instance, cancer cells have long been known to rely on glycolysis even when sufficient oxygen is available, and may use nutrients that are not likely sources for non-malignant cells (6). As a consequence of this flexibility, cancer cells are much less hindered by hypoxia than healthy cells are. Instead, hypoxia in cancer tissue is typically associated with highly unfavorable tumor biology and clinical outcome (7). It appears that the HIF1α-driven gene expression programs that function to salvage normal tissue, endow cancer cells with increased malignant properties. In fact, some tumors may even overexpress HIF1α under normoxic conditions to initiate the transcription of genes that support their proliferative, invasive and therapy resistant capacities (8).

One cancer type in which metabolic flexibility is particularly high and thought to contribute to poor outcome is the most common form of pancreatic cancer; pancreatic ductal adenocarcinoma (PDAC) (9). These cancers are characterized by an abundance of non-tumor cells and extracellular material together known as stroma (10). The mechanical properties of the dense stroma hamper perfusion which limits the penetrance of for instance chemotherapeutics, but also nutrients such as oxygen. In addition, mechanisms that drive HIF1α accumulation and transcriptional activity in cases (or tumor regions) in which oxygen is sufficiently present may also be at play. Given the extremely poor prognosis of PDAC, and frequent occurrence of HIF1α expression in this disease, the contributions of hypoxia to poor outcome are of large (pre) clinical interest (7).

In the study by Zoa *et al.* published in this issue of *TCR*, the contributions of HIF1α expression to outcome in PDAC are reported (11). The authors performed a systematic search for publications that report HIF1α expression (by immunohistochemistry) and clinical data,

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and performed a meta-analysis on the key outcome variables from 11 publications including 764 patients. In this group, 408 patients were reported as HIF1α-high and 356 were defined as HIF-1α low. In line with previous observations from biomedical and clinical studies, the authors found that high HIF1α levels strongly associate with unfavorable tumor characteristics such lymph node metastases, higher tumor staging, and as a result poor prognosis with hazard ratios approaching 2. An interesting finding is that tumor size, which is often associated with poor vascularization and thus hypoxia, was not significantly associated with HIF1α.

This also brings up a possible caveat of the study: whether the HIF1α in the included sections is upregulated by hypoxia, or molecular mechanisms that drive HIF1α accumulation in normoxic conditions [e.g., *VHL* mutations (12)] cannot be discerned. Therefore, it is hard to untangle the contributions of true hypoxia from a more general genetic dysregulation that may impact on HIF1α but also numerous other tumor-promoting pathways. In addition, immunohistochemical assessments rely on sampling of the tumor and are subject to intratumor heterogeneity. Indeed, the very high prognostic signal from by direct imaging-based measurements of hypoxia in the entire pancreas [see (13)] suggests that HIF1α staining may under-report hypoxic foci in the tumor mass that are all at risk of generating highly malignant populations. A final concern that also pertains to heterogeneity between the studies included: patient characteristics, analysis methods, biomarker cutoff levels, and clinical annotation may differ widely (as also commented on by the authors). It is likely that a more homogenous group, analyzed by standardized means, and with much richer clinical annotation, would yield much more information.

These limitations notwithstanding, the work by Zoa *et al.* (11) is a solid basis from which to initiate follow-up research. The link between HIF1α and poor outcome has been further consolidated, which will hopefully accelerate the development of clinically applicable inhibitors or biomarkers to guide current treatments, for instance radiation.

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