Nerve fibers in the tumor microenvironment

Chapter 9

Impact paragraph

Societal impact and scientific relevance

Globally, cancer ranks as a leading cause of death and a critical burden of disease. PCA is the 14th most commonly diagnosed malignancy and the 7th leading cause of cancer mortality. Furthermore, research shows the incidence and mortality are overall increasing[1]. The incidence of PCA shows regional differences in distribution: the regions with high incidence are developed countries including North America, Europe, Australia and Asia, the rates in low-income nations are much lower than those in North America and Europe[2].

Although the incidence of CCA shows geographical variation worldwide as well, the global incidence of CCA is < 2/100,000, therefore it is considered a rare cancer globally[3]. The highest incidence of iCCA is in Asia (6.1/100,000), while the lowest incidence of iCCA is in Oceania (1.8/100,000). In general, we need to continue to investigate and improve our understanding of the basic biology of PDAC and CCA to reach more effective personalized treatment approaches for CCA and PDAC patients and potentially extend life expectancy and increase treatment options.

The research field of the TME in cancer is evolving, however we conclude that research focusing on small nerve fibers in PDAC and CCA is still limited. In the current thesis, we propose that high nerve fiber density is a potential prognostic biomarker. This is a valuable finding from a clinical point of view as it might lead to the development of a new reliable prognostic biomarker for CCA and PDAC patients after surgery. The evaluation of nerve fiber density can be easily analyzed with one additional immunohistochemical staining and could be integrated in the routine pathology report.

This thesis provides first steps for further research in neuroscience and PDAC and CCA. Our target population included PDAC and CCA cohorts from the University Hospital RWTH Aachen, because these cohorts were available in the archives of the pathology department. All patients had localized disease and underwent surgical resection with curative intent. The study design in this thesis was retrospective.

Novelty of the concept

In this thesis, we focused on the density of small nerve fibers in different types of "neurotropic cancer" rather than the well-known concept “perineural invasion (PNI)”. Nerve fiber density (NFD) is determined as the number of small nerve fibers in the TME, while perineural invasion refers to larger nerve fibers with the presence of tumor cells invading the perineurium.

PDAC and CCA are in close anatomical location but they have some different histological characteristics. These histological differences reflect the molecular heterogeneity of cancer entities. We observed that high NFD is predictive for a good outcome and can be used as a novel prognostic biomarker in both CCA and PDAC patients. In contrast to this, we could not identify NFD as a prognostic biomarker in Hepatocellular carcinoma (HCC) (not in this thesis)[4].

Nerve fibers are a component of the TME but have not been highlighted much, more is known about the role of fibroblasts and immune cells in cancer initiation and progression. PDAC and CCA are known for the PNI growth pattern, associated with a poor outcome. Here, we presented the novel hypothesis of a dual role of nerve fibers: besides the aggressive PNI, also protective nerve fibers exist. The underlying pathway behind the presence of NFD needs to be further investigated. Also, the potential role for new therapeutically targets is still under investigation.

Future plan

Valorization

We described high nerve fiber density in PDAC, pCCA and iCCA patients to be associated with a better outcome. In this thesis, we conclude that our results provide basic evidence for exploration of future nerve fiber research in cancer patients. The underlying pathway still must be identified, and further research is needed. Next steps would be to further unravel the spatial context of the small nerve fibers combined with a spatial genomic approach. New techniques allow single cell RNA sequencing on FFPE blocks with the advantage the spatial context is kept. Using these methods, it will allow to closely investigate the transcriptomic status of the patients with high and low NFD. Recent work has demonstrated that in a mouse model axonal sprouting from pre-existent nerve fiber trunks is protective in PDAC[5]. Increasing knowledge on the role of nerve fibers in cancer is important to improve personalized medicine for cancer patients.

Reference

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