Immune profiling of combined hepatocellular-cholangiocarcinoma

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INTRODUCTION

Combined Hepatocellular-Cholangiocarcinomas (cHCC-CCA) represent 1 to 5% of primary liver cancers and are characterized by a poor prognosis.
No systemic therapy has shown any efficacy. There are few available data on the immune microenvironment of this type of tumors, and it is unknown whether patients could be candidates for immune-modulating therapies.

AIM

Our work aimed to characterize the immune profile and its impact on the prognosis of cHCC-CCA.

METHOD

We conducted a multicenter study of 96 patients with cHCC-CCA from four French and one Vietnamese centers. The immune microenvironment was investigated by means of gene expression profiling and immunohistochemistry/digital pathology. Total mRNA of tumor tissue was extracted from formalin-fixed paraffin-embedded tissue blocks. The Nanostring Immuno-Oncology 360 panel was used to obtain the expression of 750 genes involved in adaptive and innate immunity, T and B cell function and proliferation, antigen presentation and immune exshaution. Immune cell densities were quantified from digital slides of immunohistochemical stainings (CD3, CD8, CD20, CD68, MPO) using Qupath image analysis software. Data were analyzed with hierarchical unsupervised clustering and functional enrichment analysis.

RESULTS

Two distinct subgroups of cHCC-CCA were identified by hierarchical clustering analysis: an "Immune-High" subtype and an "Immune Low" subtype (Figure 1). Immune-high tumors represented approximately 60% of cases. Our results showed that anti-tumor immune responses were more active in this group with overexpression of genes involved in antigen presentation, immune cells recruitment, cytotoxicity and adaptive and innate immunity (Figure 2). The densities of main immune cells (CD3+ and CD8+ T cells, CD20+ B cells, CD68+ macrophages, and MPO+ neutrophils) were higher in immune-high tumors (Figure 3). Finally, patients with immune-high cHCC-CCA had better overall survival (multivariate analysis, p = 0.034). (Figure 4)

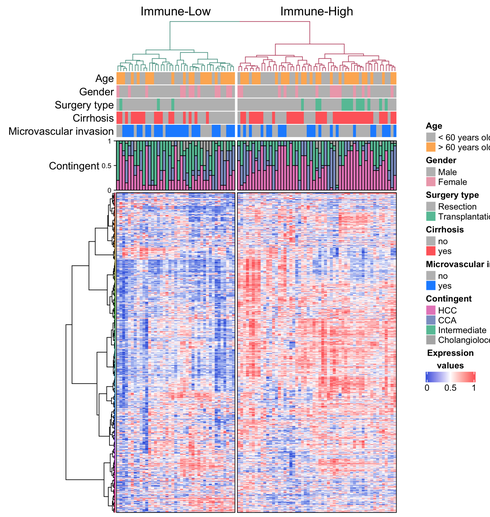

Figure 1. Unsupervised hierarchical clustering of 96 cHCC-CCA identifies two main immune subtypes

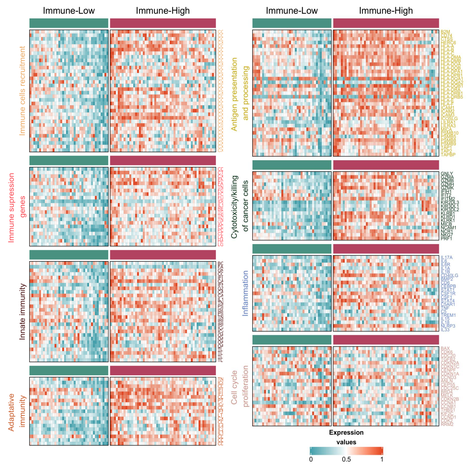

Figure 2. Activation of various immune pathways in immune-high cHCC-CCA

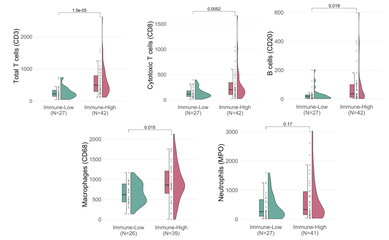

Figure 3. Quantitative immunohistochemistry shows increased densities of main immune cell subsets in immune-high cHCC-CCA

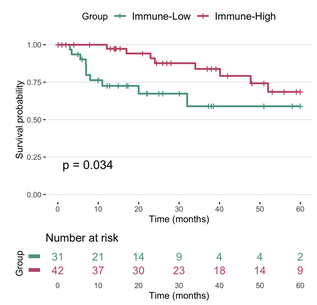

Figure 4. Prognostic impact of the immune-high subtype of cHCC-CCA

CONCLUSIONS

We have identified an Immune-High subtype of cHCC-CCA characterized by on going *in situ* immune responses and a better prognosis.

Patients with this subtype of cHCC-CCA may benefit from immunomodulating therapeutic approaches.

The immune subtype could also be used patients stratification/prognosis prediction.

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