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The intratumor mycobiome promotes clear cell renal cell carcinoma progression via neutrophil-mediated immune suppression

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Background

Polymorphic microbiota profoundly influences tumor progression, yet the renal tumor mycobiome remains largely unexplored.

Methods

Fluorescent in situ hybridization and fungal cultures from ccRCC tissues were applied to roughly estimate the fungal loads. Fungi-enriched DNA extraction followed by deep shotgun metagenomic sequencing comprehensively characterized the mycobiome within 52 paired ccRCC cancerous and paracancerous tissues from patients. Subcutaneous RCC murine models were employed to assess the influence of intratumor mycobiome on tumor growth. Landscape of tumor-infiltrating immune cells was measured through single-cell RNA-seq, flow cytometry, and immunofluorescence staining.

Results

Upon confirming the presence of culturable live fungi within renal tumor tissues, we identified enriched tumor-resident *Rhizopus delemar* (*R.delemar*) in ccRCC cancerous tissues. We demonstrated that intratumor injection of *R.delemar* promoted tumor progression in murine models. Furthermore, fungal depletion by amphotericin B blocked the tumor progression. Notably, *R.delemar* significantly increased the abundance of tumor-infiltrating neutrophils while reduced that of $CD8^+$T cells, particularly CD8 effector T (Teff) cells. The infiltration of neutrophils was negatively correlated with the abundance of $CD8^+$T cells (R=-0.65, p=0.042). Indeed, *R.delemar*-induced neutrophils expressed elevated levels of immunosuppressive genes. Interestingly, depletion of neutrophils or $CD8^+$ T cells markedly reduced the tumor-promoting effect of R. delemar, indicating their essential roles in this process. Mechanistically, *R.delemar* administration specifically increased secretion of CXCL3 in RCC cells and recruit $CXCR2^+$ neutrophils into the tumor microenvironment.

Conclusions

Our study reveals alterations of intratumor mycobiome landscape in patients with ccRCC and demonstrates that intratumoral colonization of *R.delemar* promotes tumor progression in murine models. Specifically, *R.delemar* recruits neutrophils via the CXCL3-CXCR2 axis and imparts tumor-promoting properties to these cells, thereby suppressing the effector function of $CD8^+$ T cells and facilitating tumor immune escape.

Legal entity responsible for the study

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Disclosure

All authors have declared no conflicts of interest.