Niche-Specific Reprogramming of Macrophages Reveals Myeloid Cell-Centric Targets During Pro-Senescence Therapy in Liver Cancer

Authors: Efi Tsouri,[1,2] Jing Xu,[3] Masami Ando-Kuri,[1,2,4] Eduardo Martin-Quintana,[1,2] Leila Akkari,[1,2] *Serena Vegna[1,2]

1. The Netherlands Cancer Institute, Amsterdam, the Netherlands
2. Oncode Institute, Utrecht, the Netherlands
3. Sun Yat-sen University Cancer Center, Guangzhou, P.R. China
4. Sanger Institute, Cambridge, UK

*Correspondence to s.vegna@nki.nl

Disclosure: Tsouri is supported by funding from Oncode. Vegna has been awarded a KWF Young Investigator grant. Ando-Kuri and Martin-Quintana are supported by the KWF Young Investigator grant awarded to Vegna. All other authors have declared no conflicts of interest.

Acknowledgements: Tsouri and Xu contributed equally.

Keywords: Hepatocellular carcinoma (HCC), hypoxia, pro-senescence therapy, tumour-associated macrophages (TAM), tumour microenvironment (TME), tumour niches, tumour vasculature.

Citation: EMJ Hepatol. 2025;13[1]:40-41. https://doi.org/10.33590/emjhepatol/QCRI8208

BACKGROUND AND AIMS

Hepatocellular carcinoma (HCC), the main form of primary liver cancer, is an increasingly prevalent and highly heterogeneous disease.[1,2] Owing to its complexity, effective therapeutic strategies remain limited, making HCC a leading cause of cancer-related deaths worldwide.[3] Recent immunomodulatory strategies have achieved unprecedented results, revolutionising the HCC treatment landscape. However, only a small proportion of patients respond to treatments, with modest survival benefit, underscoring the need for novel combinatorial strategies targeting the tumour microenvironment (TME).

One such strategy involves the use of pro-senescence therapy, whereby cellular senescence is enforced in cancer cells to restrict their proliferation.[4] Beyond their cell-autonomous tumour-suppressive effects, senescent tumour cells can also influence the TME, offering promising therapeutic potential.

CDC7 inhibition (CDC7i) was previously identified as a promising pro-senescence treatment in *Tp53*-deficient tumours in earlier work from this group.[5,6] This study investigates the dynamic interactions between senescent tumour cells and the TME, focusing on tumour-associated macrophages (TAM) and their niche-specific roles during pro-senescence therapy.

METHODS

In this study, a *Tp53*-deficient HCC mouse model was used to evaluate the effects of CDC7i-induced cancer cell senescence on the liver TME. Two time points were selected for in-depth TME analyses, based on the kinetics of senescence induction in cancer cells, allowing TME changes during distinct phases of therapy response to be captured. At these stages, histological and spatial analyses were performed to study vasculature remodelling, T cell infiltration, and TAM distribution. To unravel TAM reprogramming during treatment, single-cell RNA sequencing was combined with high-dimensional spectral flow cytometry. Finally, to assess the translational relevance of the findings, tissue microarrays of 488 human HCC samples were analysed,[7] integrating TAM profiles and location with patient survival data.

RESULTS

Two distinct phases of therapy response were observed following CDC7i treatment. The initial response phase, characterised by progressive senescence induction in cancer cells, was accompanied by extensive extracellular matrix reorganisation, tumour vascular

remodelling, accumulation of exhausted T cells, and increased abundance of TAMs. Following this response phase, senescence induction was lost (therapy resistance, non-response phase), and the effects on tumour vasculature and T cell responses waned. In contrast, TAM accumulation persisted, suggesting a role for TAMs in limiting therapy response. Supporting this hypothesis, pan-macrophage blockade through anti-CSF-1R treatment enhanced pro-senescence therapy efficacy *in vivo*.

Analysis of TAM functions revealed that TAM subsets displayed enhanced T cell activation features during the treatment response phase, along with angiogenic capacities. This corroborated the enhanced T cell engagement and tumour vasculature remodelling observed during the initial response phase to CDC7i. As resistance emerged, TAMs were enriched in angiogenic CD36+ subsets localised in perivascular and hypoxic niches, with the latter displaying heightened immunosuppressive features. These findings highlight the influence of local microenvironmental cues in shaping TAM phenotype during pro-senescence therapy.

Spatial analysis of a large human HCC dataset[7] confirmed the perivascular and hypoxic localisation of CD36+ TAMs, corroborating findings from the HCC mouse model. Importantly, niche-specific CD36+ TAMs significantly correlated with different patient prognoses, suggesting distinct functions for these cells depending on the tumour niche they reside in.

CONCLUSION

This study reveals that pro-senescence therapy reshapes the HCC TME in a niche-specific manner, mainly by modulating TAMs. The identification of angiogenic and immunosuppressive CD36+ TAMs within hypoxic niches underscores their role in tumour progression and therapy resistance. This highlights CD36 as a potential therapeutic target to improve the efficacy of pro-senescence strategies in liver cancer.

References

1. Tsouri E et al. Crosstalk between senescent cancer cells and the TME reveals myeloid cell centric therapeutic targets in HCC. Abstract OS-005-YI. EASL Congress, 7-10 May, 2025.
2. Llovet JM et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.
3. Sung H et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
4. Wang L et al. Exploiting senescence for the treatment of cancer. Nat Rev Cancer. 2022;22(6):340-55.
5. Wang C et al. Inducing and exploiting vulnerabilities for the treatment of liver cancer. Nature. 2019;574(7777):268-72.
6. Ramirez CF et al. Cancer cell genetics shaping of the tumor microenvironment reveals myeloid cell-centric exploitable vulnerabilities in hepatocellular carcinoma. Nat Commun. 2024;15(1):2581.
7. Wu C et al. Myeloid signature reveals immune contexture and predicts the prognosis of hepatocellular carcinoma. J Clin Invest. 2020;130(9):4679-93.