The Q for immune evasion in HCC: ER stress in myeloid cells

Charlotte Rennert , Maike Hofmann

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. In most cases, HCC develops in an already perturbed liver microenvironment with pre-existing liver cirrhosis and tissue remodelling. Once a tumour nodule evolves, a complex ecosystem comprising tumour, immune, structural cells and extracellular matrix develops and forms the so-called tumour microenvironment (TME).[1] This TME is shaped by distinct metabolic networks particularly driven by metabolic reprogramming of tumour cells, which supports their function, as one of the hallmarks of cancer.[2] For example, in many cancer types, tumour cells mostly depend on glucose consumption for their energy supply, leading to lactate production and acidic conditions in the TME even with enough oxygen (Warburg effect).[3] In addition, tumour cells also heavily rely on the amino acid glutamine (single letter code: Q) for their nucleotide biosynthesis and thus proliferation as well as for lipid biosynthesis and energy supply.[4] On the other hand, similar metabolic demands also apply for highly active and proliferative immune cells such as T cells and macrophages, cell populations depending on glucose and glutamine for cell function and proliferation.[5] Consequently, harsh conditions with low nutrient availability, metabolic competition and an acidic milieu in the TME emerge and impair immunosurveillance thus fuelling immune evasion.[6] Yet, the exact mechanisms of how metabolic reprogramming of tumour cells results in immune evasion remain only partly understood.

In Gut, *Yang et al* addressed this question in a preclinical setting using mouse models and employing human samples.[7] The study was based on the observation, that in human HCC the expression of the vitamin B3 receptor, GPR109A, was associated with a poor outcome. In further analyses, the authors showed that GPR109A is primarily expressed in the infiltrating myeloid cells rather than the tumour cells themselves. GPR109A expression in myeloid cells was driven by the IRE1-α/XBP1 signalling axis of the ER stress/unfolded protein response (UPR) that in turn was triggered by a shortage of glutamine/Q. Q shortage in myeloid cells was due to metabolic competition for the amino acid with the tumour cells. In particular, tumour cells seemed to outcompete immune cells in Q uptake due to an upregulated expression of the Q receptor SLC1A5 in tumour cells. Finally, GPR109A-mediated extracellular-signal-regulated kinase (ERK) activation led to an immunosuppressive polarisation of the myeloid compartment that subsequently limited CD8+T cells' antitumour function. Thus, metabolic reprogramming of tumour cells enabling increased Q uptake resulted in Q shortage in myeloid cells thereby forming a glutamine metabolism-endoplasmic reticulum (ER) stress-immune evasion axis in HCC (figure 1). The concept of metabolic reprogramming in HCC TME eventually affecting immunosurveillance and resulting in immune evasion for example, by M2 polarisation of macrophages or inhibition of CD8+T cell-mediated tumour control through programmed cell death protein 1/ligand 1 (PD1/PD-L1) axis is established.[6] However, the findings by *Yang et al* add considerably to our knowledge of how metabolic reprogramming in tumour cells is linked to immune evasion by the induction of ER stress within myeloid cells.

ER stress can occur in various contexts such as accumulation of unfolded or misfolded proteins, loss of calcium homoeostasis, hypoxia or nutrient deprivation.[8] For instance, Q metabolism has already been associated with protein homoeostasis in the past and lack of Q has been reported to induce ER stress.[9 10] In addition, glucose deprivation, acidic microenvironment with high lactate or hypoxia are also known stimuli of ER stress within the TME.[11] In different cancer types, induction of ER stress has been associated with increased proliferation and survival of the tumour cells.[12] In liver tumourigenesis, for example, a role for upregulated ER stress signalling in combination with hepatic steatosis has already been shown[13] and reported to be linked with a more aggressive histological grading in human HCC.[14] From a more mechanistic perspective, a role for ER stress in metabolic reprogramming of tumour cells is becoming increasingly recognised, especially concerning the Warburg effect. As such, ER stress in cancer-initiating cells of head and neck cancer promotes the Warburg effect through NRF2-signalling[15] and in HCC, ER stress has also been found to be associated with metabolic reprogramming and increased risk of metastasis.[16] However, the

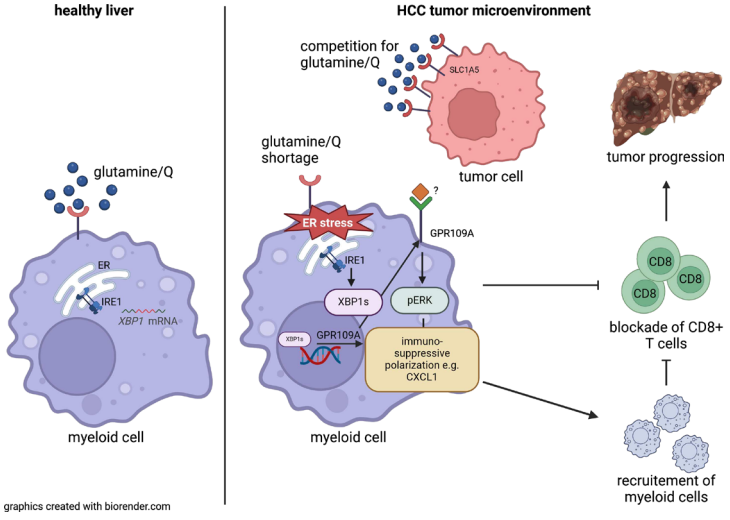

Figure 1 A glutamine metabolism-ER stress-immune evasion axis in HCC. In HCC, metabolic competition with tumour cells leads to glutamine/Q shortage in myeloid cells. Q shortage induces ER stress in myeloid cells and increases the expression of the vitamin B_3 receptor GPR109A. GPR109A activation results in immunosuppressive polarisation and additional recruitment of myeloid cells. Subsequently, antitumour CD8+ T-cell immunity is impaired. ER, endoplasmic reticulum; HCC, hepatocellular carcinoma.

Department of Medicine II, Medical Center - University of Freiburg, Freiburg, Baden-Württemberg, Germany

Correspondence to Maike Hofmann, Department of Medicine II, Medical Center - University of Freiburg, Freiburg, Baden-Württemberg, Germany; Maike.Hofmann@uniklinik-freiburg.de

impact of ER stress stimuli within the TME on tumour-associated immune cells remains poorly understood.

The study by *Yang et al* reports a clear link between a metabolite shortage-dependent ER stress response in myeloid cells and myeloid cell-mediated immune evasion in the context of HCC. In response to ER stress stimuli, the UPR serves as a basic signalling cascade ensuring protein homoeostasis and survival of cells. More precisely, three different UPR signalling cascades (IRE1-α/XBP1; PERK/CHOP; ATF6) can be activated and orchestrate the cellular ER stress response including, for example, reduction of protein synthesis, refolding or degradation of proteins. If the ER stress cannot be resolved by the UPR machinery, apoptosis is eventually induced.[8] Of the three UPR branches, the IRE1-α/XBP1 axis is evolutionary the most conserved.[17] Upon ER-stress the endonuclease IRE1-α gets activated, splices the preformed mRNA for XBP1 thus leading to protein translation of the transcription factor XBP1s.[18] *Yang et al* now showed that XBPs activate and augment GPR109A expression and thereby enable GPR109A-mediated immunosuppressive polarisation and recruitment of HCC-associated myeloid cells reflected by arginase-1, VEGF, IL-10 and CXCL1 production. While it is tempting to speculate that GPR109A is stimulated by its endogenous ligand lactate[19] that is also increased in HCC-associated TME,[6 20] future studies will have to further test this potential vicious circle and other GPR109A ligands in HCC. Nevertheless, *Yang et al* have introduced an additional role of ER stress favouring HCC progression by directing tumour-associated immune cells intrinsically toward immune evasion.

Yet, several open questions remain. First, the role of the other branches of the UPR on glutamine shortage has not been elucidated so far. Thus, it remains open, whether the seen effects are specific for the IRE1-α/XBP1 axis or rather result from a general activation of the UPR. Second, other drivers of metabolic reprogramming like the Warburg effect or hypoxia in HCC may also influence ER stress in general or the IRE1-α/XBP1 axis in particular, further shaping 'metabolic crosstalk' between tumour and immune cells. Third, metabolic reprogramming in HCC may also lead to ER stress in non-myeloid immune cells, potentially further hampering immune control of the tumour.

In sum, the study by *Yang et al* introduces a new concept on how tumour-immune crosstalk through metabolic factors and ER stress is mediated. Surely, we will learn more about this concept in future studies in order to develop further therapeutic concepts for HCC immunotherapy.

Acknowledgements We thank Robert Thimme for support.

Contributors Both authors contributed equally.

Funding Funding was obtained from the German Research Foundation (DFG), CRC 1479 (project no. 441891347) and the Heisenberg program to MH. Funding was obtained from the EXCEL program of Else Kröner-Fresenius-Stiftung to CR.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gutjnl-2024-333249).

To cite Rennert C, Hofmann M. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2024-333249

Received 11 August 2024
Accepted 19 August 2024

Gut 2024;**0**:1–2.
doi:10.1136/gutjnl-2024-333249

ORCID iDs
Charlotte Rennert http://orcid.org/0000-0003-2186-2606
Maike Hofmann http://orcid.org/0000-0001-8410-8833

REFERENCES

1 Rennert C, Lang-Meli J, Gromak M, *et al*. Perspectives for novel therapeutic concepts in hepatocellular carcinoma targeting the stromal and innate immune microenvironment. *L C Int* 2023;4:42–57.
2 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.
3 O'Sullivan D, Sanin DE, Pearce EJ, *et al*. Metabolic interventions in the immune response to cancer. *Nat Rev Immunol* 2019;19:324–35.
4 Jin J, Byun J-K, Choi Y-K, *et al*. Targeting glutamine metabolism as a therapeutic strategy for cancer. *Exp Mol Med* 2023;55:706–15.
5 Leone RD, Powell JD. Metabolism of immune cells in cancer. *Nat Rev Cancer* 2020;20:516–31.
6 Li X, Ramadori P, Pfister D, *et al*. The immunological and metabolic landscape in primary and metastatic liver cancer. *Nat Rev Cancer* 2021;21:541–57.
7 Yang Y, Pei T, Liu C, *et al*. Glutamine metabolic competition drives immunosuppressive reprogramming of intratumour GPR109A^{+} myeloid cells to promote liver cancer progression. *Gut* 2024;0:gutjnl-2024-332429.
8 Hetz C, Papa FR. The Unfolded Protein Response and Cell Fate Control. *Mol Cell* 2018;69:169–81.
9 Denzel MS, Storm NJ, Gutschmidt A, *et al*. Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell* 2014;156:1167–78.
10 Shanware NP, Bray K, Eng CH, *et al*. Glutamine deprivation stimulates mTOR-JNK-dependent chemokine secretion. *Nat Commun* 2014;5:4900.
11 Yadav RK, Chae S-W, Kim H-R, *et al*. Endoplasmic reticulum stress and cancer. *J Cancer Prev* 2014;19:75–88.
12 Zhang W, Shi Y, Oyang L, *et al*. Endoplasmic reticulum stress-a key guardian in cancer. *Cell Death Discov* 2024;10:343.
13 Nakagawa H, Umemura A, Taniguchi K, *et al*. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell* 2014;26:331–43.
14 Shuda M, Kondoh N, Imazeki N, *et al*. Activation of the ATF6, XBP1 and grp78 genes in human hepatocellular carcinoma: a possible involvement of the ER stress pathway in hepatocarcinogenesis. *J Hepatol* 2003;38:605–14.
15 Chang C-W, Chen Y-S, Tsay Y-G, *et al*. ROS-independent ER stress-mediated NRF2 activation promotes warburg effect to maintain stemness-associated properties of cancer-initiating cells. *Cell Death Dis* 2018;9:194.
16 Hu C, Xin Z, Sun X, *et al*. Activation of ACLY by SEC63 deploys metabolic reprogramming to facilitate hepatocellular carcinoma metastasis upon endoplasmic reticulum stress. *J Exp Clin Cancer Res* 2023;42:108.
17 Yang Z, Zhang J, Jiang D, *et al*. A Human Genome-Wide RNAi Screen Reveals Diverse Modulators that Mediate IRE1α-XBP1 Activation. *Mol Cancer Res* 2018;16:745–53.
18 Chen X, Shi C, He M, *et al*. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. *Signal Transduct Target Ther* 2023;8:352:352:.
19 Ahmed K, Tunaru S, Offermanns S. GPR109A, GPR109B and GPR81, a family of hydroxy-carboxylic acid receptors. *Trends Pharmacol Sci* 2009;30:557–62.
20 Yang F, Hilakivi-Clarke L, Shaha A, *et al*. Metabolic reprogramming and its clinical implication for liver cancer. *Hepatology* 2023;78:1602–24.