Epigenetic modulation of immunity: towards new therapeutic avenues in hepatocellular carcinoma?

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Liver cancer is the second leading cause of cancer-related deaths worldwide, for which therapeutic options are very limited and novel strategies alarmingly needed. The leading risk factor for hepatocellular carcinoma (HCC) is cirrhosis due to HBV and HCV viruses, alcohol abuse, genotoxic exposure and metabolic disorders increasingly associated with diabetes and obesity. HCC is the paradigm of inflammation-associated cancer, with >80% of HCC emerging consecutively to a vast remodelling of liver stroma. To restrain inflammatory response, liver parenchyma physiologically harbours a specific microenvironment to prevent the establishment of inflammation. Immune cells largely orchestrate liver protection, in particular Kupffer cells, the liver macrophages, in partnership with fibroblasts. Nevertheless, when it gets into chronicity, liver inflammation sensitises to cancer development, tumor-associated stroma being recognised as a major hallmark of cancer, as described by Hanahan and Weinberg in 2011.[1] During hepatocyte transformation, the surrounding cells, including cancer-associated fibroblasts, hepatic stellate cells, tumour-infiltrating leukocytes and tumour-associated macrophages (TAM) are abnormally activated and/or recruited. These cells secrete a cocktail of growth factors, cytokines and chemokines, which exacerbate liver inflammation and injury in favour of hepatocarcinogenesis.[2] Macrophages are the major part of immune cell infiltrates in solid tumours, and the density of macrophages is strongly correlated to poor overall survival, including in HCC. Inversely, myeloid-derived suppressor cells (MDSCs) have emerged as central players in the immunosuppressive tumour microenvironment existing in pathologic conditions such as chronic inflammation and cancer.[3] In case of tumour development, the cytokines and chemokines released from tumour microenvironment induce MDSC recruitment from the bone marrow, which in turn activates other suppressive actors like TAM or regulatory T cells and inversely impairs CD8 T cell action. Despite new insights recently provided, understanding the molecular mechanisms driving HCC immune landscape remains a challenge to unravel new therapeutic avenues.

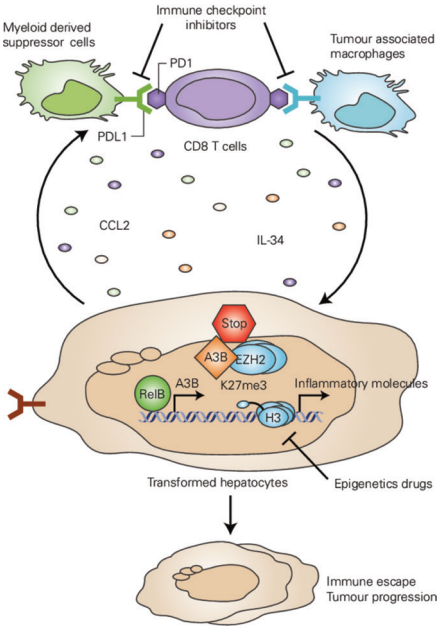

Figure 1 Immune escape in HCC is dependent on epigenetic events In inflammatory conditions, RelB induced APOBEC3B (A3B) expression by direct binding on its promoter. A3B thus impaired EZH2 activity and decreased H3K27me3 marks on the promoter regions of CCL2 and IL-34. In turn, CCL2 favors the recruitment of myeloid derived suppressor cells and tumor-associated macrophages PDL1+. Together with CD8 T cells exhibiting PD1 marker, this favors immune evasion and tumor progression. Consequently, using epigenetic drugs in combination with immune checkpoint inhibitors could be of great benefit for HCC treatment.

In these last decades, epigenetic mechanisms have emerged as crucial decision-makers of cell fate determination (proliferation, metabolic reprogramming, invasion and so on). Epigenetic modifications integrate in space and time environmental and cell inputs to finely regulate gene expression. Conventionally, the epigenetic code is divided into three major mechanisms: DNA methylation, non-coding RNA-driven regulations and histone modifications (acetylation, methylation and so on) mainly occurring on H3 and H4 histones. For example, H3K4me3 on promoter regions is a mark of actively transcribed genes. Inversely, H3K27 trimethylation driven by EZH2 (enhancer of zeste homolog 2) is associated with transcriptional repression. Interestingly, there is a growing body of evidence that epigenetic modifiers play key roles during cancer, including HCC, and could constitute future therapeutic options. In HCC, prevalent mutations in epigenetic modifiers have been largely described, such as mutations in chromatin remodellers of the SWI/SNF family, histone methyltransferases and imprinting clusters.[4] More recently, numbers of works support the importance of epigenetic events in immune response during liver tumourigenesis, via alterations in immune cell phenotype, function and infiltration. Of note, subsets of inflammatory gene promoters have been found epigenetically deregulated in cancer, that is, several inflammatory gene promoters exhibit H3K27me3 marks in macrophages and their expression required mark removal by the Jmjd3 demethylase.[5]

In the present manuscript, Wang and coworkers have interestingly shown that the promoter regions of CCL2 and IL-34, two pro-inflammatory factors, exhibited H3K27me3 marks at the basal level, which could be inhibited by the cytosine deaminase APOBEC3B (A3B) in HCC cells[6] (figure 1). By their study, the authors demonstrated that A3B, frequently found overexpressed in patients with HBV and HCC, titrated EZH2 and decreased its methylation activity. In upstream process, A3B expression was regulated by RelB, member of the non-canonical NF-κB pathway, through RelB direct binding on A3B promoter. RelB-dependent A3B expression was observed in response to lymphotoxin and lipopolysaccharide exposure, two inflammatory inducers. Several studies converge towards an interplay between the NF-κB pathway and epigenetic events during cancer: (1) the activation of histone demethylases such as Jmjd3 is dependent on NF-κB, (2) NF-κB response is influenced by chromatin state and nucleosome position and (3) NF-κB actors are regulated by microRNAs.[7] In sum, this present work unveiled that in inflammatory conditions, NF-κB pathway induces A3B expression in HCC cells promoting secretion of CCL2, which favours the accumulation

Correspondence to Dr Angelique Gougelet, UMRS1138-Team 24, Centre de Recherche des Cordeliers, Paris 75006, France; angelique.gougelet@inserm.fr

of TAMs and MDSCs displaying immunosuppressive properties such as expression of Programmed death-ligand 1 and CD8 T cells positive for the checkpoint protein Programmed death 1. Altogether, this immune contexture promotes immune escape and is therefore associated with poor overall survival in patients. A similar epigenetic-driven MDSC-dependent immunosuppression in HCC has been unveiled last year under an axis EZH2/NF-κB/IL6 orchestrated by the cell cycle-related kinase CCRK.[8] All these findings support the central role of epigenetic circuitries, which remain to be precisely defined, as a way for solid tumours to modify their microenvironment and escape from immunosurveillance.

Regarding their pleiotropic effects, epigenetic regulators have emerged as promising therapeutic targets for cancer treatment. However, epigenetic drugs have been already tested in HCC with unsatisfactory results.[9] Regarding the present findings, the impact of epigenetic remodelling occurring in cancer cells on the surrounding cells could be one cause of this failure. Accordingly, a recent work using the EZH2 inhibitor GSK126 unravelled that this drug increased MDSC infiltration and inversely decreased the level of CD4+ and IFNγCD8+T cells.[10] In consequence, it appears crucial to understand how epigenetic mechanisms could modulate immune response. This would improve the efficiency of epigenetic drugs, notably in combination with immunomodulatory therapies, which showed promising antitumour effects in HCC these recent years. Indeed, for several cancers, epigenetic drugs have been demonstrated to sensitise cancer cells to immune checkpoint blocking therapies.[11]

To conclude, the epigenetic interplay between immune and cancer cells could offer new therapeutic strategies for cancer including HCC, but it is now important to address the resulting epigenetic and transcriptional changes induced by tumour cells on their neighbouring immune cells in the near future.

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