PWE-290

ACTIVELY CONSUMING INDUCES FUNCTIONAL IMMUNE PARESIS BUT PARADOXICALLY PROMOTES ENDOTOXIN TOLERANCE IN THOSE WITH ADVANCED ALCOHOL-RELATED CIRRHOSIS

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MAPK SIGNALING REGULATES THE DEVELOPMENT OF A CHOLANGIOCELLULAR PHENOTYPE FROM HCC IN POST-TACE LIVER TRANSPLANTS

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Introduction During normal liver wound-healing, tissue injury causes inflammation and cell death, which in turn orchestrates compensatory cell proliferation and regeneration.1 If resolution of the injury cannot be obtained the resulting unchecked healing process can lead to cancer. Similar injury-induced repair mechanisms occur in response to chemotherapeutic treatments.1 We recently found that the use of pre-transplantation TACE for HCC promotes the development of a mixed cholangiocellular phenotype that is associated with the expression of CD133, a marker of hepatic progenitor cells (HPC). This phenomenon is associated with higher post-transplantation tumour recurrence.2 The molecular bases for the development of the cholangiocellular phenotype have not been investigated before. In this study we identified key oncogenic effectors involved with a “switch” from HCC to cholangiocellular phenotype resulting from liver injury induced by TACE treatment.

Methods Ten cases of post-TACE (doxorubicin/lipiodol) treated HCC examined after transplantation at King’s College Hospital were selected for the study. HCC patients not treated by TACE before transplantation were used as control group. Formalin-fixed section from main tumour mass embedded in paraffin blocks were used to perform immunohistochemistry in order to delineate which component of the MAPK signalling pathway is associated with the hepatocellular/cholangiocellular phenotype and expression of HPC markers (CD133 and CK19).

Results Among the post-TACE liver explants, approximately 50% of the neoplastic cells resembling bile ductules (cholangiocellular differentiation) showed nuclear expression of a specific phospho-activated component of the MAPK cascade. Furthermore, half of the cells positive for activated-MAPK showed proliferative activity, as determined by Ki67 staining. Expression of activated-MAPK was not detected in the non-TACE treated group of liver transplant.

Conclusion The development of the mixed hepatocellular-cholangiocellular phenotype in HCC patients after TACE-inflicted liver injury relates to activation of a specific MAPK signalling pathway that promotes proliferation of HPC. Attenuation of this signalling pathway could be used to prevent the “uncontrolled” proliferation and differentiation of progenitor cells before liver transplantation in HCC patients, and thus improving the tumour recurrence rate.

Competing interests None declared.

REFERENCES