Hepatocellular carcinoma (HCC) commonly arises in chronically inflamed livers, but may also provoke (anti-tumoral) immune responses. Using non-inflammatory diethylnitrosamine (DEN)-induced liver cancer in mice, we demonstrate that distinct axes of the adaptive immune system, which are also prognostic in human HCC, actively suppress hepatocarcinogenesis by controlling tumor formation and progression.
an essential role in controlling tumor initiation and growth within the liver. Interestingly, liver cancer apparently promotes B-cell activation, which in turn contributes to control established tumor nodules.

In order to translate our findings to human HCC, we analyzed gene array data sets from 139 human HCC samples with respect to pathways of innate and adaptive immunity (www.genome.jp.kegg). T and B cell related genes from these pathways clustered in HCC samples and defined distinct groups of favorable or poor prognosis. Downregulation of B cell related genes was associated with poor outcome, indicating that immunological mechanisms identified in the murine DEN model may also be relevant in human liver cancer.

Together, our findings and the current literature revealed important aspects on the complex role of the adaptive immune system in the establishment and growth of liver cancer (Fig. 1): On the one hand, adaptive immune mechanisms facilitate high cell turnover in inflamed livers by deleting e.g., infected hepatocytes and thereby boost the risk of malignant transformation. This is suggested by the abrogated tumor formation in inflammation-based liver cancer models through immune suppression. On the other hand, once cells are transformed, adaptive immune mechanisms play an important role in restricting liver cancer, as described in the concept of tumor equilibrium which is CD4 and CD8 T cell dependent and emphasized by the recent work of Kang et al. which elucidated the critical role of CD4 T cells for detecting and clearing precancerous senescent hepatocytes. This is in accordance with our observations of enhanced numbers of neoplastic nodules in Rag1-deficient mice, because high cell turnover is not needed for malignant transformation in the genotoxic DEN-model and the amount of transformed cells giving rise to a tumor nodule is expected to be higher due to the lack of tumor suppressive immunological surveillance mechanisms. With respect to the role of B cells, one has to keep in mind that, despite a common presence of antibodies directed against tumor-associated antigens, B cells are widely regarded as tumor promoting. This function is thought to be facilitated by inhibition of Th1-mediated anti-tumor immunity and, depending on M2-like macrophages, through Fc-gamma receptor-dependent signaling. However, the latter B-cell function was demonstrated in an inflammatory tumor model. Our data indicate that (hepatic) B cells are clearly activated in the tumor environment and exert suppressive functions on tumor growth in liver cancer, once a nodule is established.

In conclusion, our work revealed that liver cancer provokes distinct adaptive immune responses, which functionally limit tumor formation and progression. Thus, future therapeutic approaches for HCC may not only target tumor-promoting inflammatory reactions, but should also augment HCC-induced anti-tumoral adaptive immune cell functions.

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