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HEPATOCELLULAR CARCINOMA

Ectopic lymphoid structures promote carcinogenesis in the liver

In many solid tumours, the presence of ectopic lymphoid structures (ELSs) is associated with a better prognosis, but the opposite scenario arises for hepatocellular carcinoma (HCC) according to new data.

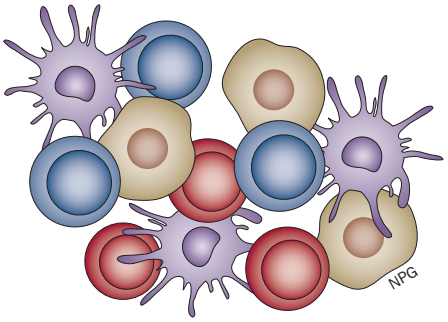
ELSs are organized clusters of leukocytes resembling secondary lymphoid organs, which infiltrate tissues often at sites of inflammation. "While ELSs are very commonly seen in certain samples, we know very little about how they are formed and how they affect immune responses," says one of the investigators Eli Pikarsky.

In the new study, high numbers of ELSs correlated with an increased risk of late HCC recurrence and decreased overall survival in patients who had undergone resection of HCC. Late-recurring HCCs are considered as new cancers rather than early recurrence, which are considered as arising from the primary tumour. The number of ELSs did not correlate with early recurrence, suggesting an involvement in the generation of new HCC.

Increased NF-κB signalling was found in liver tissue samples from patients with high numbers of ELSs. The authors developed a mouse model with hepatocyte-specific constitutive activation of IκB kinase to evaluate the effect of NF-κB on ELSs and HCC. Continual activation of NF-κB resulted in ELS formation at 7 months and at 20 months 100% of the mice had HCC.

Histological analysis revealed that the earliest malignant HCC cells expressed HCC progenitor cell markers and were found in ELSs and not anywhere else. A 3D reconstruction of serial histology sections illustrated that these progenitor HCC cells budded out of the ELSs to form independent tumours.

Various cytokines such as lymphotoxin-β were overexpressed in ELSs and the authors hypothesize that cytokines act in a paracrine fashion on hepatocytes and have a protumorigenic effect. Blocking lymphotoxin cytokines at early stages reduced the number and size of HCC in mice.



"We plan to define the immunological-cell subtypes and the relevant signalling pathways affecting growth of tumour progenitors within ELSs in mice and humans, as well as how tumour cells emerge from ELSs," concludes Pikarsky.

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Original article Finkin, S. *et al.* Ectopic lymphoid structures function as microniches for tumor progenitor cells in hepatocellular carcinoma. *Nat. Immunol.* doi:10.1038/ni.3290