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Cell-type specific functions of EGFR are involved in development of hepatocellular carcinoma

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Inflammatory microenvironment is regulated by EGF-EGFR signaling and is associated with development of Hepatocellular Carcinoma (HCC). Precise mechanisms by which EGFR-dependent inflammation causes development of HCC have not been elucidated. In the recent Nature Cell Biology paper (1), Lanaya and colleagues have shown that EGFR has different functions in Kupffer cells and in hepatocytes and that the deletion of EGFR in microphages inhibited HCC; while deletion of EGFR in hepatocytes promotes HCC (Lanaya H, Natarajan A, Komposch K, Li L, Amberg N, Chen L, Wculek SK, Hammer M, Zenz R, Peck-Radosavljevic M, Sieghart W, Trauner M, Wang H, Sibilia M. EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation. Nat Cell Biol. 2014; 10:972-981). The main results of this paper are summarized in Figure 1.

Development of HCC is a multistep process which involves alterations in a number of signaling pathways which synergistically contribute to liver cancer. HCC is usually associated with inflammation and cirrhosis as pre-neoplastic stages (2). Although the link between inflammation and HCC has been well established, molecular mechanisms are not completely understood. The epidermal growth factor receptor (EGFR) is a transmembrane protein receptor which might be activated by epidermal growth factor (EGF) and by several additional extracellular ligands. This activation triggers a variety of signaling pathways including Stat3, PI3K, Shc, SH1 and SHIP2 and Cbl E3 ubiquitin ligase (3). The growth promotion activities of EGFR have been initially investigated in partial hepatectomy model of liver proliferation/regeneration. It has been shown that hepatocyte-specific deletion of EGFR1 in mice and in rats significantly inhibits liver proliferation after surgical resections (4, 5). In agreement with this growth promotion role of EGFR, further studies revealed that expression of EGFR and copy numbers are increased in patients with HCC (6) suggesting that EGFR plays a critical role in development of HCC. These observations prompted clinical trials with inhibitors of EGFR signaling which, unfortunately, did not show improvements at advanced stages of HCC (7). It is interesting that further studies of effects of an inhibitor of EGFR, erlotinib, on liver cancer in an orthotopic rat model of HCC showed no antitumor effect (8).

These unsuccessful trials and negative results in animal models called into question if our knowledge of the molecular basis for EGFR-inflammation in hepatocellular carcinoma is sufficient for the generation of a strategy for treatments of patients with HCC. To better understand the role of EGFR in liver cancer, Lanaya et al generated several animal models with a cell-type-specific deletion of EGFR within the liver and examined the development of

liver cancer under conditions of diethylnitrosoamine (DEN)-mediated carcinogenesis (1). The response of WT livers to DEN includes DNA damage, apoptosis to remove death hepatocytes followed by proliferation to replace the dead hepatocytes. The authors showed that the deletion of EGFR in all liver cells ($EGFR^{\Delta Mx}$, mice), leads to a significant decrease in proliferation and an increase in apoptosis. These initial studies were consistent with previous reports showing the tumor promoting activities of EGRF. Subsequent studies of liver tumor development in mice with deletion of EGFR in parenchymal cells (hepatocytes and bile duct cells, $EGFR^{\Delta hep}$mice), however, provided surprising observations that livers of $EGFR^{\Delta hep}$ mice develop cancer significantly faster and with bigger sizes. The authors also found that proliferation is significantly increased in livers of $EGFR^{\Delta hep}$ mice during development of HCC. On the other hand, $EGFR^{\Delta hep}$ mice were characterized by increased apoptosis, similar to $EGFR^{\Delta Mx}$ mice.

The striking differences in the development of liver cancer between $EGFR^{\Delta hep}$ mice and $EGFR^{\Delta Mx}$ mice prompted the authors to perform a detailed examination into the development of HCC at different additional time points after injection of DEN. It has been found that damaged areas and serum ALT/AST levels are significantly increased in these two animal models after DEN injection and that that the necrotic response is also much stronger in $EGFR^{\Delta hep}$ and $EGFR^{\Delta Mx}$ mice clearly indicating that expression of EGFR in hepatocytes is required for hepatoprotection. Searching for molecular differences between WT and $EGFR^{\Delta hep}$/$EGFR^{\Delta Mx}$ mice, the authors examined levels of several cytokines and found that expression of IL-1β is significantly increased after DEN injections in both EGFR mutant mouse models.

The differences in development of HCC between $EGFR^{\Delta hep}$ and $EGFR^{\Delta Mx}$ mice suggested that EGFR also displays a functional role in non-parenchymal cells. Immunochemical examination of non-parenchymal cells in $EGFR^{\Delta hep}$ tumors revealed a four-fold increase of Kupffer cells/liver macrophages. To directly test the role of EGFR in Kupffer cells, the authors have generated two additional mouse models which had a deletion of EGFR in both parenchymal and Kupffer cells and in Kupffer cells only. Examination of DEN-mediated liver tumor in these mice demonstrated that the deletion of EGFR in Kupffer cells inhibits development of HCC. In agreement with these observations, the expression of EGFR is increased in Kupffer cells of livers of WT mice after DEN-mediated injury. A quite significant part of the article is a demonstration that EGFR-expressing Kupffer cells/liver macrophages are abundant in human HCC with poor prognosis. Examination of two large cohorts of patients with HCC from China and from Europe showed that there is no relationship between increased expression of EGFR in hepatocytes to prognosis. However, tumor sections of HCC patients revealed high levels of EGFR in CD68 (macrophage marker)- positive cells; while the adjacent non-tumor tissues had no EGFR in CD68-positive cells. These studies demonstrated that the increase of EGFR-positive macrophages in human HCC predicts a poor prognosis.

The identification of EGFR-expressing macrophages as the origin of HCC led to questioning the mechanisms by which EGFR signaling in macrophages promotes liver cancer. Kupffer cells produce IL-6 in response to IL-1β which is derived from damaged hepatocytes. Examination of plasma of DEN-injected mice revealed a significant increase of IL-6 in

EGFR$^{\Delta hep}$/EGFR$^{\Delta Mx}$ mice, but not in mice with macrophages-specific deletion of EGFR. Consistent with this observation, levels of IL-6 have been found to be increased in plasma of patients with HCC. Further studies showed that IL-1β induces IL-6 production in WT macrophages, but not in EGFR-deleted macrophages. In summary, the authors showed that the mechanism of IL-1β-mediated activation of EGFR in macrophages includes induction of EGFR ligands and ADAM17 with subsequent phosphorylation of EGFR by p38 kinase.

The liver contains several cell types which communicate with each other and have the potential to be reprogrammed by specific transcription factors. Although cell-to-cell communications have been previously implicated in regulation of liver biology and in development of liver cancer, the precise role of these communications in liver cancer has not been determined. The paper by Lanaya presents an excellent example of the studies of the role of EGFR in different cell types of the liver and the significance of these observations for treatments of HCC. Given the tumor promoting role of EGFR in macrophages, the therapeutic approaches should be designed for a specific inhibition of EGFR only in macrophages and should not affect EGFR in parenchymal cells since the latter scenario might promote tumorigenesis (see Fig 1). The data from this paper also suggest that the inhibition of EGFR could be beneficial at early stages of liver cancer and that patients with advanced HCC will not benefit from EGFR-based therapy.

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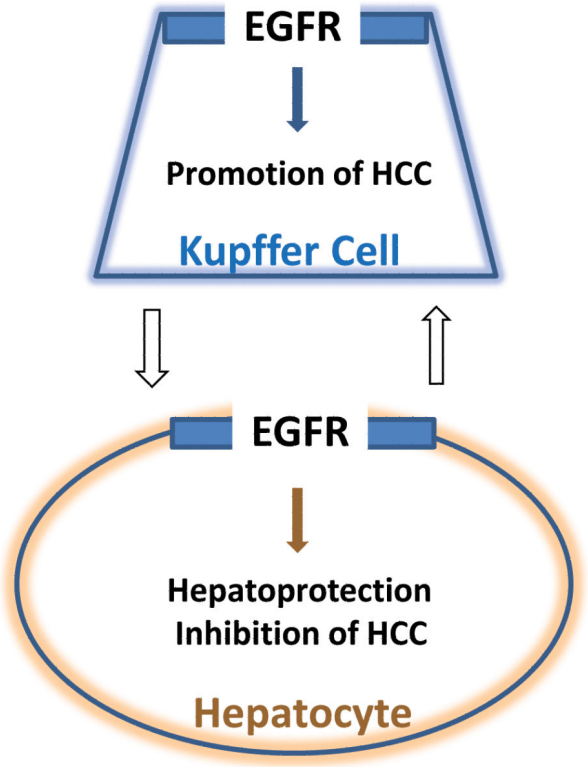

Figure 1.
EGFR is elevated in Kupffer cells and promotes HCC; while EGFR plays different functions in hepatocytes. White arrows show that interaction between Kupffer cells and hepatocytes is likely to be involved in liver-specific EGFR functions.