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Establishing a cancer cell in the inflammatory tissue: an epigenetic circuit

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Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide. Risk factors, such as viral infection, aflatoxin intake, and alcohol abuse, induce frequent hepatic cell death and chronic liver pathologies. It has now been well accepted that dead hepatocytes trigger a local inflammatory response, including increased inflammatory cytokines secretion and immune cell infiltration. Repeated cell death and compensatory proliferation in a background of chronic inflammation is believed to lead to the transformation of surviving cells that may carry genetic mutations; therefore, ultimately enhancing tumor initiation and promotion [1].

The nuclear factor-κB (NF-κB) signaling pathway has been shown to promote hepatocyte survival by controlling the expression of a panel of growth factors and cytokines in response to liver inflammation [2,3]. One of these cytokines is interleukin-6 (IL-6), which is best known for its role in activating signal transducer and activator of transcription-3 (STAT3) in both inflammatory and epithelial cells. Persistent activation of STAT3 induces up-regulation of key genes involved in cell proliferation and survival. In addition, mitogen-activated protein kinases, activator protein-1, and p53 have also been reported to play important roles in deregulated cell proliferation and cell survival during HCC development [4]. On the other hand, several studies reported that upon aberrant activation of oncogenes or restoration of tumor suppressors, normal hepatocytes can enter a cellular senescence program [5,6]. In a normal scenario, senescent cells trigger an immune-mediated clearance. However, impaired immune surveillance of pre-malignant senescent hepatocytes results in the initiation of HCC, which may explain the increased rates of HCC observed in immunosuppressed patients.

Taken together, previous findings have indicated that the role of inflammation extends far beyond protection of the injured tissues from infectious agents or removal of damaged cells. Both chronic activation of inflammation and impaired immune surveillance can lead to tumorigenesis. The crucial role of inflammation in carcinogenesis suggests that inflammation is a promising target for cancer therapy and preventive strategies. Nevertheless, it remains elusive whether and by which mechanism the inflammatory cytokines transform a normal cell into a cancer cell.

In a recent study published in *Cell* [7], Iliopoulos and his colleagues focused on how inflammatory stimuli contribute to the transformation of normal cells into cancer cells. They showed an epigenetic circuit linking inflammation to liver cancer initiation using multiple HCC cell lines, a chemical-induced mouse HCC model, and human HCC samples. Transient inactivation of hepatocyte nuclear factor-4α (HNF4α) in immortalized human hepatocytes acted as the initiating signal, which promotes cellular transformation and further increases tumor formation. However, the persistent low level of HNF4α lasted beyond the initiation stage to the advanced stage, suggesting that a continuous feedback loop may be required to maintain low levels of HNF4α.

Instead of searching for transcriptional regulators of HNF4α, the authors discovered that miR-24 and miR-629 play a key role in controlling HNF4α and liver cancer initiation and maintenance. Through promoter analyses and ChIP assays, these two miRNAs were found to be direct targets of IL-6/STAT3 signaling, which indicates a link to inflammation. Strikingly, the author demonstrated that HNF4α is in the center of a negative feedback to the IL-6/STAT3 signaling at least partly via enhancing the expression of miR-124. Moreover, the expression pattern of the components involved in this sophisticated regulatory loop was similar between primary HCC samples developed in the background of chronic inflammation and cultured cell lines. Finally, systemic delivery of miR-124 at initiation stage significantly prevents diethylnitrosamine (DEN)-induced hepatocellular carcinogenesis. Further, delivery of miR-124 at advanced stage of DEN-induced hepatocellular carcinogenesis greatly reduced tumor size. These data establish an essential role of this epigenetic circuit which is not only

required in the inflammation-triggered liver cancer initiation, but is inherited following removal of the inflammatory trigger signals.

A previous study by Iliopoulos and colleagues also described an epigenetic circuit in breast cancer initiation. In that study, transient induction of the Src oncogene in non-transformed human mammary epithelial cells initiates and maintains cells in a transformed state mediated by a positive feedback loop including NF-κB, Lin28, Let-7, and IL-6 [8]. Together, these two studies supported a general mechanism by which epigenetic circuits are regulatory events for cancer initiation and maintenance in addition to mutational events. This mechanism is different from cell death or senescence associated with inflammation. Importantly, activation of any positive factor or inhibition of any negative factor in this circuit transforms immortalized hepatocytes, indicating that the loop can be affected at any step.

Iliopoulos and colleagues not only bring us many surprising and exciting findings, but also raise additional questions. First, the role of HNF4α in liver carcinogenesis and the underlying mechanisms are far from clear. Since HNF4α is an essential transcription factor controlling expression of functional enzymes in terminally differentiated hepatocytes, the potential link between HNF4α and the HCC inflammatory response would need to be further characterized beyond the miRNA feedback loop. Interestingly, a recent study using temporally controlled HNF4α deletion in mouse livers showed unchanged IL-6 and TNFα expression [9]. Instead, it proposed a role of HNF4α in liver steatosis and hepatocyte proliferation through regulating bone morphogenic protein-7 and p53/p63 [9]. Since HCC usually progresses in a background of chronic hepatitis, steatosis, and cirrhosis, this finding adds another layer of complexity how HNF4α controls liver tumorigenesis.

On the other hand, the authors conclude that the HNF4α-miRNA inflammatory feedback circuit impacts many steps during HCC tumorigenesis, from initiation, promotion, to malignant conversion. Considering the heterogeneous nature of HCC, it is striking that liver cancer development at different stages is under the control of the same signaling circuit. It would be interesting to investigate whether other factors are involved in this inflammation-triggered circuit at different stages of HCC development.

The study by Iliopoulos and colleagues depicts a paradigm highlighting the importance of an epigenetic circuit in inflammation-associated liver tumor initiation and progression. The crucial position of miRNA in the epigenetic circuit largely expands the knowledge of miRNA in liver carcinogenesis. Over the past decade, increasing efforts have been made to identify deregulated miRNAs in human HCCs. Chromosome gain of miR-151 largely facilitates liver tumor cell migration and metastasis through down-regulating RhoGDIA [10]. By whole genome sequencing of miRNA, miR-199a/b-3p was found to play a tumor suppressive function through inhibiting the PAK4/Raf/MEK/ERK pathway, and low miR-199a/b-3p expression correlates with the markedly reduced survival of HCC patients [11]. It is predictable that with more miRNAs being identified as cancer genes, a systematic approach to correlate the miRNA signatures and sub-classification of human HCC would greatly facilitate the development of personalized therapeutics. Moreover, for patients with malignant tumors who have no option for resection or transplantation, combination of miRNA targeting with traditional chemotherapeutic agents might become a novel therapeutic strategy.

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