Gastroenterology 2016;151:607–615

BRIEF REVIEW

Ernst J. Kuipers and Vincent W. Yang, Section Editors

Regulation of Transdifferentiation and Retrodifferentiation by Inflammatory Cytokines in Hepatocellular Carcinoma

Florian Cabillic[1,2,3] and Anne Corlu[1,2]

[1]Institut National de la Santé et de la Recherche Médicale, UMR 991, Liver Metabolism and Cancer, Hôpital Pontchaillou, Rennes, France; [2]Université de Rennes 1, Rennes, France; and [3]Laboratoire de Cytogénétique et Biologie Cellulaire, Centre Hospitalier Universitaire de Rennes, Rennes, France

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e14. Learning Objective: Upon the completion of this CME exam, successful learners will be able to explain the role of an inflammatory environment in (1) the retrodifferentiation process of differentiated hepatic cells and (2) its contribution to the initiation and progression of poor prognosis hepatocellular carcinomas (HCC) with stemness-related features.

Liver cancers are typically inflammation-associated cancers characterized by close communication between the tumor cells and the tumor environment. This supportive inflammatory environment contributes to the establishment of a pathologic niche consisting of transformed epithelial cells, tumor-educated fibroblasts, endothelial cells, and immunosuppressive immature myeloid cells. Stromal and infiltrated immune cells help determine tumor fate, but the tumor cells themselves, including cancer stem cells, also influence the surrounding cells. This bidirectional communication generates an intricate network of signals that promotes tumor growth. Cell plasticity, which includes transdifferentiation and retrodifferentiation of differentiated cells, increases tumor heterogeneity. Plasticity allows non−cancer stem cells to replenish the cancer stem cell pool, initiate tumorigenesis, and escape the effects of therapeutic agents; it also promotes tumor aggressiveness. There is increasing evidence that an inflammatory environment promotes the retrodifferentiation of tumor cells into stem or progenitor cells; this could account for the low efficacies of some chemotherapies and the high rates of cancer recurrence. Increasing our understanding of the signaling network that connects inflammation with retrodifferentiation could identify new therapeutic targets, and lead to combined therapies that are effective against highly heterogeneous tumors.

Keywords: Hepatocellular Carcinoma; Cancer Stem Cell; Retrodifferentiation; Transdifferentiation; Inflammatory Environment.

Cancer Heterogeneity and Retrodifferentiation

An important concern regarding solid tumors arises from phenotypical and functional heterogeneities that make the eradication of all tumor cells difficult and allow cancer recurrence from untargeted cells. Heterogeneity is a well-known hallmark of hepatocellular carcinoma (HCC) and occurs even within the same nodule.[1] It results from the cellular origin of HCC and the landscape of genetic/epigenetic alterations. Such alterations rely on both the intrinsic genomic instability of tumor-initiating cells and stimuli from the tumor environment, which constitute an additional source of genetic instability that promotes oncogenic events.[2,3] Indeed, fibrosis and extracellular matrix remodeling, mechanical stress, hypoxia, acidosis, metabolic changes, immune cell infiltration, and even chemotherapy-induced inflammation, contribute to the generation of chronic inflammation that exerts a selective pressure. Such a selective pressure induces a high cellular turnover, overcomes DNA repair mechanisms, and contributes to malignant transformation. In addition to the accumulation of stochastic genetic/epigenetic changes in tumor cells, the identification of stem cells in various tissues raises the hypothesis that a subset of cells with stem/progenitor cell features and tumorigenic capacity contributes to tumor heterogeneity.[4] Similarities between tumors and embryonic tissues also suggest that tumors can arise from an interrupted differentiation of a population of stem cells.[5]

Abnormal stem/progenitor cells, called cancer stem cells (CSCs), display high metastatic potential and radiotherapy/chemotherapy resistance, resulting in poor outcomes for patients. CSCs, which share many features with normal stem cells, have the ability to self-renew by symmetric division and to give rise to proliferating progenitors and more differentiated dividing cells that are not tumorigenic by asymmetric division. The paradigm for the CSC hierarchical model is that once cells have left the stemness state, they cannot revert back. Although some studies have provided evidence for the CSC hierarchical model in some cancers,

Abbreviations used in this paper: **CSC, cancer stem cell; EMT, epithelial to mesenchymal transition; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; IL, interleukin; NF-κB, nuclear factor−κB; TAM, tumor-associated macrophages; TGF, transforming growth factor; TNF, tumor necrosis factor.**

Most current article

© 2016 by the AGA Institute
0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.06.052

including HCC, the generalization of this unidirectional model can be questioned. Indeed, it does not consider cell plasticity, which includes the ability to undergo retrodifferentiation (ie, the retrograde differentiation toward fetal/embryonic states[6]) and transdifferentiation (ie, the conversion of one differentiated cell type into another[7]). Indeed, adult differentiated cells are not arrested in a terminal state but, conversely, display an unexpected plasticity. Therefore, in addition to the involvement of facultative liver stem cells, cells undergoing transdifferentiation or retrodifferentiation could provide a physiologic response to massive cell loss and chronic injury. In mice, the ablation of >99% of pancreatic β-cells causes glucagon-producing α-cells to transdifferentiate into functional β-cells.[8] In the liver, after bile duct ligation or toxin exposures, hepatocytes undergo transdifferentiation into ductal biliary epithelial cells that facilitate clearance of toxins.[9] The transdifferentiation of hepatocytes into ductal biliary epithelial cells also occurs upon forced genetic modulation of the developmental Notch and Hippo pathways.[10,11] Whether or not transdifferentiation requires a dedifferentiated intermediate cell is still under debate.[12,13] Interestingly, Tarlow et al[13] recently proposed that retrodifferentiation is a way for human and mouse adult hepatocytes to escape the chronic injury induced by 6 weeks of 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine diet. Indeed, chronically injured hepatocytes retrodifferentiate into bipotential adult liver progenitors that retain the memory of their origin and, after expanding, redifferentiate into hepatocytes upon cessation of injury.

The transdifferentiation or retrodifferentiation process also occurs in the context of liver primary tumors. Using a human HepaRG cell line isolated from a differentiated tumor developed consecutively to chronic hepatitis C virus infection,[14] we demonstrated few years ago that highly differentiated tumor-derived hepatocytes could either proliferate without loss of differentiation or retrodifferentiate into bipotent progenitors that are able to differentiate into biliary- and hepatocyte-like cells.[15] After retrodifferentiation, HepaRG stem/progenitor cells expressed embryonic stem cell–related genes, as well as hepatoblast and hepatic stem cell markers (eg, CD44, LGR5, SOX9, ICAM-1, CK19, NCAM, GATA4, NANOG, OCT4).[15–17] They also showed enrichment of gene signatures representative of the human HCC: 1) "S1 subclass" described by Hoshida et al,[18] which is associated with WNT and transforming growth factor (TGF)–β signaling activation, more invasive/disseminative phenotype and significantly greater risk of earlier recurrence; 2) "human liver cancer proliferative subclass" described by Chiang et al,[19] which is correlated with IGF1R and RPS6 phosphorylation and macrovascular invasion. In vivo demonstrations showing that neoplastic epithelial cells can transdifferentiate, transiently revert to an immature state, or retrodifferentiate into a stem cell state were also provided in the liver and the gut. In mouse models of intrahepatic cholangiocarcinoma, hepatocytes can convert into biliary-like cells, which were previously thought to be derived exclusively from cholangiocytes.[20,21] Side by side comparison of liver tumorigenesis, after controlled oncogenic transformation of adult hepatocytes, hepatoblasts and hepatic progenitors by H-RAS and SV40LT, revealed that HCC can be derived from different cells of origin. In addition, oncogenic events can reprogram any cell type into CSCs. This study also revealed a significant up-regulation of epithelial to mesenchymal transition (EMT)- and embryonic stem cell–related genes in reprogrammed cells (progenitor cells, hepatoblasts, and adult hepatocytes).[22] At the same time, in a genetic model of intestinal tumor, it was demonstrated that intestinal epithelial cells can re-acquire stem cell–like properties.[23] Thus, it can be expected that cancer may be derived from the malignant transformation of stem/progenitor cells or mature cells and that bidirectional plasticity between CSC and non-CSC populations allows non-CSCs to adapt to stress, escape cell death, and replenish the CSC pool (Figure 1). In addition, cell plasticity could reconcile hierarchical and stochastic models, considering that the capacity of retrodifferentiation may be either inherited or acquired.[24] Finally, these observations must be analyzed in the light of successful ex vivo reprogramming of differentiated cells into induced pluripotent stem cells through enforced expression of transcription factors.[25] Therefore, it is reasonable to postulate that cells have the capacity to retrodifferentiate in vivo if signaling pathways involved in phenotype reprogramming are strongly activated.

Inflammation and Retrodifferentiation

The liver is especially exposed to chronic infections or environmental insults (eg, alcohol, obesity), and the resulting unresolved inflammation state is associated with an increased risk of cancer. Therefore, up to 80% of HCCs occur during the course of chronic liver diseases (hepatitis, alcoholic or nonalcoholic steatohepatitis).[26] Consistently, the presence of pro-inflammatory cytokines in peritumoral tissues or systemic circulation contributes to tumor progression and is associated with a higher risk of recurrence and poor prognosis in HCC.[27,28] Significant efforts have been made over the past few years to unravel cellular crosstalks within the HCC niche. They provided new data that improved understanding of the molecular mechanisms that generate and maintain a pro-inflammatory environment in the liver.[29,30] The inflammatory environment sustains tumor development through various mechanisms, such as accelerated cell proliferation, increased invasiveness, and increased abilities to escape the immune system.[29] In addition, some studies have recently highlighted the role of inflammatory signaling in cell retrodifferentiation and acquisition of stemness features.[4,17,31]

The main sources of pro-inflammatory cytokines, chemokines, and growth factors are supposed to be hepatic stellate cells (HSCs), cancer-associated fibroblasts, endothelial cells, and infiltrated immune cells (Figure 2). As examples, HSCs promote tumor cell proliferation through the secretion of pro-inflammatory cytokines (interleukin [IL] 6, IL1β) and growth factors.[30] Cancer-associated fibroblasts secrete pro-angiogeneic cytokines (CXCL12, vascular endothelial growth factor) and hepatocyte growth

Download English Version:

https://daneshyari.com/en/article/3291861

Download Persian Version:

https://daneshyari.com/article/3291861

Daneshyari.com