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The Puzzle of Liver Homeostasis: The Centrilobular Hepatocyte, A Novel Master Piece on The Chessboard?

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As the largest internal organ, the liver has numerous essential functions, such as glucose and fatty acid metabolism or detoxification of endogenous and exogenous substances/drugs. Such functions are mainly attributed to the hepatocytes, which count for eighty percent of the liver cells population. As a result, loss of liver function results in organ failure and subsequent death within days. From a metabolic perspective, the liver of mammals is organized into functional units, called hepatic lobules, limited on one side by a central vein and on the other by a portal vein [1]. The hepatocytes specialize as a function based on their position along this porto-central axis of the liver lobule, for example being responsible for gluconeogenesis in a periportal position and for glycolysis around the central vein [2-5].

Cellular complexity and multitasking of the liver maybe explain why this organ is gifted with remarkable regenerative abilities [1,6]. Most organs preserve homeostasis via two main non-mutually exclusive ways: cellular replication and differentiation from stem or progenitor cells. It is well established that differentiated hepatocytes that are in a quiescent state in the normal liver, are able to re-enter the cell-cycle and proliferate after a partial hepatectomy reconstituting the lost hepatic mass in record time. To elucidate the mechanisms that contribute to the liver repair in pathological conditions, the scientists have developed technical tricks to artificially induce liver damage in rodents by the "2-hits" strategies (first hit inhibits the proliferation of mature hepatocytes and the second hit hurts the parenchyma).The general admitted conclusion is that in both acute and chronic diseases, the liver activates terminally differentiated epithelium to proliferate and repair the organ. When this capacity fails, the liver activates a population of liver progenitor cells, located around the portal vein, and which are able to proliferate, migrate and differentiate in order to restore both hepatic architecture and liver function. Nevertheless, while countless studies illustrate the ability of different cell types to replenish the liver parenchyma with different degrees of contribution, less fruitful is the discovery of the true nature of this stem cell compartment [1,7, 8]. Basically, until now, two theories were in conflict: the existence of a stem cell pool supplying the liver by maturation into functional hepatocytes by their offspring along the porto-central axis of the hepatocyte ("streaming liver" hypothesis), and the concept that the regeneration results solely from the adult hepatocyte dedifferentiation and/or division, without the intervention of a residual stem cell. In light with the recent work of Kaneko [9] it is clear that assuming that the liver stem cells are individual entities carrying specific markers, detaching from the biliary ducts to gradually spread out freely from the periportal toward the pericentral regions for liver repair is rather an outdated fact. The latest publications favor the hypothesis that virtually all hepatocytes hold a virtuoso performance in liver reconstitution, dedifferentiating to better proliferate or to change their fate whenever required [1,6-8,10]. The recently published study in the journal Nature, proposing a "counter-streaming" hypothesis in which hepatocytes located around the central vein reconstitute at least 1/3 of the liver lobule in one year, following a centro-portal axis sounds thus almost provocative!

Whereas, animal models remain the primary if not the only lens through which scientists evaluate stem cell functions, very few of these models reproduce the etiology, natural history and progression of human liver diseases [11]. In addition, remarkable heterogeneity displayed by liver stem cells in rodent models of stem cell-mediated liver regeneration has been demonstrated, part of it depending of the used artificial models of injury [12]. To avoid biases, the scientists actually returned to an old concept: the use of unmanipulated mice that have a regular homeostasis. Less appreciated and understood is indeed the liver's ability to maintain itself day-by-day, replacing uninjured cells that die off naturally. In such a situation, the cell renewal rate is so low that it is supposed to be the result of an intrinsic proliferation phenomenon of mature hepatocytes. But do all hepatocytes play this role or are some hepatocytes more competent than others to fulfill this function?

The group of Nusse tackles these questions and distinguishes a certain category of hepatocytes, located close to the central vein that ensures hepatic homeostasis [13]. The use of a molecular lineage tracing strategy allowing the final labeling with GFP (Green Fluorescent Protein) of cells, which expressed the Axin-2 at the start of the analysis, in fact reveals the presence of a narrow ring of fluorescent hepatocytes along the central vein [13]. These cells are distinguished from most other hepatocytes by expression of the transcription factor TBX3, important in the maintenance of pluripotency, and their diploid character, often associated with a proliferative capacity greater than that of other hepatocytes, which are mostly polyploid. During homeostatic renewal, the progeny of such labeled cells are hepatocytes lacking Axin-2 and TBX3, evolving towards polyploidy and replacing the hepatocytes along the portal centro-axis of the hepatic plate. In one year, these cells replenish up to 30% of the hepatocyte mass [13]. Notably, these Axin-2^+ hepatocytes are never replaced by Axin-2^- hepatocytes suggesting that these cells self-renew and never give rise to biliary cells. By various approaches, the authors show that these Axin-2^+ hepatocytes proliferate twice as fast as the others; thus, the authors called these hepatocytes stem cells because they self-renew and although they are unipotent. They unexpectedly replenish hepatocyte plate "against the stream".

What is the mechanistic underlying the existence of this centrilobular

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hepatocyte? Following their progeny for a year, the scientists have discovered that these cells acquire different expression profiles of genes based on their position in the hepatic lobule. Away from the central vein, they lose the expression of glutamine synthetase (GS) and axin-2 but gain the expression of carbamoyl-phosphate synthetase (CPS), while the closest to central vein they keep GS, Axin-2 expression and are devoid of CPS expression [13]. Liver zonation is controlled by the Wnt pathway and in particular by the existence of two opposite gradients of expression of genes APC and β-catenin along the porto-central axis [4]. Thus, the β-catenin stimulated Wnt pathway determines the centrilobular hepatocytes identity where the APC gene is repressed. In contrast, β-catenin is repressed in periportal hepatocytes, where the APC gene is active. Axin-2 gene is a direct known target of β-catenin. Due to their molecular structure, the Wnt ligands are forced to act over short distances [9]. In this study [13], it is shown that endothelial cells of the central veins provide the Wnt signal (Wnt2 and wnt9a) necessary to maintain the plasticity of Axin-2$^+$ hepatocytes, thereby constituting a separate niche from the one of the portal region since these signals are not present. When the progenies of these Axin-2$^+$ hepatocytes migrate outside the zone of action of the Wnt signal, then they rapidly lose their ability to divide and acquire the characteristics of more conventional mature hepatocytes. Confirming the role of Wnt signaling in the Axin2$^+$ hepatocyte identity, when Wntless -a Wnt-specific transporter molecule required for proper Wnt secretion- was specifically inhibited in endothelial cells, there was a loss of pericentral zonation with a decreased proliferation rate of pericentral hepatocytes. Thus, as the stem cells located in the intestinal crypt in the vicinity of Wnt secreting Paneth cells, the self-renewing and progenitor liver cell compartment answers to a direct Wnt stimulation to reconstitute the parenchyma.

Can we reconcile these results with the existence of periportal progenitor cells?

One possibility is that each sub-population of hepatocytes located at each pole of the hepatic lobule has a proliferative advantage allowing each to simply renew its lobular region. In fact, in almost one-year mouse life, only 30% of the liver is reconstituted from Axin-2$^+$ hepatocytes raising the issue of the periportal zone renewal. A subpopulation of periportal Sox9+ cells has been recently identified in a quiescent normal liver in mouse as in humans [14] that harbor better capacities for liver repopulation after injury than mediolobular hepatocytes. Because these cells express ductal markers, they have been named hybrid hepatocytes. Although it is not demonstrated here that this specific population is also working in normal homeostatic conditions, these new data, put into perspective with the Nature paper, could suggest the existence of two different hepatocyte sub-populations, both less differentiated and with a higher proliferative potential at each extremity of the lobule. Indeed, the ability to take advantage of multiple cellular sources scattered at distinct regions of the hepatic lobule could be seen as a favorable evolutionary strategy, allowing flexibility and plasticity in regenerative liver response to various stresses. In this scenario, even if the models in rodents are not perfect, it would be interesting to know the contribution of each sub-population of hepatocytes that are facing specific damage at portal or central area.

Another possibility is that each sub-population of hepatocytes is well-delimitated inside the lobule in order to preserve the functionality of the hepatic functions. The liver has a remarkable metabolic plasticity, defined by a heterogeneous distribution of metabolic functions determined themselves by the position of hepatocytes on porto-central axis [2-5]. Although it is now accepted that the hepatocyte is a plastic cell [15], the existence of two niches would therefore have some relevance in preserving this metabolic gymnastics. In this scenario, it would be interesting to shift the hepatic zonation by playing on the direction of blood flow in order to observe whether these 2 niches irrevocably dedicated to portal or centrilobular zones can be inverted.

The discovery that centrilobular hepatocytes, along with potential others [1], contribute to liver homeostasis opens up many opportunities for further studies to broaden the findings presented here. For instance, it would be of interest to investigate how the newly identified centrilobular hepatocytes might contribute to the repair process of hepatic tissue after injury. Likewise, it will also be important to explore whether liver cancers tend to originate from these replicating cells. In this line, it has been shown that hybrid periportal hepatocytes, despite their higher regenerative potential, do not participate to hepatocellular carcinoma in three different models of liver carcinogenesis [14]. While previous studies suggested that both hepatocytes and facultative progenitor cells within the biliary tree were capable of generating hepatocellular carcinomas, it has been recently elegantly demonstrated that hepatocellular carcinomas as cholangiocarcinomas arose exclusively from hepatocytes in mice [16,17]. Nevertheless, two things must be underlined: (i) all hepatocytes are not equal not only on a metabolic point of view but also in their liver reconstitution ability and (ii) their plasticity is remarkable. It has indeed been shown that induction of Notch was sufficient to reprogram the hepatocyte toward a biliary differentiation [18], or that activation of YAP in an adult hepatocyte dedifferentiates it in a progenitor cell with typical stem-cell characteristics such as self-renewal and multipotency [19]. Depending on the type of lesion, the modified microenvironment could induce Notch or Wnt pathways, orienting epithelial cells towards a hepatocyte or a cholangiocyte fate [20].

Beside the periportal and centrilobular hepatocytes, already a third subset of hepatocytes, the peribiliary hepatocyte that is directly adjacent to the canal of Hering has been hypothesized to play a different role in liver maintenance and/or repair [21]. This hypothesis highlights the importance of these peribiliary hepatocytes for the re-establishment of the hepato-biliary function by providing biliary drainage rather than to increase the number of functional hepatocytes. One is then forced to pointing out that the hepatocytes are not equivalent and they have not yet revealed all their secrets.

Although these studies seem to reconcile some contradictory data, they also bring substantial interrogations: Is it the end of the quest for liver stem cells? Is there also an endothelial ligand responsible for the induction of hybrid hepatocytes at the periportal side? Is there an exhaustion of these progenitor cells with ageing? Waiting for the answers, one can affirm that the hepatocytes are still the best pawns that the liver comprises to warrant an adequate liver reconstitution and strengthen its play area.

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References

1. Miyajima A, Tanaka M, Itoh T (2014) Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. Cell Stem Cell 14: 561-574.
2. Gebhardt R (1992) Metabolic zonation of the liver: regulation and implications for liver function. Pharmacol Ther 53: 275-354.
3. Jungermann K, Kietzmann T (1996) Zonation of parenchymal and nonparenchymal metabolism in liver. Annu Rev Nutr 16: 179-203.
4. Benhamouche S, Decaens T, Godard C, Chambrey R, Rickman DS, et al. (2006) Apc tumor suppressor gene is the "zonation-keeper" of mouse liver. Dev Cell 10: 759-770.
5. Gebhardt R, Hovhannisyan A (2010) Organ patterning in the adult stage: the role of Wnt/beta-catenin signaling in liver zonation and beyond. Dev Dyn 239: 45-55.

6. Michalopoulos GK (2014) The liver is a peculiar organ when it comes to stem cells. Am J Pathol 184: 1263-1267.

7. Itoh T, Miyajima A (2014) Liver regeneration by stem/progenitor cells. Hepatology 59:1617-1626.

8. Tanimizu N, Mitaka T (2014) Re-evaluation of liver stem/progenitor cells. Organogenesis 10: 208-215.

9. Kaneko K, Kamimoto K, Miyajima A, Itoh T (2015) Adaptive remodeling of the biliary architecture underlies liver homeostasis. Hepatology 61: 2056-2066.

10. Reid LM (2015) Paradoxes in studies of liver regeneration: Relevance of the parable of the blind men and the elephant. Hepatology 62: 330-333.

11. Dollé L, Best J, Mei J, Al Battah F, Reynaert H, et al. (2010) The quest for liver progenitor cells: a practical point of view. J Hepatol 52: 117-129.

12. Jelnes P, Santoni-Rugiu E, Rasmussen M, Friis SL, Nielsen JH, et al. (2007) Remarkable heterogeneity displayed by oval cells in rat and mouse models of stem cell-mediated liver regeneration. Hepatology 45: 1462-1470.

13. Wang B, Zhao L, Fish M, Logan CY, Nusse R (2015) Self-renewing diploid Axin2(+) cells fuel homeostatic renewal of the liver. Nature 524: 180-185.

14. Font-Burgada J, Shalapour S, Ramaswamy S, Hsueh B, Rossell D, et al. (2015) Hybrid Periportal Hepatocytes Regenerate the Injured Liver without Giving Rise to Cancer. Cell 162: 766-779.

15. Gilgenkrantz H (2015) The hepatocyte is the only stem cell in the liver. Med Sci (Paris) 31: 357-359.

16. Fan B, Malato Y, Calvisi DF, Naqvi S, Razumilava N, et al. (2012) Cholangiocarcinomas can originate from hepatocytes in mice. J Clin Invest 122: 2911-2915.

17. Mu X, Espanol-Suner R, Mederacke I, Affo S, Manco R, Sempoux C, et al. (2015) Hepatocellular carcinoma originates from hepatocytes and not from the progenitor/biliary compartment. J Clin Invest. Sep 8. pii: 77995 doi: 10.1172/JCI77995.

18. Yanger K, Zong Y, Maggs LR, Shapira SN, Maddipati R, et al. (2013) Robust cellular reprogramming occurs spontaneously during liver regeneration. Genes Dev 27: 719-724.

19. Yimlamai D, Christodoulou C, Galli GG, Yanger K, Pepe-Mooney B, et al. (2014) Hippo pathway activity influences liver cell fate. Cell 157: 1324-1338.

20. Boulter L, Govaere O, Bird TG, Radulescu S, Ramachandran P, et al. (2012) Macrophage-derived Wnt opposes Notch signaling to specify hepatic progenitor cell fate in chronic liver disease. Nat Med 18: 572-579.

21. Theise ND, Dollé L, Kuwahara R (2013) Low hepatocyte repopulation from stem cells: a matter of hepatobiliary linkage not massive production. Gastroenterology 145: 253-254.