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Gastrointestinal Stem Cells.

III. Emergent themes of liver stem cell biology: niche, quiescence, self-renewal, and plasticity

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Theise, Neil D. Gastrointestinal Stem Cells. III. Emergent themes of liver stem cell biology: niche, quiescence, self-renewal, and plasticity. *Am J Physiol Gastrointest Liver Physiol* 290: G189–G193, 2006; doi:10.1152/ajpgi.00041.2005.—This essay will address areas of liver stem/progenitor cell studies in which consensus has emerged and in which controversy still prevails over consensus, but it will also highlight important themes that inevitably should be a focus of liver stem/progenitor cell investigations in coming years. Thus concepts regarding cell plasticity, the existence of a physiological/anatomic stem cell niche, and whether intrahepatic liver stem/progenitor cells comprise true stem cells or progenitor cells (or both) will be approached in some detail.

liver; progenitor cells

WHY “emergent themes of liver stem cell biology?” In part, of course, because the topics briefly addressed in this essay are those that are currently emerging in the study of liver stem/progenitor cells (LSPC). But it is also intended in a technical sense, as the *emergent* self-organization that arises from complex adaptive systems: describing evolving concepts arising within the stem cell field as a whole, as well as the emergence of liver tissue arising from all of the cells and signaling processes that the liver comprises. But this is just a teaser—emergence and complex systems will not, in fact, be a focus of this essay; for that, I would point you to other sources (7, 19). But even those areas covered here to a fuller degree, are still just touched on, as pointers, to whet the appetite of people for whom liver regeneration is either of practical interest or a passion.

This essay will therefore address areas of LSPC studies in which consensus has emerged and in which controversy still prevails over consensus, but it will also highlight important themes that will inevitably be a focus of LSPC investigations in coming years. Thus concepts regarding cell plasticity, the existence of a physiological/anatomic stem cell niche, and whether LSPC comprise true stem cells or progenitor cells (or both) are approached in some detail.

INTRAHEPATIC LSPC

There is little argument today that there are facultative LSPC in the liver. These cells largely arise from the biliary tree, primarily from the most proximal branches, in particular, it seems, from the canals of Hering (23). Confirmation of this fact has been found in anatomic studies and in *ex vivo* investigations in which such cells are manipulated to develop into both

hepatocytes and cholangiocytes, thereby experimentally demonstrating bipotentiality (15).

This may be all that is readily agreed on by researchers in the field. There are, for example, other locations for LSPC (4). An even more fundamental question yet to be fully addressed is whether the LSPC harbored within the biliary tree fulfill the criteria to be called true “stem cells” or whether they are merely “progenitor cells.” There are essentially two requirements for a cell to be displaying “stemness”: that they are self-renewing and pluripotent. The *in vivo* self-renewal capacity of LSPC has not yet been completely documented as they have for other organ systems, such as the bone marrow, skin and adnexal structures, and gastrointestinal tract. The pluripotency, though, seems generally accepted: these are hepatobiliary cells that can give rise to either hepatocytes or cholangiocytes depending on the presence of injury or on manipulations in culture.

Stem cell self-renewal may be understood in two ways. The first is that each stem cell, when it divides, gives rise to another stem cell and to a second cell that has some differentiated features of the lineage down which it must progress. The alternate possibility is that there is a stochastic element involved in stem cell division: the stem cell can give rise either to two stem cells, two differentiated cells, or one of each. In this second model, the self-renewal is demonstrated over a population rather than on a cell by cell basis. A corollary to self-renewal is that the stem cell itself is relatively slow cycling. It is the more differentiated daughter cell that proliferates more rapidly, constituting what is often referred to as the “transit amplifying population.” These are concepts that have been extensively discussed and explored in studies of other organ systems but remain largely unexplored for the liver.

A LIVER STEM/PROGENITOR CELL NICHE?

In other organs, the concept of a “stem cell niche” has proven very useful [reviewed by Fuchs et al. (6)]. It is conceived of as a restricted locale in an organ that regulates stem cell division through microenvironmental signaling, supporting their self-renewal, inhibiting or maintaining normative baseline differentiation in normal physiological states, and promoting proliferation and differentiation in response to injury. The niche concept, particularly as it was first elucidated in the ovarian stem cell niche of *Drosophila*, specifies a microenvironment comprising stem/progenitor cells, stromal cells, and extracellular matrix and basement membrane. Other cell-cell interactions are also hypothesized. Interactions between these various compartments, usually mediated by direct cell-cell contact, accomplish the homeostatic regulation of stem/progenitor cell functioning.

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A varying amount of information is known about the stem cell niches of various organs. Some principles seem to apply across organ boundaries, whereas others appear to be organ specific. Organs with most precisely localized and defined niches seem to be those that have a steady-state high rate of turnover. These would include the hematopoietic system, the testis, skin and adnexa, and the gastrointestinal tract. But other organs with less obvious steady-state cell turnover also appear to have defined stem cell niches, including the brain (in the subventricular zone) and epidermal melanocytes.

The coordinated signaling between the component cells and matrix that form a stem cell niche represent a weblike integrated system of interactions. Investigative techniques that isolate single cells for examination in cell culture are thus limited in their ability to establish details of niche functioning and effects. It is not on the relatively reductionist cell biological level of investigations that the key processes are active but on the higher-order tissue biological scale of investigation (18). Whereas reductive approaches will of course provide vital information, such work will proceed more efficiently when hypotheses can be drawn from the actual in-tissue relationships of the involved cell types and matrix, both in normal tissue and in response to injury. Moreover, it will be in returning to a systems analysis at the tissue level that the *ex vivo* cell studies will find their fullest applications and impact (5).

As opposed to these other organs in which there has been a years- or decades-long consensus that a tissue-specific stem cell exists, in the liver the open question of its existence has prevented advancement into developing a niche concept. There are currently three putative locations for resident LSPC: cells contained within the canals of Hering (CoH) (23), cells located within the interlobular bile ducts (1), and periductular cells (15, 16). Of these locations, only the CoH represents an anatomically definable entity. This structure represents the most proximal branch of the biliary tree and is comprised of the smallest cholangiocytes on one side of the canal itself and of hepatocytes on the other side of the canal. Whereas it had long been thought to extend just to the limiting plate of the portal tract in humans, we showed that it in fact usually extends considerably beyond that location, as much as one-third of the way into the hepatic lobule (23). Furthermore, by examining how it is structurally and proliferatively altered in response to acetaminophen toxicity, we were able to demonstrate that it was a source of regenerating hepatocytes in humans (23). We have gone on to show that small intraseptal clusters of hepatocytes in cirrhosis of diverse, human, chronic diseases are also likely to arise from the CoH (4). However, that work also demonstrated the likelihood of derivation from progenitor cells in other locations of the biliary tree as well (4).

Thus studies of proliferating cells and regeneration in animal and human models of hepatic injury indicate three possible stem/progenitor cell compartments, only one of which is, as yet, anatomically defined. The other two, intrabiliary and periductal stem/progenitor cells, have been identified by inference, by morphology, and by marker studies, but not in clearly defined anatomic locations. None of these cell populations, moreover, have been defined, *in situ*, by a functional assay for the quiescent stem cell at rest in the absence of activation. This represents vital information already obtained in many other organ stem cell compartments but still largely unexplored in the liver.

STEM CELL QUIESCENCE AND THE "LABEL-RETAINING CELL"

By examining studies of the stem cell niche already accomplished in other organs, hints as to which features might best be targeted for investigation of the liver may be gleaned. First, the stem cell itself needs to be identified. Whereas some markers have been suggested as useful, particularly in hematopoietic stem cells (e.g. c-kit, SCA-1, thy-1), these only specify populations of cells that are likely to contain cells with stem cell functioning, rather than exclusively and specifically identify the stem cells themselves. This is particularly true in the liver (12). Indeed, it seems unlikely at the present time that there will be stem cell-specific markers with which one can highlight the stem cell, *in situ*, independent of function. Rather, "stem cellness" is perhaps best considered as "function," not "entity" (2). Thus identification of a stem cell, within intact tissue, requires some way to mark cells with a given function.

The most well-established approach to this problem returns to the classic definition of stem cells, considering quiescence during physiological normative states as a primary aspect of stem cell functioning along with self-renewal and pluripotency. Marking a cell as quiescent, compared with its progeny in the transit amplifying compartment, would then support its identification as a tissue resident stem cell (14). The original approaches to this problem involved labeling of dividing cells with either tritiated thymidine or BrDU. Animals were exposed to either of these compounds for periods in which it was likely a stem cell would undergo at least one asymmetric cell division and thus incorporate the label and retain it. Such periods included exposure through fetal life and into the early neonatal period or for postnatal periods of time that were likely to encompass the relatively rare cell division of the stem cells. As cells within the transit amplifying population or in the compartment of more "terminally differentiated" cells divided, they would rapidly dilute the label to undetectable levels, leaving the relatively quiescent stem cells highlighted as "label retaining." Indeed, such cells, when identified, could be isolated and tested in culture for features that further support their stem cell functioning, such as with clonogenic assays (10). More recently, a highly innovative approach to identification of label-retaining cells in a putative stem cell niche has been developed in the laboratory of E. Fuchs at the Rockefeller Institute. With the use of transgenic animals with inducible, composite protein histone-2B-green fluorescent protein (H2B-GFP) expression under the control of a stem cell-marking cytokeratin promoter, this group has convincingly confirmed label-retaining cell (LRC) in the bulge region of skin adnexa (24).

CELL-CELL RELATIONSHIPS IN THE NICHE

In different organs, different cell-cell relationships have been identified as important. What seems clear is that once the postnatal tissue forms, the intraorgan stem cells take up (or maintain) long-term residence within the niche (6). What keeps them there is a primary question, the answer to which has been provided most efficiently through studies of the *Drosophila* ovarian niche and the germ stem cells (GSCs) contained therein. These studies show that direct physical interactions between stem cells and their nonstem cell neighbors in the niche are critical for maintaining stem cells in the niche and for controlling their relative quiescence or activation. In the *Dro-*

sophila ovarian and testicular niches, it is the “cap cell” that directly contacts the GSCs. Similar niche architecture governs mammalian testis and other vertebrate stem cell niches. In particular, direct contact with some type of stromal cell appears to be a consistent feature in most, providing vital input for hematopoietic stem cells, intestinal stem cells, and epidermal stem cells.

The “molecular glue” that anchors the stem cells to their niche stromal cells has been partially defined in some models (25, 27). Adherens junctions between stem cells and corresponding stromal cells have been identified in *Drosophila* and have been preliminarily identified in mammalian stem cell niches. On a gene expression basis, roles for Notch and WNT signaling pathways have also been suggested, again through direct stem cell-stromal cell contact, in stem cell niches in *Drosophila* (various organs) and in vertebrate retinal neuroepithelium, skeletal muscle, and hematopoiesis.

In the liver, several stromal cell candidates present themselves as candidates for the “partner cell” of the hepatic stem cell, including hepatic stellate cells, either quiescent or activated, and portal myofibroblasts. To our knowledge, however, analysis of an anatomic relationship between these cells and any of the putative hepatic stem cells has not been reported.

STEM CELL-MATRIX INTERACTIONS

Another important player in establishing the stem cell:niche are integrins mediating adhesion of cells to a basal lamina. Elevated levels of integrins have been reported in different stem cell populations, and loss of function studies in mice reveals that both integrins and adherens junctions play important roles in maintaining the location, adhesiveness, and proliferative quiescence of epithelial cells (25). In the liver, there is extensive analysis of basement membrane and integrin expression of the biliary tree. Basement membrane of bile ducts comprises laminin and type IV collagen (17, 28). Tenascin is expressed during development but is not seen in normal postnatal liver (17). Fibronectin expression may be seen in the hepatic sinusoids (28). The integrins that are predominantly represented on human biliary epithelium include $\alpha 2$, $\alpha 3$, $\alpha 5$, $\alpha 6$, and $\alpha 9$, which dimerize with $\beta 1$ (28). Similar analyses, however, have not been performed on the CoH themselves, mostly because the structure and location of the CoH have only recently been defined.

NERVE-NICHE INTERACTIONS

The importance of innervation of the stem cell niche remains highly speculative. Anatomic juxtapositions of nerves and epithelial stem cell niches in the intestinal crypts and bulge of the hair follicle have been demonstrated histologically. For the intestine, this area has remained relatively unexplored. However, in the vicinity of the epidermal niche, neurotrophin production (such as nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 and -4) by nerves has been demonstrated. Some of these factors are stimulatory, but others are inhibiting of niche activation (3).

In all these cases, however, it is not yet clear whether the nerves interact directly via cell-cell junctions (synaptic or otherwise) with the stem cells and/or stromal cells. If not, other mechanisms for neural interactions with the niche may be hypothesized, including secretion of factors into the periniche

milieu or autonomic control of vascular supply to these micro-environments. In the liver, neural involvement in regulation of the hepatic progenitor cell response has been demonstrated in elegant studies from the laboratories of Roskams and Diehl, demonstrating that sympathetic nervous system inhibition promotes oval cell proliferation and improves healing (11). The mechanism by which this takes place is unclear, however, though muscarinic receptors have been identified on human and rodent LSPC (11).

INSIGHTS FROM TRANSCRIPTIONAL PROFILING OF STEM CELLS IN THEIR NICHES

With the advent of microarray technology, a concerted effort to define patterns of gene expression that may be indicative of stem cellness has been underway for several years [reviewed by Lemischka (9)]. Published data for hematopoietic, neuronal, mesenchymal, embryonic, and intestinal stem cells have now appeared. However, much of these data has been performed on cells isolated from tissue and then maintained and expanded in culture. Only a few attempts have been made to obtain transcriptional profiles of stem cells isolated directly from their niche without subsequent *ex vivo* manipulation and propagation. Of these, only hematopoietic, intestinal, and skin stem cells have then been compared with their proliferative progeny, generated either via culture or through injury to the source tissues. Intriguing parallels arise from comparisons of these data sets. For example, members of the TGF- β pathway, so prominent in self-renewal in male and female fly GSCs, are also enriched in all of the other studied stem cell populations (6). JAK/STAT and Notch signaling pathways are also prominently represented, consistent with data already derived from *ex vivo* cell investigations or studies of in-tissue expression (6).

Petkov et al (13) have performed a variant of this work comparing gene expression profiles of rat hepatoblasts at varied time points during fetal development on through the adult liver, although to our knowledge such expression profiling has not yet been performed on cells isolated from the adult hepatic niche. To relate some of these findings to those noted above, *Hey1* was found to be upregulated in fetal livers; whereas the precise function of this gene is not known, the *Hey* proteins in general are known to be effectors of Notch signaling. Of significant note in this particular type of study is that 28 genes were identified as specifically upregulated in fetal liver that were not present in the adult cells. The authors note that these may represent markers of stem/progenitor cell functioning in fetal liver. It will be interesting to also see whether any of these are specifically active in active or inactive epithelial cells of the hepatic niche when the precise location of the niche is defined. Or, conversely, might they help to define the niche?

Although these and other similarities between stem cells of different origins are intriguing, the differences between them are equally important. Such differences may reflect tailoring of stem cells to their particular niche and the properties they may have to display to participate in other tissue-specific functions: to interact with tissue-specific matrices, respond to differences in vascular supply, mechanical effects, etc. Of particular interest, also, is that gene expression profiling of both the stem cell and the related niche cell often complementary, showing that the cross-talk is not unidirectional, but that the two (or more)



cells have a more complex interactive life. Few such studies, however, have as yet been performed (9). It seems that maintenance of the niche, then, is a result of a symbiotic interplay between the stem cells and the cells of the niche. This conception again points to the need to begin thinking in terms of a systems approach for stem cell phenomena (5, 18) and of the importance of identifying the stromal (or other) niche cell that exists in such a close relationship with the stem cell.

Thus comparison with other organ systems in which stem cells have been affirmed and studied for longer periods of time than has been done in the liver is useful in pointing out important directions for the future of intrahepatic LSPC research. But one must keep an open mind that the liver may also be unique in some ways, displaying different features than are seen in those other systems.

EXTRAHEPATIC SOURCES OF HEPATOBILIARY CELLS

The most extravagantly controversial area regarding LSPC is the recent development that hepatobiliary (and other) cells of the liver can derive from extrahepatic, circulating cells [reviewed by Theise (20)]. As it turns out, cells that are marrow derived (at least) can enter the liver and engraft, their genetic expression becoming reprogrammed, in some measure or completely, to function as a true liver cell. Much of the controversy is motivated by sincere and appropriate scientific skepticism inherent in any paradigm shift, although much debate in this area is also motivated by secondary influences (21). The scientific questions will be the focus here.

The first papers to investigate the possibility of extrahepatic cells contributing to liver mass came in the context of whole bone marrow transplantation or transplantation of the liver (20). Hepatocytes and cholangiocytes marked either by Y-chromosome in gender mismatched transplantation experiments or by products of transgenes that can be detected in tissue sections (e.g. DPPIV, green fluorescent protein, β -galactosidase) were identified, indicating derivation for the transplanted marrow cells. The presumed process at the time of these earliest publications was direct differentiation on entry and incorporation into the liver.

An early "confirmatory" study (8), however, which seemed to localize these plasticity phenomena to the c-kit⁺lin⁻Sca1⁺Thy^{lo} hematopoietic stem cell-enriched fraction of the marrow ("KTLS cells"), is now known to have been interpreted incorrectly (26). In the experimental animal, the FAH-null mouse (a partial mimic of human tyrosinemia type I), cited by many to be the best confirmation because of functional metabolic rescue from the otherwise lethal defect, turned out to be a different process altogether. Further investigation by the initial reporting laboratory demonstrated that, in this model, the process was one of fusion between circulating, marrow-derived monocytes with pre-existing hepatocytes, rather than engraftment of progenitor cells undergoing direct, nonfusion-based differentiation.

Subsequently, confirmatory experiments of both plasticity pathways have been published, and reviews have been written and rewritten rapidly (20). The balanced conclusion is that circulating cells can contribute to hepatic mass by two processes: by direct differentiation and by cell-cell fusion (sometimes followed by nuclear-nuclear fusion). The direct differentiation pathway has now been confirmed both in vivo and in vitro. The fusion phenomenon has been demonstrated in vivo,

as already described, and is the direct physiological correlate of the in vitro heterokaryon studies of Blau and colleagues (2) from two decades ago.

Two large questions hover over the proliferating studies of these two phenomena, the lack of answers to which increases the likelihood of controversy. The first is the role played by the experimental design and, related to this, the differences in LSPC activation, and/or recruitment in different injury models. The second relates to the cells in the marrow that may be most physiologically poised to migrate to the liver and engraft there as hepatobiliary cells.

It is particularly notable that among the many studies regarding stem cell plasticity and the liver, few, if any, reproduce the actual experiments that they seek to confirm or refute. Each laboratory has its own version(s) of injury that are employed. Age, strain, and even species differences are often ignored. Standardization of methods in transplantation experiments has not yet occurred. These differences may be significant. Although little has been done to directly compare injury models, for example, data accumulating in my own laboratory (unpublished) indicates that the physiology of response to different injuries varies greatly. Timing and extent of LSPC proliferation, production of chemokines, and their receptors, which have been shown to be of importance to plasticity phenomena (e.g. stromal derived factor 1, stem cell factor), and hepatocyte ploidy vary tremendously in different models. Thus the inattentive comparison of results derived from different models serves to confuse the field, generating more empty controversy than shedding light. This issue clearly requires much more extensive analysis (22).

As for the second issue, i.e. which cell in the marrow may have the major role to play in engraftment and plasticity phenomena, there are some vague hints about a unifying solution to this question. If one groups the mass of published plasticity studies into those that find the phenomenon and those that don't, there appears to be a trend. Those that most readily identify it either employ organ transplantation, whole bone marrow transplantation, or mesenchymal stem cells. Is it possible that the hematopoietic stem cell is not the likeliest player in this game? In our own work, where one "hematopoietic stem cell" demonstrated embryonic stem cell-like, trilineage differentiation, the cell may perhaps have been a precursor of both hematopoiesis and of stromal cells. The methods used to isolate it may have selected a more "primitive" cell than more classic hematopoietic stem cells, such as the KTLS cell (22). Thus, for example, studies that focused on the KTLS cell may have been finding "little evidence for stem cell plasticity" for a reason. This, too, is an area that requires greater attention than it has yet received in order for the field to advance from chaos and controversy to order and consensus.

Some of these areas, like the question of a stem cell niche and of self-renewal and quiescence of intrahepatic stem cells, have barely been addressed as yet. The argumentative and polemical aspects of the field are a sign that the field is truly leading to paradigmatic shifts in thinking about the liver, about the body as a whole, and, as such, are predictable, early developmental stages of our emerging understanding. However, progress in the field of liver stem cell biology is inevitable: the number of researchers plunging into the field, from diverse backgrounds, ensures continued creativity and produc-

tive investigations. Hopefully, some of the ideas presented here will tease a few more creative minds to enter the fray.

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