Review

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Space of Disse: a stem cell niche in the liver

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Abstract: Recent evidence indicates that the plasticity of preexisting hepatocytes and bile duct cells is responsible for the appearance of intermediate progenitor cells capable of restoring liver mass after injury without the need of a stem cell compartment. However, mesenchymal stem cells (MSCs) exist in all organs and are associated with blood vessels which represent their perivascular stem cell niche. MSCs are multipotent and can differentiate into several cell types and are known to support regenerative processes by the release of immunomodulatory and trophic factors. In the liver, the space of Disse constitutes a stem cell niche that harbors stellate cells as liver resident MSCs. This perivascular niche is created by extracellular matrix proteins, sinusoidal endothelial cells, liver parenchymal cells and sympathetic nerve endings and establishes a microenvironment that is suitable to maintain stellate cells and to control their fate. The stem cell niche integrity is important for the behavior of stellate cells in the normal, regenerative, aged and diseased liver. The niche character of the space of Disse may further explain why the liver can become an organ of extra-medullar hematopoiesis and why this organ is frequently prone to tumor metastasis.

Keywords: hepatic stellate cells; liver; mesenchymal stem cells; pericytes.

Introduction: liver regeneration

The liver has an outstanding regenerative capacity, which normally relies on the proliferation of hepatocytes and non-parenchymal cells after loss of liver mass (Michalopoulos and DeFrances, 1997). When the proliferation of hepatocytes is impaired, liver progenitor cells (LPC) seem to be involved in the reconstitution of liver tissue. LPC can be detected in diseased human and rodent liver and are induced in certain injury models (Wilson and Leduc, 1958; De Vos and Desmet, 1992). For instance, LPC, which are called oval cells in rodents, are inducible in rats after surgical removal of the two largest liver lobes (70% of the liver; partial hepatectomy) and simultaneously restricted hepatocyte proliferation by 2-acetylaminofluorene intoxication (Tatematsu et al., 1984). These LPC can contribute to liver regeneration through differentiation into hepatocytes and bile duct cells (cholangiocytes) in the case of severe liver damage (Michalopoulos and Khan, 2005). However, the origin and function of LPC during repair of an injured liver is not completely resolved and has been controversially discussed (Kordes and Häussinger, 2013; Michalopoulos and Khan, 2015; Kopp et al., 2016). Several studies indicate that LPC emanate from the portal field and seem to derive from putative stem cells within the canals of Hering, which are the most proximal branches of the biliary tree consisting of cholangiocytes and parenchymal cells (Theise et al., 1999; Dorell et al., 2011; Furuyama et al., 2011; Espanol-Suner et al., 2012; Miyajima et al., 2014). In addition, thymus cell antigen 1 (THY1/CD90)-positive bone marrow cells and hepatic stellate cells are facultative sources of LPC (Petersen et al., 1999; Kordes et al., 2014). To add further complexity, monitoring of pericentral cells that express the WNT target gene *Axin2* suggest that the liver tissue is slowly replenished over time by hepatocytes that derived from precursor cells close to the central vein (Wang et al., 2015). Thus, two different sites for new hepatocytes are suggested, one for homeostatic renewal (central vein) and one for tissue restoration after severe liver injury (portal field).

Recent studies indicate that the contribution of LPC to the reconstitution of liver mass largely depends on the severity of tissue injury in rodent models (Chien et al., 2018), which may explain discrepant observations in the past. Moreover, cholangiocytes, which share markers with LPC, have been identified as facultative LPC capable of restoring hepatocytes only if the proliferation of parenchymal cells is permanently suppressed (Raven et al., 2017). Hepatocytes have also been shown to contribute to LPC

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in vitro and *in vivo* using animal models of chronic liver injury (Chen et al., 2012; Tarlow et al., 2014). Recent findings suggest a fetal reprograming of hepatocytes that leads to LPC which is dependent on yes-associated protein-1 (YAP1) and insulin-like growth factor-2 RNA-binding protein-3 (IGF2BP3) (Hyun et al., 2019). It seems that the high plasticity of preexisting epithelial cells (i.e. hepatocytes and cholangiocytes) could explain the origin of LPC without the need of a stem cell compartment in the liver.

Stem cell niches

The stem cell niche hypothesis was developed by Raymond Schofield (Schofield, 1978) who supposed a spatially limited protective environment that maintains and controls the number of hematopoietic stem cells in the bone marrow. The first experimental evidence for the existence of stem cell niches came much later from the research of Ting Xie and Allan Spradling, who observed that germ line stem cells in *Drosophila* germarium require direct contacts to cap cells in order to maintain stemness (Xie and Spradling, 2000). Later on stem cell niches were also discovered in vertebrates. Besides the hematopoietic stem cell niches in the bone marrow (endosteal niche, vascular niches at arterioles and sinusoids), stem cell niches are present in the hair follicles (bulge), gut crypts, gonads, skeletal muscle fibers, subventricular and subgranular zones of the brain, as comprehensively reviewed elsewhere (Morrison and Spradling, 2008; Goldman and Chen, 2011; El-Hayek and Clarke, 2016; Gonzales and Fuchs, 2017; Yoshida, 2018; Schmidt et al., 2019). Important components of stem cell niches are neighboring cells that interact with the stem cells by establishing direct cell-cell contacts and release of soluble factors (chemokines, WNT ligands, growth factors, etc.), extracellular matrix composition, physical factors (substrate elasticity, shear forces), low oxygen-tension and metabolism (Morrison and Spradling, 2008; Marthiens et al., 2010; Nishimura et al., 2010; Lane et al., 2014). To enable communication with distant organs and to control stem cell recruitment, a contact of niche cells to the peripheral nervous system was also been reported (Katayama et al., 2006). However, the presence of a stem cell ultimately defines the stem cell niche.

Mesenchymal stem cells

The term ‘mesenchymal stem cell’ (MSC) was originally created by Arnold I. Caplan (Caplan, 1991). MSCs form a heterogenous group of somatic, multipotent stem cells first described as fibroblasts in the bone marrow that represent an important component of the hematopoietic stem cell niche (Maximov, 1906, 1928; Friedenstein et al., 1970; Kfoury and Scadden, 2015). MSCs secrete immunomodulatory and trophic factors to support regenerative processes but can also differentiate into adipocytes, osteoblasts, chondrocytes and myocytes as well as liver epithelial cells such as hepatocytes (Pittenger et al., 1999; Schwartz et al., 2002; Sato et al., 2005). Therefore, MSCs became an important research topic in regenerative medicine (Farini et al., 2014; Alfaifi et al., 2018; Spitzhorn et al., 2018). Moreover, MSCs are pivotal elements for the hematopoietic stem cell niche in the bone marrow and their depletion by experimental intervention or aging impairs blood formation (Eaves et al., 1991; Méndez-Ferrer et al., 2010; Maryanovich et al., 2018). However, MSCs are not restricted to the bone marrow but rather occur in all organs and are associated with blood vessels (da Silva Meirelles et al., 2006; Crisan et al., 2008). For a long time, it was not clear, whether MSCs themselves require a niche to maintain their characteristics. Now the perivascular zone is considered to be the MSC niche *in vivo* (da Silva Meirelles et al., 2006, 2008). If their niche is affected by aging, an altered MSC behavior and elevated expression of senescence-associated factors such as interleukin-6 are accompanied by disturbed support of hematopoietic stem cells (Li et al., 2015; O’Hagan-Wong et al., 2016; Sui et al., 2016; Maryanovich et al., 2018). Thus, maintenance of the perivascular MSC niche is essential for tissue homeostasis.

Like MSCs, pericytes are in direct contact with endothelial cells and are microscopically visible on the basement membrane of microvessels without smooth muscle cell layer (Sims, 1986). MSCs and pericytes are both multipotent cells that share many molecular characteristics and it was suggested that MSCs originate from pericytes (Caplan, 2008; da Silva Meirelles et al., 2008; Sá da Bandeira et al., 2017). Pericytes express nerve-glial antigen 2 (NG2/CSPG4/chondroitin sulfate proteoglycan 4) and nestin. They are important for angiogenesis and maintenance of blood vessel integrity and function. This is evidenced by the release of platelet-derived growth factor-B (PDGF-B) from sprouting endothelial cells sending out signals to PDGF receptor β (PDGFRβ)-expressing pericytes in a paracrine manner. Interfering with this pathway disturbs blood vessel formation by endothelial cells and developmental processes in pericytes as reviewed elsewhere (Gerhardt and Betsholtz, 2003).

Stellate cells are hepatic pericytes

Hepatic stellate cells are associated with fenestrated sinusoidal endothelial cells which constitute microvessels in the liver. At least in their quiescent state hepatic stellate cells can be clearly separated from pericytes and MSCs known from other organs, as stellate cells express glial fibrillary acidic protein (GFAP), embryonic stem cell-derived RAS (ERAS) and store fluorescent retinoids in lipid vesicles (Wake, 1971, 1980; Gard et al., 1985; Hendriks et al., 1985; Nakhaei-Rad et al., 2016) (Figures 1 and 2A,B). During their activation, however, hepatic stellate cells lose their retinoid stores, lower ERAS and GFAP expression, and acquire the expression profile of typical MSCs as indicated by the appearance of nestin, NG2 and CD44 (Niki et al., 1999; Kikuchi et al., 2005; Kordes et al., 2013; Nakhaei-Rad et al., 2016). This may indicate that hepatic stellate cells represent a quiescent state of MSCs in liver sinusoids (Figure 1). Although differences in the expression profile of isolated individual MSCs from one organ and between MSC populations from different organs are well known (Rennerfeldt and Van Vliet, 2016; McLeod and Mauck, 2017), comparative transcriptome and secretome analyses of hepatic stellate cells with pericytes and/or other MSCs demonstrate a close relationship and similar functional phenotype (Covas et al., 2008; Chinnadurai et al., 2019). The differences can originate from varying environmental cues and may reflect different states of activation or development. For instance, comparison of freshly isolated hepatic stellate cells (day 0) with culture-activated hepatic stellate cells (day 7) by transcriptome analysis results in 4066 differentially expressed genes. In contrast to this, early activated (day 3) and activated (day 7) stellate cells vary in the expression of only 420

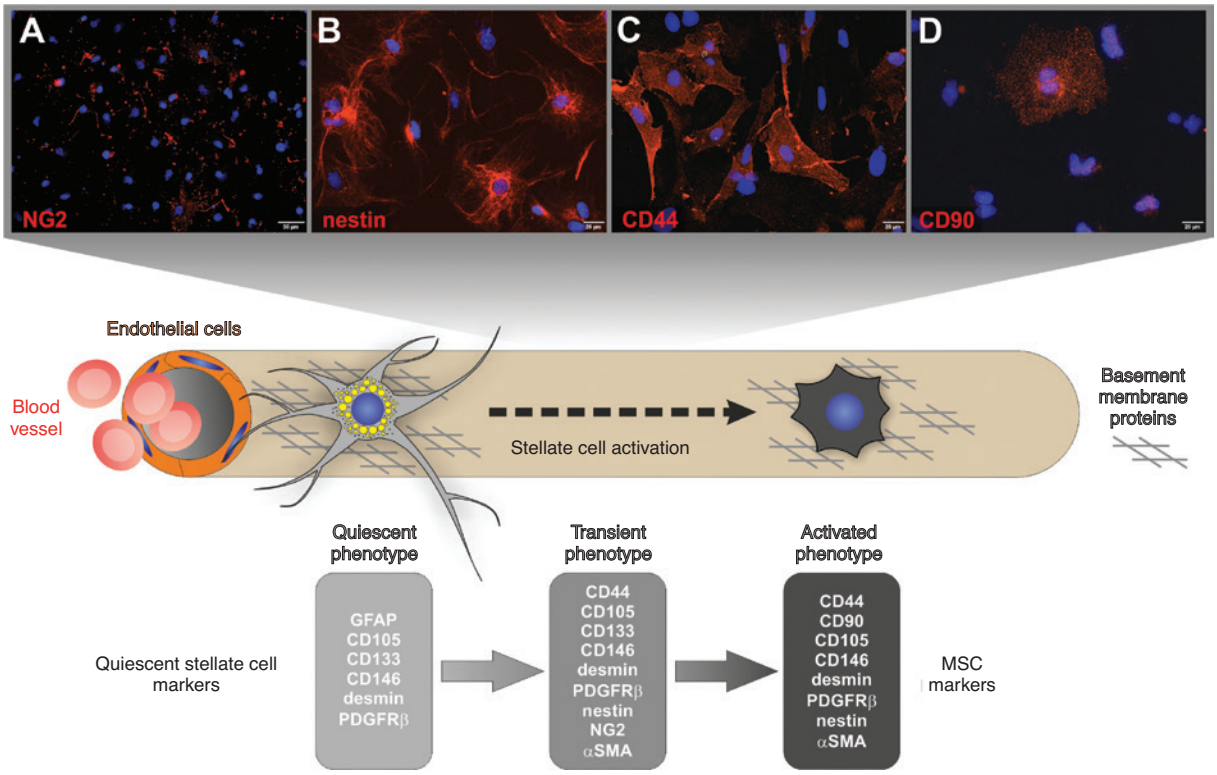

Figure 1: Hepatic stellate cells acquire typical characteristics of MSC during activation.
Endothelial cells are covered by basement membrane proteins and associated with quiescent stellate cells in normal liver. Hepatic stellate cells share the molecular markers CD105, CD146, desmin and PDGFRβ with pericytes and MSCs known from other organs. Initially they differ from these cells, since quiescent stellate cells lack the expression of nestin, NG2, CD44 and αSMA. During their activation, however, stellate cells become positive for many molecular markers commonly used to discriminate these three cell types. (A) NG2, (B) nestin, (C) CD44 and (D) CD90 become detectable along with αSMA (not shown) in activating hepatic stellate cells at day 3–4 of culture by immunofluorescence (red). In contrast to NG2, nestin and CD44, only a small subset of activated stellate cells show CD90 at protein level. (A) The pericyte marker NG2 is transiently detectable in all activated stellate cells at day 3 but disappears at protein level during prolonged culture (not shown). Other markers such as GFAP and CD133 are downregulated during activation of hepatic stellate cells. Cell nuclei are stained by DAPI (4′,6-diamidino-2-phenylindole) (blue). The scale bars represent in (A) 50 μM and in (B–D) 20 μm.

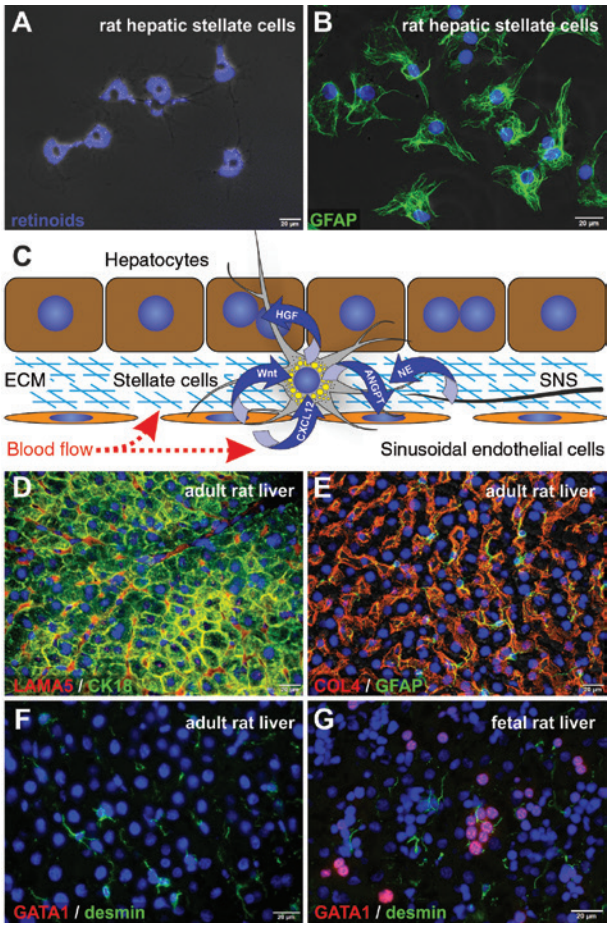

Figure 2: Hepatic stellate cells in the fetal and adult rat liver. (A) Freshly isolated hepatic stellate cells contain fluorescent retinoids in membrane-coated lipid droplets (blue) and (B) show GFAP filaments (green). (C) Scheme of the space of Disse bordered by fenestrated sinusoidal endothelial cells and hepatocytes contain extracellular matrix proteins (ECM). Stellate cells reside in this perisinusoidal space and release factors such as hepatocyte growth factor (HGF), angiopoietins (ANGPT1/2), and vascular endothelial growth factor (VEGF) to support neighboring cells and, thus, to maintain/create their own niche. Endothelial cells in turn release CXCL12 to attract stellate cells via the chemokine receptor CXCR4 and to keep them in their niche. Moreover, sinusoidal endothelial cells release WNT ligands such as WNT2 and can potentially influence stellate cell behavior. Systemic signals reach the stellate cells via the blood stream through the fenestrated endothelium and sympathetic nervous system (SNS), which release norepinephrine (NE). The perisinusoidal space of Disse between hepatocytes (CK18, green) and endothelial cells contain ECM proteins such as (D) the laminin-α5 chain (LAMA5, red) and (E) collagen 4 (COL4, red) known from basement membranes. (E) Hepatic stellate cells reside in the space of Disse and express GFAP (green). (F) Another filamentous protein typically expressed by stellate cells is desmin (green). The adult liver is normally devoid of blood-forming cells such as GATA1-positive myeloid progenitor cells (red). (G) The developing fetal liver, in contrast, is an important site for hematopoietic cells including GATA4-expressing cells (red) that are closely associated with desmin-positive stellate cells (green) within the liver sinusoids. Cell nuclei are stained by DAPI (blue). The scale bars represent 20 µm.

genes (Schumacher et al., 2017). The activation process of hepatic stellate cells is accompanied by dynamic changes in epigenetics, as the global DNA methylation is lowered by 60% mainly in non-coding areas of the genome by enzyme-mediated active mechanisms and the expression profile is drastically altered to enable cell proliferation and development (Götze et al., 2015; Schumacher et al., 2017). Thus, quiescent hepatic stellate cells are silenced by epigenetic mechanisms and their direct relation to MSCs becomes visible during their activation. This explains why hepatic stellate cells were only recently identified as liver resident MSCs (Kordes et al., 2013).

During liver development, stellate cells initially exhibit myofibroblast-like features and typical perisinusoidal reticular networks by stellate-shaped cells with long cellular extensions and retinoid storage becomes gradually prominent later (Enzan et al., 1997; Friedman, 2008). This indicates that myofibroblasts are a transient phenotype of stellate cells that is reversible (Kisseleva et al., 2012; Rohn et al., 2018). In the adult rodent liver, the stellate cell network can be shown by immunostaining of the intermediate filament proteins desmin and GFAP (Yokoi et al., 1984; Gard et al., 1985). The presence of GFAP protein is typical for quiescent hepatic stellate cells and increases with time during liver development, whereas nestin is expressed in their activated state (Niki et al., 1999; Suzuki et al., 2008). Another indicator for hepatic stellate cells is their retinyl palmitate content. The retinoids are stored in membrane-coated lipid vesicles, which show autofluorescence after excitation with ultraviolet light and were shown to maintain the quiescent state of hepatic stellate cells (Shiratori et al., 1987; Davis et al., 1990) (Figure 2A).

Hepatic stellate cells as stem cells

Our studies have demonstrated that stellate cells exhibit the expression pattern and functional characteristics of MSCs (Kordes et al., 2013, 2015). In line with this, stellate cells can originate from and home in the bone marrow (Baba et al., 2004; Russo et al., 2006; Kordes et al., 2014), where MSCs were originally discovered. They can also fulfill functions of bone marrow MSCs, as stellate cells are associated with hematopoietic stem/progenitor cells in the fetal liver and support *in vitro* hematopoiesis (Kordes et al., 2013). Stellate cells from primary culture and the human stellate cell line LX-2 can further differentiate into adipocytes, chondrocytes and osteocytes (Castilho-Fernandes et al., 2011; Kordes et al., 2013; Chinnadurai et al., 2019). These functional characteristics are frequently used to identify MSCs. Moreover, stellate cells from liver

and pancreas are also transplantable and can contribute to liver regeneration *in vivo* through differentiation into hepatocytes and cholangiocytes (Kordes et al., 2012, 2014, 2015; Michelotti et al., 2013; Swiderska-Syn et al., 2014). Although the participation of mesodermal cells to epithelial tissue regeneration remains controversial, compelling evidence exists that MSCs from bone marrow, adipose tissue or induced pluripotent stem cells can reconstitute injured liver tissue by cell differentiation (Sato et al., 2005; Aurich et al., 2007; Chamberlain et al., 2007; Kordes et al., 2015; Spitzhorn et al., 2018). This direct involvement of MSCs in the recovery of epithelial cells may depend on the severity of tissue injury, as epithelial cells such as parenchymal cells are known to contribute to liver regeneration in the first place. As transplanted stellate cells migrate to sites of organ injury, show tissue-specific engraftment, participate in tissue repair by differentiation, and are retransplantable, important properties of MSCs are fulfilled by stellate cells (Kordes et al., 2012, 2014). In addition, bone marrow MSCs and stellate cells can also participate in regenerative processes through the release of growth factors, cytokines, chemokines and extracellular vesicles containing miRNA to guide the behavior of neighboring cells (Caplan and Dennis, 2006; Parekkadan et al., 2007; Taura et al., 2008; Wang et al., 2010; Kordes et al., 2015; Castoldi et al., 2016). In this way MSCs are presumably permanently involved in tissue homeostasis and regeneration throughout the body.

The perivascular niche of hepatic stellate cells

The maintenance of stem cell characteristics in stellate cells requires a niche, which is provided in the liver by a unique perivascular space, the space of Disse (Sawitza et al., 2009), originally described by the German anatomist and histologist Joseph Disse. This perivascular niche contains ECM proteins and is bordered by hepatocytes and fenestrated sinusoidal endothelial cells (Figure 2C). Hepatic sinusoids lack typical pericytes known from microvessels of other organs (Sims, 1986) and it is likely that stellate cells fulfill a similar function.

Basement membrane proteins in the space of Disse

A non-electron dense basement membrane-like structure with reticular collagen 4 and laminin is present in normal liver within the space of Disse (Figure 2D, E). Laminins are composed of three laminin protein chains (α, β, γ) and recent analysis of the laminin composition of the liver has demonstrated the presence of the laminin α5 chain in hepatic sinusoids (Figure 2D). In addition to the laminin α5 chain, proteome analysis of decellularized rat liver revealed the prevalence of the laminin β1, β2, and γ1 chains (Rohn et al., 2018), suggesting that the laminin heterotrimers α5-β2-γ1 and α5-β1-γ1 are abundant in normal liver. Both heterotrimers are known to sustain self-renewal in pluripotent stem cells (Rodin et al., 2010; Laperle et al., 2015). When stellate cells are isolated from rat liver and cultured on laminin-521, their quiescent state and expression of stem cell-associated markers is promoted (Rohn et al., 2018), which emphasizes the importance of laminins for the perivascular stellate cell niche. Alterations of the composition and abundance of ECM proteins occur in liver diseases and play a role in initiating stellate cell activation and migration (Matsumoto et al., 1999; Yang et al., 2003). Moreover, the stiffness of the ECM substrate critically influences stellate cell activation (Georges et al., 2007). Thus, ECM composition and stiffness are important for the maintenance of hepatic stellate cells and alterations of the ECM in liver diseases affect the integrity of their niche (Figure 3).

Cell-matrix and cell-cell contacts of stellate cells

The contact of cells via membrane-bound integrins, dystroglycan, syndecans and Lutheran blood group protein/basal cell adhesion molecule (Lu/BCAM) to other basement membrane proteins such as collagen 4 is mediated by laminins (Durbeej, 2010). The β1-integrin subunit (CD29) is frequently used to identify MSC populations (Semon et al., 2010) and is weakly present in quiescent stellate cells but becomes up-regulated at protein level during their activation. In addition to β1-integrin, Lu/BCAM, β3-integrin and β4-integrin are expressed by hepatic stellate cells (Carloni et al., 1996; Kubota et al., 2007; Rohn et al., 2018), which could mediate the effects of laminin-521 on stellate cell quiescence (Rohn et al., 2018).

In the liver, stellate cells can establish homotypic cadherin junctions with hepatocytes via N-cadherin (Kozyraki et al., 1996), which are important adhesion molecules in stem cell niches (Marthiens et al., 2010). Also signaling pathways such as notch signaling require a direct physical contact of signal-sending and signal-receiving cells. Notch1 receptor is expressed by bone marrow MSCs and hepatic stellate cells (Hiraoka et al., 2006; Sawitza et al., 2009; Schumacher et al., 2017) and was reported to be

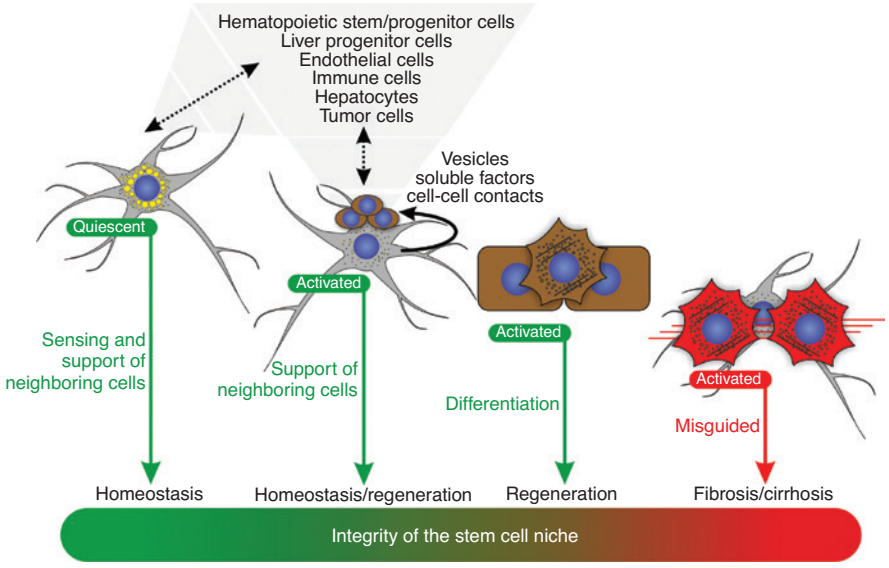

Figure 3: The niche integrity governs stellate cell maintenance and behavior.
In normal adult liver, stellate cells preserve a quiescent state in their perivascular niche, the space of Disse. They receive systemic signals from distant organs via sympathetic nerves and the blood ('sensing'). Stellate cells, in turn, release factors to maintain their surrounding microenvironment, thereby, contributing to liver homeostasis. During liver development and injury, hepatic stellate cells become activated and support neighboring cells to facilitate fetal hematopoiesis or tissue regeneration. Extracellular vesicles, soluble-factors, and cell-cell contacts are provided by stellate cells that could mediate supportive or immunosuppressive effects. Through the release of trophic factors also tumor cells might be attracted and supported as reported for MSCs in other organs. If the stem cell character of stellate cells cannot be maintained, cell differentiation into epithelial cell lineages such as hepatocytes can be induced to promote liver tissue reconstitution. If appropriate signals from their surrounding environment are missing, stellate cells sustain their activated state and deposit ECM proteins leading to fibrosis and cirrhosis. In chronic diseases associated with fibrosis/cirrhosis, the perivascular niche of stellate cells seems to be severely affected and may explain impaired liver regeneration and prevention of metastasizing tumor cell homing in liver sinusoids.

essential for the maintenance of neuronal stem cells in their niche and to suppress cell differentiation (Nyfeler et al., 2005; Basak et al., 2012; Shan et al., 2017). Conflicting reports are available for the notch 3 receptor, which seems to promote self-renewal and differentiation of stem cells (Edwards et al., 2017; Low et al., 2018; Sandel et al., 2018). In the liver, signal-sending cells that present notch ligands such as jagged1 (JAG1) are liver parenchymal cells and bile duct cells, whereas quiescent hepatic stellate cells exhibit no JAG1 protein synthesis (Jensen et al., 2004; Köhler et al., 2004; Sawitza et al., 2009). However, JAG1 appears together with notch3 during the activation of stellate cells (Sawitza et al., 2009; Schumacher et al., 2017). By providing JAG1 activated stellate cells can also support the development of neighboring cells. At present, the functional relevance of notch1 and notch3 signaling for stellate cells remains unclear. However, notch1 expression is mainly observed in freshly isolated stellate cells, indicating that notch1 could be involved in the maintenance of their quiescence state. In line with this, loss of notch1 or inhibition of notch signaling induces stellate cell activation and promotes angiogenesis (Banerjee et al., 2015).

Interactions between stellate and endothelial cells

Originally it was assumed that endothelial cells are only constituents of blood vessels, but many studies have shown that endothelial cells are also required for proper embryonal organ development and tissue regeneration (Lammert et al., 2001; Matsumoto et al., 2001; Ding et al., 2010; Hu et al., 2014; Rafii et al., 2016; Lorenz et al., 2018). In line with this, endothelial cells represent a basic element of the perivascular niche for MSCs. Indeed, endothelial cells of the bone marrow and liver sinusoids release C-X-C motif ligand 12 (CXCL12), also called stromal cell-derived factor 1 (SDF1) (Imai et al., 1999; Sawitza et al., 2009) (Figure 2C), which is the only ligand for the C-X-C motif receptor 4 (CXCR4). A CXCL12/CXCR4-dependent cell migration is known for MSCs from other organs (Wynn et al., 2004; Hong et al., 2009). Hepatic stellate cells express also CXCR4 and migrate to sinusoidal endothelial cells in response to CXCL12 (Sawitza et al., 2009). Moreover, stellate cells follow endothelial cells that invade the developing liver

as demonstrated in the zebrafish (*Danio rerio*) (Yin et al., 2012). The expression of CXCL12 is not limited to endothelial cells in the liver. Also hepatic stellate cells start to release CXCL12 after their activation as described for other MSCs (Kubota et al., 2007; Hong et al., 2009; Sawitza et al., 2009). Through the CXCL12 secretion stellate cells may not only attract migrating stem/progenitor cells but also metastasizing tumor cells expressing CXCR4 (Correa et al., 2016). The interaction of CXCL12 and CXCR4 is an essential process to initiate and maintain stem cell niches, since the recruitment of stem cells from the bone marrow is partly mediated by local downregulation of CXCL12, which facilitates their mobilization from the bone marrow into the blood stream (Lapidot et al., 2005; Méndez-Ferrer et al., 2008).

As pericytes were shown to be important for angiogenesis and vessel maturation (Teichert et al., 2017) and endothelial cells release factors such as CXCL12, a mutual dependency between these cells can be expected. Indeed, hepatic stellate cells release vascular endothelial growths factors (VEGF), which maintain fenestration of sinusoidal endothelial cells (Ankoma-Sey et al., 2000; DeLeve et al., 2004), and angiopoietins (ANGPT1/2), which have been shown to promote the maturation of endothelial cells (Shimizu et al., 2005; Taura et al., 2008; Teichert et al., 2017). These findings indicate a tight relationship between stellate cells and sinusoidal endothelial cells in the liver that may stabilize the hepatic sinusoids and, thus, the perivascular niche in the space of Disse (Figure 2C).

Apart from CXCL12, other soluble factors such as WNT ligands can control the behavior of stellate cells, as β-catenin-dependent WNT (canonical) signaling maintains their quiescence (Kordes et al., 2008). Current knowledge points to endothelial cells of the central veins as a source for WNT ligands (WNT2 and WNT9b), which are involved in maintaining metabolic liver zonation (Leibing et al., 2018; Russell and Monga, 2018; Zhao et al., 2019). However, sinusoidal endothelial cells from normal and injured liver also express WNT2 (Klein et al., 2008; Ding et al., 2010), which can potentially contribute to sustain quiescence of stellate cells by canonical WNT signaling. This pathway can also preserve quiescence in hematopoietic stem cells and is essential to maintaining stemness (Reya et al., 2003; Sato et al., 2004; Fleming et al., 2008). However, non-canonical WNT pathways via the receptor frizzled 8 also seems to support hematopietic stem cells (Sugimura et al., 2012). Non-canonical WNT signaling can counteract canonical WNT signaling and may represent a regulatory mechanism involved in stabilizing hematopoietic stem cells in their niche. Further research is required to elucidate the WNT ligands that effectively control quiescence and activation of hepatic stellate cells.

During their activation, however, stellate cells significantly elevate the expression of non-canonical WNT ligands such as WNT4, WNT5a and WNT11 (Jiang et al., 2006; Kordes et al., 2008; Corbett et al., 2015). This 'WNT switch' can also be found in bone marrow MSCs (Davis and Zur Nieden, 2008). The relevance of an increased release of non-canonical WNT ligands is not yet clear but it can be assumed that non-canonical WNT ligands released by activated hepatic stellate cells influence the development of adjacent stem/progenitor cells as reported for the hematopoietic stem cell niche (Sugimura et al., 2012). Experimental evidence for this is provided by co-cultures of hepatic stellate cells with liver progenitor cells and hematopoietic stem cells (Wang et al., 2010; Kordes et al., 2013, 2015). This implies, that the stem cell niche character of the space of Disse should become apparent during fetal development, when the liver harbors hematopoietic stem/progenitor cells and supports blood formation before hematopoietic stem cells migrate into the bone marrow. In fact, GATA1-expressing myeloid progenitor cells are distributed throughout the liver parenchyma and are in close contact with desmin-positive stellate cells in the fetal rat liver (Kordes et al., 2013) (Figure 2F, G). The hematopoiesis in the fetal liver provides clear evidence for the existence of a stem cell niche in the space of Disse.

Innervation of the space of Disse

Humoral signals from different organs are carried via the blood stream to stem cell niches, but also the peripheral nervous system is involved in signal transmission. The egress of hematopoietic stem cells from the bone marrow into the blood is initiated by the sympathetic nervous system via innervation of MSCs (Katayama et al., 2006; Lucas et al., 2012). Norepinephrine release by the peripheral sympathetic nervous system triggers a decrease of CXCL12 and initiates hematopoietic stem cell mobilization (Katayama et al., 2006; Ferraro et al., 2011), which is enhanced by granulocyte colony-stimulating factor (G-CSF). Bone marrow MSCs synthesize G-CSF and are known to be associated with nerves (Haynesworth et al., 1996; Isern and Méndez-Ferrer, 2011). Nerve endings are also found in close contact to hepatic stellate cells. An α-adrenergic stimulation triggers Ca^{2+} transients, the release of myoinositol, RANTES, interleukin-8, and of prostaglandins and upregulate collagen and transforming growth factor expression in hepatic stellate cells

(Häussinger et al., 1987; Athari et al., 1994; Reinehr et al. 1998; vom Dahl et al., 1999; McCuskey, 2004; Sancho-Bru et al., 2006; Sigala et al., 2013). Stellate cell-derived prostaglandins activate glycogenolysis in neighboring hepatocytes and, thereby, elevate local glucose concentration (Häussinger et al., 1987; Athari et al., 1994). Thus, stellate cells can integrate signals from sympathetic nervous system to influence the behavior of neighboring cells in their niche.

Alterations of the niche in the regenerating liver

In the injured liver, the composition of growth factors, cytokines and chemokines in the blood and tissue is altered and also cell-cell contacts are transiently lost when cells divide in order to restore liver mass. Changes in niche components of the regenerating or diseased liver can control the behavior of hepatic stellate cells. In normal liver, stellate cells remain quiescent and can contribute to liver homeostasis through the release of hepatocyte growth factor or in response to sympathetic nerve signals (Schirmacher et al., 1991; Ramadori et al., 1992; vom Dahl et al., 1999; Sumii et al., 2016). After partial hepatectomy, stellate cells first transiently loose cell-cell contacts with neighboring parenchymal cells and then deplete retinoid stores on the third day (Budny et al., 2007). Thereafter, activated stellate cells form clusters and intensify their cell contacts with parenchymal cells and finally increase their lipid stores again when tissue repair proceeds (Budny et al., 2007), showing that stellate cells strongly respond to changes in their microenvironment. This demonstrates that activated stellate cells can regain the quiescent state. After more severe liver injury, when the proliferative capacity of parenchymal cells is exhausted and LPC appear to reconstitute parenchymal cells and cholangiocytes through differentiation, stellate cells can also support the differentiation of LPC as demonstrated by co-culture experiments (Wang et al., 2010) (Figure 3). However, stellate cells themselves can acquire a LPC-phenotype and differentiate into hepatocytes and cholangiocytes (Kordes et al., 2014) (Figure 3). To ensure their supportive effects and developmental potential, stellate cells can survive even under adverse environmental conditions. Despite expression of CD95/Fas in quiescent hepatic stellate cells, these cells are resistant towards CD95 ligand-induced apoptosis (Reinehr et al., 2008; Sommerfeld et al., 2009). Here, CD95 ligand triggers an inactivating tyrosine nitration of CD95/Fas and simultaneously stimulates stellate cell proliferation through shedding of epidermal growth factor (EGF) followed by autocrine EGF receptor activation (Reinehr et al., 2008).

Hedgehog (HH) signaling is important for liver development and regeneration but in the uninjured adult liver HH signaling is silenced and only few cells around portal tracts exhibit an active HH pathway (Sicklick et al., 2006; Gao et al., 2018). Therefore, HH signaling seems to be dispensable for the stellate cell niche in the normal liver. In line with this, quiescent hepatic stellate cells express the inhibitory HH-interacting protein, which is down-regulated after their activation in culture (Choi et al., 2009). However, evidence has been presented that HH signaling determines stem cell development in their niche (Brownell et al., 2011). After liver injury, hepatocytes release the HH ligands sonic hedgehog (SHH) and indian hedgehog (IHH) that can activate the HH pathway in neighboring stellate cells and LPC, thereby promoting cell viability and growth (Sicklick et al., 2005, 2006). Thus, HH ligands alter the niche environment of stellate cells, triggers their activation, and may influences their development as observed for bone marrow MSCs (Spinella-Jaegle et al., 2001).

The stellate cell niche in liver diseases

In chronic liver diseases, activated stellate cells lose their beneficial effects on tissue regeneration, are misguided and deposit collagens, thereby, contributing to fibrosis (Friedman et al., 1985). The situation, however, is more complex than previously anticipated, as other cells such as portal and bone marrow-derived myofibroblasts as well as mesenchymal cells that originate from epithelial cells via epithelial-to-mesenchymal transition (EMT) were also described to be involved in fibrogenesis (Forbes et al., 2004; Russo et al., 2006; Beaussier et al., 2007; Kalluri and Weinberg, 2009). Chronic inflammation usually precedes fibrosis, which is associated with long-lasting alterations of niche components such as ECM composition in the space of Disse. Under these conditions regenerative processes through resident epithelial cells, stellate cells and other MSCs of the body are obviously impaired but can be restored to a certain extent by transplantation of allogenic MSCs (Zhao et al., 2005; Oyagi et al., 2006). Although transplanted MSCs are capable of ameliorating liver fibrosis, evidence has accumulated that MSCs contribute to fibrosis in many organs such as muscle, lung, heart and liver (Marriott et al., 2014; Kramann et al., 2015; Liu et al., 2015; Ieronimakis et al., 2016; Trial et al., 2016). Thus, whether MSCs are fibrotic or fibrolytic seems to be

context-dependent and to be controlled by environmental cues. An age-related decline in stem cell niche integrity is known (Mayack et al., 2010; Maryanovich et al., 2018) and most likely responsible for these differential effects. The accumulation of somatic DNA damage and oxidative stress are major triggers of cell aging. Stem cell senescence, apoptosis, and differentiation can lead to successive stem cell depletion and impair the regenerative capacity of aged tissues. DNA damage of melanocyte stem cells for instance can trigger their differentiation into melanocytes within the hair follicle, thereby decreasing the melanocyte stem cell pool, which can ultimately lead to graying of hair (Inomota et al., 2009). Age-related impairment of osteogenic differentiation of bone marrow MSCs is due to effects of oxidative stress on HH signaling (Kim et al., 2010). Chronic inflammation can elicit enhanced telomere shortening and defects in DNA repair mechanisms, which lead to DNA damage in adult stem cells (Mimeault and Batra, 2009) and could be one reason that causes niche alterations in chronic liver disease. An altered perivascular niche in chronic inflammation may be involved in dysregulation of MSCs and their contribution to fibrosis.

Niches formed by activated stellate cells can also have adverse effects through supporting cancer stem cells and promotion of tumor cell progression as observed in hepatocellular carcinoma (Amann et al., 2009; Knaak et al., 2018; Wen et al., 2019). Hepatic stellate cells can further enable the engraftment of metastasizing melanoma cells in liver sinusoids via a CD146-dependent mechanism (Correa et al., 2016). Immunosuppressive functions, which can contribute to tumor cell survival, are consistently reported for stellate cells and bone marrow MSCs (McIntosh and Bartholomew, 2000; Krampera et al., 2003; Lee et al., 2005; Chen et al., 2006; Schildberg et al., 2011). Stellate cell engagement in niche formation may critically depend on their activation, as non-activated stellate cells seem to support the quiescence-associated phenotype of pancreatic ductal adenocarcinoma cells via interleukin-8 release while this positive effect is lost when stellate cells activate and become myofibroblasts as investigated *in vitro* (Lenk et al., 2017). The stem cell-friendly microenvironment in the space of Disse and the provision of niche elements by activated stellate cells in conjunction with their immunosuppressive functions could be the reason for the frequent homing of migrating tumor cells in the liver, predisposing this organ for metastasis. Alterations of this perivascular niche in chronic diseases may explain impaired homing of intrahepatic metastasis in liver cirrhosis (Ruebner et al., 1961).

Conclusions

The finding that stellate cells represent liver-resident MSCs allows for explanations of seemingly discrepant observations regarding ECM deposition and hepatic stellate cell function as MSCs made in the past. Stellate cells can, on the one hand, be seen as triggers of liver fibrosis and on the other hand, MSC transplantation can ameliorate liver fibrosis in experimental settings. We postulate that the niche integrity determines whether stellate cells/MSCs have pro- or antifibrotic properties. Moreover, this concept may enable new therapeutic approaches for the treatment of chronic liver disease. Further aspects are offered by the potential of stellate cells to acquire a quiescent state in their niche, to influence neighboring cells by immunomodulatory and trophic factors, and to differentiate. First attempts are made to enforce differentiation of stellate cell-derived myofibroblasts in fibrotic liver of mice into hepatocytes by overexpression of defined hepatic transcription factors (Rezvani et al., 2016; Song et al., 2016). Identification of perivascular niche components that are lost in chronic liver diseases and reestablishment of these factors may not only offer new therapeutic approaches to treat patients with liver fibrosis but also new aspects on the aging liver.

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References

Alfaifi, M., Eom, Y.W., Newsome, P.N., and Baik, S.K. (2018). Mesenchymal stromal cell therapy for liver diseases. J. Hepatol. *68*, 1272–1285.

Amann, T., Bataille, F., Spruss, T., Mühlbauer, M., Gäbele, E., Schölmerich, J., Kiefer, P., Bosserhoff, A.K., and Hellerbrand, C. (2009). Activated hepatic stellate cells promote tumorigenicity of hepatocellular carcinoma. Cancer Sci. *100*, 646–653.

Ankoma-Sey, V., Wang, Y., and Dai, Z. (2000). Hypoxic stimulation of vascular endothelial growth factor expression in activated rat hepatic stellate cells. Hepatology *31*, 141–148.

Athari, A., Hänecke, K., and Jungermann, K. (1994). Prostaglandin F2alpha and D2 release from primary Ito cell cultures after stimulation with noradrenaline and ATP but not adenosine. Hepatology *20*(1 Pt 1), 142–148.

Aurich, I., Mueller, L.P., Aurich, H., Luetzkendorf, J., Tisljar, K., Dollinger, M.M., Schormann, W., Walldorf, J., Hengstler, J.G., Fleig, W.E., et al. (2007). Functional integration of hepatocytes derived from human mesenchymal stem cells into mouse livers. Gut *56*, 405–415.

Baba, S., Fujii, H., Hirose, T., Yasuchika, K., Azuma, H., Hoppo, T., Naito, M., Machimoto, T., and Ikai, I. (2004). Commitment of bone morrow cells to hepatic stellate cells in mouse. J. Hepatol. *40*, 255–260.

Banerjee, D., Hernandez, S.L., Garcia, A., Kangsamaksin, T., Sbiroli, E., Andrews, J., Forrester, L.A., Wei, N., Kadenhe-Chiweshe, A., Shawber, C.J., et al. (2015). Notch suppresses angiogenesis and progression of hepatic metastases. Cancer Res. *75*, 1592–1602.

Basak, O., Giachino, C., Fiorini, E., Macdonald, H.R., and Taylor, V. (2012). Neurogenic subventricular zone stem/progenitor cells are Notch1-dependent in their active but not quiescent state. J. Neurosci. *32*, 5654–5666.

Beaussier, M., Wendum, D., Schiffer, E., Dumont, S., Rey, C., Lienhart, A., and Housset, C. (2007). Prominent contribution of portal mesenchymal cells to liver fibrosis in ischemic and obstructive cholestatic injuries. Lab. Invest. *87*, 292–303.

Brownell, I., Guevara, E., Bai, C.B., Loomis, C.A., and Joyner, A.L. (2011). Nerve-derived sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. Cell Stem Cell *8*, 552–565.

Budny, T., Palmes, D., Stratmann, U., Minin, E., Herbst, H., and Spiegel, H.U. (2007). Morphologic features in the regenerating liver – a comparative intravital, lightmicroscopical and ultrastructural analysis with focus on hepatic stellate cells. Virchow's Arch. *451*, 781–791.

Caplan, A.I. (1991). Mesenchymal stem cells. J. Orthop. Res. *9*, 641–650.

Caplan, A.I. (2008). All MSCs are pericytes? Cell Stem Cell *3*, 229–230.

Caplan, A.I., and Dennis, J.E. (2006). Mesenchymal stem cells as trophic mediators. J. Cell Biochem. *98*, 1076–1084.

Carloni, V., Romanelli, R.G., Pinzani, M., Laffi, G., and Gentilini, P. (1996). Expression and function of integrin receptors for collagen and laminin in cultured human hepatic stellate cells. Gastroenterology *110*, 1127–1136.

Castilho-Fernandes, A., de Almeida, D.C., Fontes, A.M., Melo, F.U., Picanço-Castro, V., Freitas, M.C., Orellana, M.D., Palma, P.V., Hackett, P.B., Friedman, S.L., et al. (2011). Human hepatic stellate cell line (LX-2) exhibits characteristics of bone marrow-derived mesenchymal stem cells. Exp. Mol. Pathol. *91*, 664–672.

Castoldi, M., Kordes, C., Sawitza, I., and Häussinger, D. (2016). Isolation and characterization of vesicular and nonvesicular microRNAs circulating in sera of partially hepatectomized rats. Sci. Rep. *6*, 31869.

Chamberlain, J., Yamagami, T., Colletti, E., Theise, N.D., Desai, J., Frias, A., Pixley, J., Zanjani, E.D., Porada, C.D., and Almeida-Porada, G. (2007). Efficient generation of human hepatocytes by the intrahepatic delivery of clonal human mesenchymal stem cells in fetal sheep. Hepatology *46*, 1935–1945.

Chen, C.H., Kuo, L.M., Chang, Y., Wu, W., Goldbach, C., Ross, M.A., Stolz, D.B., Chen, L., Fung, J.J., Lu, L., et al. (2006). *In vivo* immune modulatory activity of hepatic stellate cells in mice. Hepatology *44*, 1171–1181.

Chen, Y., Wong, P.P., Sjeklocha, L., Steer, C.J., and Sahin, M.B. (2012). Mature hepatocytes exhibit unexpected plasticity by direct dedifferentiation into liver progenitor cells in culture. Hepatology *55*, 563–574.

Chien, C.S., Chen, Y.H., Chen, H.L., Wang, C.P., Wu, S.H., Ho, S.L., Huang, W.C., Yu, C.H., and Chang, M.H. (2018). Cells responsible for liver mass regeneration in rats with 2-acetylaminofluorene/partial hepatectomy injury. J. Biomed. Sci. *25*, 39–52.

Chinnadurai, R., Sands, J., Rajan, D., Liu, X., Arafat, D., Das, R., Anania, F.A., Gibson, G., Kisseleva, T., and Galipeau, J. (2019). Molecular genetic and immune functional responses distinguish bone marrow mesenchymal stromal cells from hepatic stellate cells. Stem Cells, doi: 10.1002/stem.3028.

Choi, S.S., Omenetti, A., Witek, R.P., Moylan, C.A., Syn, W.K., Jung, Y., Yang, L., Sudan, D.L., Sicklick, J.K., Michelotti, G.A., et al. (2009). Hedgehog pathway activation and epithelial-to-mesenchymal transitions during myofibroblastic transformation of rat hepatic cells in culture and cirrhosis. Am. J. Physiol. Gastrointest. Liver Physiol. *297*, G1093–1106.

Corbett, L., Mann, J., and Mann, D.A. (2015). Non-canonical Wnt predominates in activated rat hepatic stellate cells, influencing HSC survival and paracrine stimulation of Kupffer cells. PLoS One *10*, e0142794.

Correa, D., Somoza, R.A., Lin, P., Schiemann, W.P., and Caplan, A.I. (2016). Mesenchymal stem cells regulate melanoma cancer cells extravasation to bone and liver at their perivascular niche. Int. J. Cancer *138*, 417–427.

Covas, D.T., Panepucci, R.A., Fontes, A.M., Silva, W.A. Jr., Orellana, M.D., Freitas, M.C., Neder, L., Santos, A.R., Peres, L.C., Jamur, M.C., et al. (2008). Multipotent mesenchymal stromal cells obtained from diverse human tissues share functional properties and gene-expression profile with $CD146^+$ perivascular cells and fibroblasts. Exp. Hematol. *36*, 642–654.

Crisan, M., Yap, S., Casteilla, L., Chen, C.W., Corselli, M., Park, T.S., Andriolo, G., Sun, B., Zheng, B., Zhang, L., et al. (2008). A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell *3*, 301–313.

da Silva Meirelles, L., Chagastelles, P.C., and Nardi, N.B. (2006). Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J. Cell Sci. *119*, 2204–2213.

da Silva Meirelles, L., Caplan, A.I., and Nardi, N.B. (2008). In search of the *in vivo* identity of mesenchymal stem cells. Stem Cells *26*, 2287–2299.

Davis, L.A. and Zur Nieden, N.I. (2008). Mesodermal fate decisions of a stem cell: the Wnt switch. Cell. Mol. Life Sci. *65*, 2658–2674.

Davis, B.H., Kramer, R.T., and Davidson, N.O. (1990). Retinoic acid modulates rat Ito cell proliferation, collagen, and transforming growth factor beta production. J. Clin. Invest. *86*, 2062–2070.

De Vos, R. and Desmet, V. (1992). Ultrastructural characteristics of novel epithelial cell types identified in human pathologic liver specimens with chronic ductular reaction. Am. J. Pathol. *140*, 1441–1450.

DeLeve, L.D., Wang, X., Hu, L., McCuskey, M.K., and McCuskey, R.S. (2004). Rat liver sinusoidal endothelial cell phenotype is maintained by paracrine and autocrine regulation. Am. J. Physiol. Gastrointest. Liver Physiol. *287*, G757–763.

Ding, B.S., Nolan, D.J., Butler, J.M., James, D., Babazadeh, A.O., Rosenwaks, Z., Mittal, V., Kobayashi, H., Shido, K., Lyden, D., et al. (2010). Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. Nature *468*, 310–315.

Dorrell, C., Erker, L., Schug, J., Kopp, J.L., Canaday, P.S., Fox, A.J., Smirnova, O., Duncan, A.W., Finegold, M.J., Sander, M., et al. (2011). Prospective isolation of a bipotential clonogenic liver progenitor cell in adult mice. Genes Dev. *25*, 1193–203.

Durbeej, M. (2010). Laminins. Cell Tissue Res. *339*, 259–268.

Eaves, C.J., Cashman, J.D., Sutherland, H.J., Otsuka, T., Humphries, R.K., Hogge, D.E., Lansdorp, P.L., and Eaves, A.C. (1991). Molecular analysis of primitive hematopoietic cell proliferation control mechanisms. Ann. NY Acad. Sci. *628*, 298–306.

Edwards, A.K., Glithero, K., Grzesik, P., Kitajewski, A.A., Munabi, N.C., Hardy, K., Tan, Q.K., Schonning, M., Kangsamaksin, T., Kitajewski, J.K., et al. (2017). Notch3 regulates stem-to-mural cell differentiation in infantile hemangioma. JCI Insight *2*, 93764.

El-Hayek, S. and Clarke, H.J. (2016). Control of oocyte growth and development by intercellular communication within the follicular niche. Results Probl. Cell. Differ. *58*, 191–224.

Enzan, H., Himeno, H., Hiroi, M., Kiyoku, H., Saibara, T., and Onishi, S. (1997). Development of hepatic sinusoidal structure with special reference to the Ito cells. Microsc. Res. Tech. *39*, 336–349.

Espanol-Suner, R., Carpentier, R., Van Hul, N., Legry, V., Achouri, Y., Cordi, S., Jacquemin, P., Lemaigre, F., and Leclercq, I.A. (2012). Liver progenitor cells yield functional hepatocytes in response to chronic liver injury in mice. Gastroenterology *143*, 1564–1575.

Farini, A., Sitzia, C., Erratico, S., Meregalli, M., and Torrente, Y. (2014). Clinical applications of mesenchymal stem cells in chronic diseases. Stem Cells Int. *2014*, 306573.

Ferraro, F., Lymperi, S., Méndez-Ferrer, S., Saez, B., Spencer, J.A., Yeap, B.Y., Masselli, E., Graiani, G., Prezioso, L., Rizzini, E.L., et al. (2011). Diabetes impairs hematopoietic stem cell mobilization by altering niche function. Sci. Transl. Med. *3*, 104ra101.

Fleming, H.E., Janzen, V., Lo Celso, C., Guo, J., Leahy, K.M., Kronenberg, H.M., Kronenberg, H.M., and Scadden, D.T. (2008). Wnt signaling in the niche enforces hematopoietic stem cell quiescence and is necessary to preserve self-renewal *in vivo*. Cell Stem Cell *2*, 274–283.

Forbes, S.J., Russo, F.P., Rey, V., Burra, P., Rugge, M., Wright, N.A., and Alison, M.R. (2004). A significant proportion of myofibroblasts are of bone marrow origin in human liver fibrosis. Gastroenterology *126*, 955–963.

Friedenstein, A.J., Chailakhjan, R.K., and Lalykina, K.S. (1970). The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Prolif. *3*, 393–403.

Friedman, S.L. (2008). Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. Physiol. Rev. *88*, 125–172.

Friedman, S.L., Roll, F.J., Boyles, J., and Bissell, D.M. (1985). Hepatic lipocytes: the principal collagen-producing cells of normal rat liver. Proc. Natl. Acad. Sci. USA *82*, 8681–8685.

Furuyama, K., Kawaguchi, Y., Akiyama, H., Horiguchi, M., Kodama, S., Kuhara, T., Hosokawa, S., Elbahrawy, A., Soeda, T., Koizumi, M., et al. (2011). Continuous cell supply from a Sox9-expressing progenitor zone in adult liver, exocrine pancreas and intestine. Nat. Genet. *43*, 34–41.

Gao, L., Zhang, Z., Zhang, P., Yu, M., and Yang, T. (2018). Role of canonical Hedgehog signaling pathway in liver. Int. J. Biol. Sci. *14*, 1636–1644.

Gard, A., White, F., and Dutton, G. (1985). Extra-neural glial fibrillary acidic protein (GFAP) immunoreactivity in perisinusoidal stellate cells of rat liver. J. Neuroimmunol. *8*, 359–375.

Georges, P.C., Hui, J.J., Gombos, Z., McCormick, M.E., Wang, A.Y., Uemura, M., Mick, R., Janmey, P.A., Furth, E.E., and Wells, R.G. (2007). Increased stiffness of the rat liver precedes matrix deposition: implications for fibrosis. Am. J. Physiol. Gastrointest. Liver Physiol. *293*, G1147–1154.

Gerhardt, H. and Betsholtz, C. (2003). Endothelial-pericyte interactions in angiogenesis. Cell Tissue Res. *314*, 15–23.

Goldman, S.A. and Chen, Z. (2011). Perivascular instruction of cell genesis and fate in the adult brain. Nat. Neurosci. *14*, 1382–1389.

Gonzales, K.A.U. and Fuchs, E. (2017). Skin and its regenerative powers: an alliance between stem cells and their niche. Dev. Cell *43*, 387–401.

Götze, S., Schumacher, E.C., Kordes, C., and Häussinger, D. (2015). Epigenetic changes during hepatic stellate cell activation. PLoS One *10*, e0128745.

Häussinger, D., Stehle, T., Gerok, W., and Sies, H. (1987). Perivascular nerve stimulation and phenylephrine responses in rat liver. Metabolic effects, Ca^{2+} and K^{+} fluxes. Eur. J. Biochem. *163*, 197–203.

Haynesworth, S.E., Baber, M.A., and Caplan, A.I. (1996). Cytokine expression by human marrow-derived mesenchymal progenitor cells *in vitro*: effects of dexamethasone and IL-1α. J. Cell Physiol. *166*, 585–592.

Hendriks, H.F., Verhoofstad, W.A., Brouwer, A., de Leeuw, A.M., and Knook, D.L. (1985). Perisinusoidal fat-storing cells are the main vitamin A storage sites in rat liver. Exp. Cell Res. *160*, 138–149.

Hiraoka, K., Grogan, S., Olee, T., and Lotz, M. (2006). Mesenchymal progenitor cells in adult human articular cartilage. Biorheology *43*, 447–454.

Hong, F., Tuyama, A., Lee, T.F., Loke, J., Agarwal, R., Cheng, X., Garg, A., Fiel, M.I., Schwartz, M., Walewski, J., et al. (2009). Hepatic stellate cells express functional CXCR4: role in stromal cell-derived factor-1alpha-mediated stellate cell activation. Hepatology *49*, 2055–2067.

Hu, J., Srivastava, K., Wieland, M., Runge, A., Mogler, C., Besemfelder, E., Terhardt, D., Vogel, M.J., Cao, L., Korn, C., et al. (2014). Endothelial cell-derived angiopoietin-2 controls liver regeneration as a spatiotemporal rheostat. Science *343*, 416–419.

Hyun, J., Oh, S.H., Premont, R.T., Guy, C.D., Berg, C.L., and Diehl, A.M. (2019). Dysregulated activation of fetal liver programme in acute liver failure. Gut *68*, 1076–1087.

Ieronimakis, N., Hays, A., Prasad, A., Janebodin, K., Duffield, J.S., and Reyes, M. (2016). PDGFRα signalling promotes fibrogenic responses in collagen-producing cells in Duchenne muscular dystrophy. J. Pathol. *240*, 410–424.

Imai, K., Kobayashi, M., Wang, J., Shinobu, N., Yoshida, H., Hamada, J., Shindo, M., Higashino, F., Tanaka, J., Asaka, M., et al. (1999). Selective secretion of chemoattractants for haemopoietic progenitor cells by bone marrow endothelial cells: a possible role in homing of haemopoietic progenitor cells to bone marrow. Br. J. Haematol. *106*, 905–911.

Inomata, K., Aoto, T., Binh, N.T., Okamoto, N., Tanimura, S., Wakayama, T., Iseki, S., Hara, E., Masunaga, T., Shimizu, H., et al. (2009). Genotoxic stress abrogates renewal of melanocyte stem cells by triggering their differentiation. Cell *137*, 1088–1099.

Isern, J. and Méndez-Ferrer, S. (2011). Stem cell interactions in a bone marrow niche. Curr. Osteoporos. Rep. *9*, 210–218.

Jensen, C.H., Jauho, E.I., Santoni-Rugiu, E., Holmskov, U., Teisner, B., Tygstrup, N., and Bisgaard, H.C. (2004). Transit-amplifying ductular (oval) cells and their hepatocytic progeny are characterized by a novel and distinctive expression of delta-like protein/preadipocyte factor 1/fetal antigen 1. Am. J. Pathol. *164*, 1347–1359.

Jiang, F., Parsons, C.J., and Stefanovic, B. (2006). Gene expression profile of quiescent and activated rat hepatic stellate cells implicate Wnt signaling pathway in activation. J. Hepatol. *45*, 401–409.

Kalluri, R. and Weinberg, R.A. (2009). The basics of epithelial-mesenchymal transition. J. Clin. Invest. *119*, 1420–1428.

Katayama, Y., Battista, M., Kao, W.-M., Hidalgo, A., Peired, A.J., Thomas, S.A., and Frenette, P.S. (2006). Signals from the sympathic nervous system regulate hematopoietic stem cell egress from the bone marrow. Cell *124*, 407–421.

Kfoury, Y. and Scadden, D.T. (2015). Mesenchymal cell contributions to the stem cell niche. Cell Stem Cell *16*, 239–253.

Kikuchi, S., Griffin, C.T., Wang, S.S., and Bissell, D.M. (2005). Role of CD44 in epithelial wound repair: migration of rat hepatic stellate cells utilizes hyaluronic acid and CD44v6. J. Biol. Chem. *280*, 15398–15404.

Kim, W.K., Meliton, V., Bourquard, N., Hahn, T.J., and Parhami, F. (2010). Hedgehog signaling and osteogenic differentiation in multipotent bone marrow stromal cells are inhibited by oxidative stress. J. Cell. Biochem. *111*, 1199–1209.

Kisseleva, T., Cong, M., Paik, Y., Scholten, D., Jiang, C., Benner, C., Iwaisako, K., Moore-Morris, T., Scott, B., Tsukamoto, H., et al. (2012). Myofibroblasts revert to an inactive phenotype during regression of liver fibrosis. Proc. Natl. Acad. Sci. USA *109*, 9448–9453.

Klein, D., Demory, A., Peyre, F., Kroll, J., Augustin, H.G., Helfrich, W., Kzhyshkowska, J., Schledzewski, K., Arnold, B., and Goerdt, S. (2008). Wnt2 acts as a cell type-specific, autocrine growth factor in rat hepatic sinusoidal endothelial cells cross-stimulating the VEGF pathway. Hepatology *47*, 1018–1031.

Knaack, H., Lenk, L., Philipp, L.M., Miarka, L., Rahn, S., Viol, F., Hauser, C., Egberts, J.H., Gundlach, J.P., Will, O., et al. (2018). Liver metastasis of pancreatic cancer: the hepatic microenvironment impacts differentiation and self-renewal capacity of pancreatic ductal epithelial cells. Oncotarget *9*, 31771–31786.

Köhler, C., Bell, A.W., Bowen, W.C., Monga, S.P., Fleig, W., and Michalopoulos, G.K. (2004). Expression of Notch-1 and its ligand Jagged-1 in rat liver during liver regeneration. Hepatology *39*, 1056–1065.

Kopp, J.L., Grompe, M., and Sander, M. (2016). Stem cells versus plasticity in liver and pancreas regeneration. Nat. Cell Biol. *18*, 238–245.

Kordes, C. and Häussinger, D. (2013). Hepatic stem cell niches. J. Clin. Invest. *123*, 1874–1880.

Kordes, C., Sawitza, I., and Häussinger, D. (2008). Canonical Wnt signaling maintains the quiescent stage of hepatic stellate cells. Biochem. Biophys. Res. Commun. *367*, 116–123.

Kordes, C., Sawitza, I., Götze, S., and Häussinger, D. (2012). Stellate cells from rat pancreas are stem cells and can contribute to liver regeneration. PLoS One *7*, e51878.

Kordes, C., Sawitza, I., Götze, S., and Häussinger, D. (2013). Hepatic stellate cells support hematopoiesis and are liver-resident mesenchymal stem cells. Cell. Physiol. Biochem. *31*, 290–304.

Kordes, C., Sawitza, I., Götze, S., Herebian, D., and Häussinger, D. (2014). Hepatic stellate cells contribute to progenitor cells and liver regeneration. J. Clin. Invest. *124*, 5503–5515.

Kordes, C., Sawitza, I., Götze, S., Schumacher, E., and Häussinger, D. (2015). Beyond fibrosis: stellate cells as liver stem cells. Z. Gastroenterol. *53*, 1425–1431.

Kozyraki, R., Scoazec, J.Y., Flejou, J.F., D'Errico, A., Bedossa, P., Terris, B., Fiorentino, M., Bringuier, A.F., Grigioni, W.F., and Feldmann, G. (1996). Expression of cadherins and alpha-catenin in primary epithelial tumors of the liver. Gastroenterology *110*, 1137–1149.

Kramann, R., Schneider, R.K., DiRocco, D.P., Machado, F., Fleig, S., Bondzie, P.A., Henderson, J.M., Ebert, B.L., and Humphreys, B.D. (2015). Perivascular Gli1^{+} progenitors are key contributors to injury-induced organ fibrosis. Cell Stem Cell. *16*, 51–66.

Krampera, M., Glennie, S., Dyson, J., Scott, D., Laylor, R., Simpson, E., and Dazzi, F. (2003). Bone marrow mesenchymal stem cells inhibit the response of naive antigen specific T-cells to their cognate peptide. Blood *101*, 3722–3729.

Kubota, H., Yao, H.L., and Reid, L.M. (2007). Identification and characterization of vitamin A-storing cells in fetal liver: implications for functional importance of hepatic stellate cells in liver development and hematopoiesis. Stem Cells *25*, 2339–2349.

Lammert, E., Cleaver, O., and Melton, D. (2001). Induction of pancreatic differentiation by signals from blood vessels. Science *294*, 564–567.

Lane, S.W., Williams, D.A., and Watt, F.M. (2014). Modulating the stem cell niche for tissue regeneration. Nat. Biotechnol. *32*, 795–803.

Laperle, A., Hsiao, C., Lampe, M., Mortier, J., Saha, K., Palecek, S.P., and Masters, K.S. (2015). α-5 laminin synthesized by human pluripotent stem cells promotes self-renewal. Stem Cell Rep. *5*, 195–206.

Lapidot, T., Dar, A., and Kollet, O. (2005). How do stem cells find their way home? Blood *106*, 1901–1910.

Lee, W.C., Yu, M.C., Lu, L., and Qian, S. (2005). Liver stellate cells suppress dendritic cells through IL-10. Transplant. Proc. *37*, 10–11.

Leibing, T., Géraud, C., Augustin, I., Boutros, M., Augustin, H.G., Okun, J.G., Langhans, C.D., Zierow, J., Wohlfeil, S.A., Olsavszky, V., et al. (2018). Angiocrine Wnt signaling controls liver growth and metabolic maturation in mice. Hepatology *68*, 707–722.

Lenk, L., Pein, M., Will, O., Gomez, B., Viol, F., Hauser, C., Egberts, J.H., Gundlach, J.P., Helm, O., Tiwari, S., et al. (2017). The hepatic microenvironment essentially determines tumor cell dormancy and metastatic outgrowth of pancreatic ductal adenocarcinoma. Oncoimmunology *7*, e1368603.

Li, C.J., Cheng, P., Liang, M.K., Chen, Y.S., Lu, Q., Wang, J.Y., Xia, Z.Y., Zhou, H.D., Cao, X., Xie, H., et al. (2015). MicroRNA-188 regulates age-related switch between osteoblast and adipocyte differentiation. J. Clin. Invest. *125*, 1509–1522.

Liu, Y., Yang, X., Jing, Y., Zhang, S., Zong, C., Jiang, J., Sun, K., Li, R., Gao, L., Zhao, X., et al. (2015). Contribution and mobilization of mesenchymal stem cells in a mouse model of carbon tetrachloride-induced liver fibrosis. Sci. Rep. *5*, 17762.

Lorenz, L., Axnick, J., Buschmann, T., Henning, C., Urner, S., Fang, S., Nurmi, H., Eichhorst, N., Holtmeier, R., Bódis, K., et al. (2018). Mechanosensing by β1 integrin induces angiocrine signals for liver growth and survival. Nature *562*, 128–132.

Low, S., Barnes, J.L., Zammit, P.S., and Beauchamp, J.R. (2018). Delta-like 4 activates notch 3 to regulate self-renewal in skeletal muscle stem cells. Stem Cells *36*, 458–466.

Lucas, D., Bruns, I., Battista, M., Mendez-Ferrer, S., Magnon, C., Kunisaki, Y., and Frenette, P.S. (2012). Norepinephrine reuptake inhibition promotes mobilization in mice: potential impact to rescue low stem cell yields. Blood *119*, 3962–3965.

Marriott, S., Baskir, R.S., Gaskill, C., Menon, S., Carrier, E.J., Williams, J., Talati, M., Helm, K., Alford, C.E., Kropski, J.A., et al. (2014). ABCG2pos lung mesenchymal stem cells are a novel pericyte subpopulation that contributes to fibrotic remodeling. Am. J. Physiol. Cell. Physiol. *307*, C684–698.

Marthiens, V., Kazanis, I., Moss, L., Long, K., and Ffrench-Constant, C. (2010). Adhesion molecules in the stem cell niche – more than just staying in shape? J. Cell Sci. *123*, 1613–1622.

Maryanovich, M., Zahalka, A.H., Pierce, H., Pinho, S., Nakahara, F., Asada, N., Wie, Q., Wang, X., Ciero, P., Xu, J., et al. (2018). Adrenergic nerve degeneration in bone marrow drives aging of the hematopoietic stem cell niche. Nat. Med. *24*, 782–791.

Matsumoto, S., Yamamoto, K., Nagano, T., Okamoto, R., Ibuki, N., Tagashira, M., and Tsuji, T. (1999). Immunohistochemical study on phenotypical changes of hepatocytes in liver disease with reference to extracellular matrix composition. Liver *19*, 32–38.

Matsumoto, K., Yoshitomi, H., Rossant, J., and Zaret, K.S. (2001). Liver organogenesis promoted by endothelial cells prior to vascular function. Science *294*, 559–563.

Maximow, A. (1906). Über experimentelle Erzeugung von Knochenmarkgewebe. [About experimental generation of bone marrow tissue]. Anat. Anz. *28*, 608–612.

Maximow, A. (1928). Cultures of blood leucocytes. From lymphocyte and monocyte to connective tissue. Arch. Exp. Zellforsch. *5*, 169–268.

Mayack, S.R., Shadrach, J.L., Kim, F.S., and Wagers, A.J. (2010). Systemic signals regulate ageing and rejuvenation of blood stem cell niches. Nature *463*, 495–500.

McCuskey, R.S. (2004). Anatomy of efferent hepatic nerves. Anat. Rec. A Discov. Mol. Cell Evol. Biol. *280*, 821–826.

McIntosh, K. and Bartholomew, A. (2000). Stromal cell modulation of the immune system. Graft *3*, 324–328.

McLeod, C.M. and Mauck, R.L. (2017). On the origin and impact of mesenchymal stem cell heterogeneity: new insights and emerging tools for single cell analysis. Eur. Cell Mater. *34*, 217–231.

Méndez-Ferrer, S., Lucas, D., Battista, M., and Frenette, P.S. (2008). Haematopoietic stem cell release is regulated by circadian oscillations. Nature *452*, 442–447.

Méndez-Ferrer, S., Michurina, T.V., Ferraro, F., Mazloom, A.R., Macarthur, B.D., Lira, S.A., Scadden, D.T., Ma'ayan, A., Enikolopov, G.N., and Frenette, P.S. (2010). Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature *466*, 829–834.

Michalopoulos, G.K. and DeFrances, M.C. (1997). Liver regeneration. Science *276*, 60–66.

Michalopoulos, G.K. and Khan, Z. (2005). Liver regeneration, growth factors, and amphiregulin. Gastroenterology *128*, 503–506.

Michalopoulos, G.K., and Khan, Z. (2015). Liver stem cells: experimental findings and implications for human liver disease. Gastroenterology *149*, 876–882.

Michelotti, G.A., Xie, G., Swiderska, M., Choi, S.S., Karaca, G., Krüger, L., Premont, R., Yang, L., Syn, W.K., Metzger, D., et al. (2013). Smoothened is a master regulator of adult liver repair. J. Clin. Invest. *123*, 2380–2394.

Mimeault, M. and Batra, S.K. (2009). Aging of tissue-resident adult stem/progenitor cells and their pathological consequences. Panminerva Med. *51*, 57–79.

Miyajima, A., Tanaka, M., and Itoh, T. (2014). Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. Cell Stem Cell *14*, 561–574.

Morrison, S.J. and Spradling, A.C. (2008). Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. Cell *132*, 598–611.

Nakhaei-Rad, S., Nakhaeizadeh, H., Götze, S., Kordes, C., Sawitza, I., Hoffmann, M.J., Franke, M., Schulz, W.A., Scheller, J., Piekorz, R.P., et al. (2016). The role of embryonic stem cell-expressed RAS (ERAS) in the maintenance of quiescent hepatic stellate cells. J. Biol. Chem. *291*, 8399–8413.

Niki, T., Pekny, M., Hellemans, K., Bleser, P.D., Berg, K.V., Vaeyens, F., Quartier, E., Schuit, F., and Geerts, A. (1999). Class VI intermediate filament protein nestin is induced during activation of rat hepatic stellate cells. Hepatology *29*, 520–527.

Nishimura, E.K., Suzuki, M., Igras, V., Du, J., Lonning, S., Miyachi, Y., Roes, J., Beermann, F., and Fisher, D.E. (2010). Key roles for transforming growth factor beta in melanocyte stem cell maintenance. Cell Stem Cell *6*, 130–140.

Nyfeler, Y., Kirch, R.D., Mantei, N., Leone, D.P., Radtke, F., Suter, U., and Taylor, V. (2005). Jagged1 signals in the postnatal subventricular zone are required for neural stem cell self-renewal. EMBO J. *24*, 3504–3515.

O'Hagan-Wong, K., Nadeau, S., Carrier-Leclerc, A., Apablaza, F., Hamdy, R., Shum-Tim, D., Rodier, F., and Colmegna, I. (2016). Increased IL-6 secretion by aged human mesenchymal stromal cells disrupts hematopoietic stem and progenitor cells' homeostasis. Oncotarget *7*, 13285–13296.

Oyagi, S., Hirose, M., Kojima, M., Okuyama, M., Kawase, M., Nakamura, T., Ohgushi, H., and Yagi, K. (2006). Therapeutic effect of transplanting HGF-treated bone marrow mesenchymal cells into CCl4-injured rats. J. Hepatol. *44*, 742–748.

Parekkadan, B., van Poll, D., Suganuma, K., Carter, E.A., Berthiaume, F., Tilles, A.W., and Yarmush, M.L. (2007). Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure. PLoS One *2*, e941.

Petersen, B.E., Bowen, W.C., Patrene, K.D., Mars, W.M., Sullivan, A.K., Murase, N., Boggs, S.S., Greenberger, J.S., and Goff, J.P. (1999). Bone marrow as a potential source of hepatic oval cells. Science *284*, 1168–1170.

Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., Moorman, M.A., Simonetti, D.W., Craig, S., and Marshak, D.R. (1999). Multilineage potential of adult human mesenchymal stem cells. Science *284*, 143–147.

Rafii, S., Butler, J.M., and Ding, B.S. (2016). Angiocrine functions of organ-specific endothelial cells. Nature *529*, 316–325.

Ramadori, G., Neubauer, K., Odenthal, M., Nakamura, T., Knittel, T., Schwögler, S., and Meyer zum Büschenfelde, K.H. (1992). The gene of hepatocyte growth factor is expressed in fat-storing cells of rat liver and is downregulated during cell growth and by transforming growth factor-β. Biochem. Biophys. Res. Commun. *183*, 739–742.

Raven, A., Lu, W.Y., Man, T.Y., Ferreira-Gonzalez, S., O'Duibhir, E., Dwyer, B.J., Thomson, J.P., Meehan, R.R., Bogorad, R., Koteliansky, V., et al. (2017). Cholangiocytes act as facultative liver stem cells during impaired hepatocyte regeneration. Nature *547*, 350–354.

Reinehr, R.M., Kubitz, R., Peters-Regehr, T., Bode, J.G., and Häussinger, D. (1998). Activation of rat hepatic stellate cells in culture is associated with increased sensitivity to endothelin 1. Hepatology *28*, 1566–1577.

Reinehr, R., Sommerfeld, A., and Häussinger, D. (2008). CD95 ligand is a proliferative and antiapoptotic signal in quiescent hepatic stellate cells. Gastroenterology *134*, 1494–1506.

Rennerfeldt, D.A. and Van Vliet, K.J. (2016). Concise review: When colonies are not clones: evidence and implications of intra-colony heterogeneity in mesenchymal stem cells. Stem Cells *34*, 1135–1141.

Reya, T., Duncan, A.W., Ailles, L., Domen, J., Scherer, D.C., Willert, K., Hintz, L., Nusse, R., and Weissman, I.L. (2003). A role for Wnt signalling in self-renewal of haematopoietic stem cells. Nature *423*, 409–414.

Rezvani, M., Español-Suñer, R., Malato, Y., Dumont, L., Grimm, A.A., Kienle, E., Bindman, J.G., Wiedtke, E., Hsu, B.Y., Naqvi, S.J., et al. (2016). *In vivo* hepatic reprogramming of myofibroblasts with AAV vectors as a therapeutic strategy for liver fibrosis. Cell Stem Cell *18*, 809–816.

Rodin, S., Domogatskaya, A., Ström, S., Hansson, E.M., Chien, K.R., Inzunza, J., Hovatta, O., and Tryggvason, K. (2010). Long-term self-renewal of human pluripotent stem cells on human recombinant laminin-511. Nat. Biotechnol. *28*, 611–615.

Rohn, F., Kordes, C., Castoldi, M., Götze, S., Poschmann, G., Stühler, K., Herebian, D., Benk, A.S., Geiger, F., Zhang, T., et al. (2018). Laminin-521 promotes quiescence in isolated stellate cells from rat liver. Biomaterials *180*, 36–51.

Ruebner, B.H., Green, R., Myiai, K., Caranasos, G., and Abbey, H. (1961). The rarity of intrahepatic metastasis in cirrhosis of the liver. a statistical explanation with some comments on the interpretation of necropsy data. Am. J. Pathol. *39*, 739–746.

Russell, J.O. and Monga, S.P. (2018). Wnt/β-catenin signaling in liver development, homeostasis, and pathobiology. Annu. Rev. Pathol. *13*, 351–378.

Russo, F.P., Alison, M.R., Bigger, B.W., Amofah, E., Florou, A., Amin, F., Bou-Gharios, G., Jeffery, R., Iredale, J.P., and Forbes, S.J. (2006). The bone marrow functionally contributes to liver fibrosis. Gastroenterology *130*, 1807–1821.

Sá da Bandeira, D., Casamitjana, J., and Crisan, M. (2017). Pericytes, integral components of adult hematopoietic stem cell niches. Pharmacol. Ther. *171*, 104–113.

Sancho-Bru, P., Bataller, R., Colmenero, J., Gasull, X., Moreno, M., Arroyo, V., Brenner, D.A., and Ginès, P. (2006). Norepinephrine induces calcium spikes and proinflammatory actions in human hepatic stellate cells. Am. J. Physiol. Gastrointest. Liver Physiol. *291*, G877–884.

Sandel, D.A., Liu, M., Ogbonnaya, N., and Newman, J.J. (2018). Notch3 is involved in adipogenesis of human adipose-derived stromal/stem cells. Biochimie *150*, 31–36.

Sato, N., Meijer, L., Skaltsounis, L., Greengard, P., and Brivanlou, A.H. (2004). Maintenance of pluripotency in human and mouse embryonic stem cells through activation of Wnt signaling by a pharmacological GSK-3-specific inhibitor. Nat. Med. *10*, 55–63.

Sato, Y., Araki, H., Kato, J., Nakamura, K., Kawano, Y., Kobune, M., Sato, T., Miyanishi, K., Takayama, T., Takahashi, M., et al. (2005). Human mesenchymal stem cells xenografted directly to rat liver are differentiated into human hepatocytes without fusion. Blood *106*, 756–763.

Sawitza, I., Kordes, C., Reister, S., and Häussinger, D. (2009). The niche of stellate cells within rat liver. Hepatology *50*, 1617–1624.

Schildberg, F.A., Wojtalla, A., Siegmund, S.V., Endl, E., Diehl, L., Abdullah, Z., Kurts, C., and Knolle, P.A. (2011). Murine hepatic stellate cells veto CD8 T cell activation by a CD54-dependent mechanism. Hepatology *54*, 262–272.

Schirmacher, P., Geerts, A., Peitrangelo, A., Dienes, H.P., and Rogler, C.E. (1991). Hepatocyte growth factor/hepatopoietin A is expressed in fat-storing cells from rat liver but not myofibroblast-like cells derived from fat-storing cells. Hepatology *15*, 5–11.

Schmidt, M., Schüler, S.C., Hüttner, S.S., von Eyss, B., and von Maltzahn, J. (2019). Adult stem cells at work: regenerating skeletal muscle. Cell. Mol. Life Sci. *76*, 2559–2570.

Schofield, R. (1978). The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells *4*, 7–25.

Schumacher, E.C., Götze, S., Kordes, C., Benes, V., and Häussinger, D. (2017). Combined methylome and transcriptome analysis during rat hepatic stellate cell activation. Stem Cells Dev. *26*, 1759–1770.

Schwartz, R.E., Reyes, M., Koodie, L., Jiang, Y., Blackstad, M., Lund, T., Lenvik, T., Johnson, S., Hu, W.S., and Verfaillie, C.M. (2002). Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. J. Clin. Invest. *109*, 1291–1302.

Semon, J.A., Nagy, L.H., Llamas, C.B., Tucker, H.A., Lee, R.H., and Prockop, D.J. (2010). Integrin expression and integrin-mediated adhesion *in vitro* of human multipotent stromal cells (MSCs) to endothelial cells from various blood vessels. Cell Tissue Res. *341*, 147–158.

Shan, T., Xu, Z., Wu, W., Liu, J., and Wang, Y. (2017). Roles of notch1 signaling in regulating satellite cell fates choices and postnatal skeletal myogenesis. J. Cell. Physiol. *232*, 2964–2967.

Shimizu, H., Mitsuhashi, N., Ohtsuka, M., Ito, H., Kimura, F., Ambiru, S., Togawa, A., Yoshidome, H., Kato, A., and Miyazaki, M. (2005). Vascular endothelial growth factor and angiopoietins regulate sinusoidal regeneration and remodeling after partial hepatectomy in rats. World J. Gastroenterol. *11*, 7254–7260.

Shiratori, Y., Ichida, T., Geerts, A., and Wisse, E. (1987). Modulation of collagen synthesis by fat-storing cells, isolated from CCl4- or vitamin A-treated rats. Dig. Dis. Sci. *32*, 1281–1289.

Sicklick, J.K., Li, Y.-X., Choi, S.S., Qi, Y., Chen, W., Bustamante, M., Huang, J., Zdanowicz, M., Camp, T., Torbenson, M.S., et al. (2005). Role for hedgehog signaling in hepatic stellate cell activation and viability. Lab. Invest. *85*, 1368–1380.

Sicklick, J.K., Li, Y.X., Melhem, A., Schmelzer, E., Zdanowicz, M., Huang, J., Caballero, M., Fair, J.H., Ludlow, J.W., McClelland, R.E., et al. (2006). Hedgehog signaling maintains resident hepatic progenitors throughout life. Am. J. Physiol. Gastrointest. Liver Physiol. *290*, G859–870.

Sigala, B., McKee, C., Soeda, J., Pazienza, V., Morgan, M., Lin, C.I., Selden, C., Vander Borght, S., Mazzoccoli, G., Roskams, T., et al. (2013). Sympathetic nervous system catecholamines and neuropeptide Y neurotransmitters are upregulated in human NAFLD and modulate the fibrogenic function of hepatic stellate cells. PLoS One *8*, e72928.

Sims, D.E. (1986). The pericyte – a review. Tissue and Cell *18*, 153–174.

Sommerfeld, A., Reinehr, R., and Häussinger, D. (2009). Bile acid-induced epidermal growth factor receptor activation in quiescent rat hepatic stellate cells can trigger both proliferation and apoptosis. J. Biol. Chem. *284*, 22173–22183.

Song, G., Pacher, M., Balakrishnan, A., Yuan, Q., Tsay, H.C., Yang, D., Reetz, J., Brandes, S., Dai, Z., Pützer, B.M., et al. (2016). Direct reprogramming of hepatic myofibroblasts into hepatocytes in vivo attenuates liver fibrosis. Cell Stem Cell *18*, 797–808.

Spinella-Jaegle, S., Rawad, G., Kawai, S., Gallea, S., Faucheu, C., Mollat, P., Courtois, B., Bergaud, B., Ramez, V., Blanchet, A.M., et al. (2001). Sonic hedgehog increases the commitment of pluripotent mesenchymal cells into the osteoblastic lineage and abolishes adipocytic differentiation. J. Cell Sci. *114*, 2085–2094.

Spitzhorn, L.S., Kordes, C., Megges, M., Sawitza, I., Götze, S., Reichert, D., Schulze-Matz, P., Graffmann, N., Bohndorf, M., Wruck, W., et al. (2018). Transplanted human pluripotent stem cell-derived mesenchymal stem cells support liver regeneration in Gunn rats. Stem Cells Dev. *27*, 1702–1714.

Sugimura, R., He, X.C., Venkatraman, A., Arai, F., Box, A., Semerad, C., Haug, J.S., Peng, L., Zhong, X.B., Suda, T., et al. (2012). Noncanonical Wnt signaling maintains hematopoietic stem cells in the niche. Cell *150*, 351–365.

Sui, B.D., Hu, C.H., Zheng, C.X., and Jin, Y. (2016). Microenvironmental Views on Mesenchymal Stem Cell Differentiation in Aging. J. Dent. Res. *95*, 1333–1340.

Sumii, T., Nakano, Y., Abe, T., Nakashima, K., Sera, T., and Kudo, S. (2016). The effect of nitric oxide on ammonia decomposition in co-cultures of hepatocytes and hepatic stellate cells. In Vitro Cell. Dev. Biol. Anim. *52*, 625–631.

Suzuki, K., Tanaka, M., Watanabe, N., Saito, S., Nonaka, H., and Miyajima, A. (2008). p75 Neurotrophin receptor is a marker for precursors of stellate cells and portal fibroblasts in mouse fetal liver. Gastroenterology *135*, 270–281.

Swiderska-Syn, M., Syn, W.K., Xie, G., Krüger, L., Machado, M.V., Karaca, G., Michelotti, G.A., Choi, S.S., Premont, R.T., and Diehl, A.M. (2014). Myofibroblastic cells function as progenitors to regenerate murine livers after partial hepatectomy. Gut *63*, 1333–1344.

Tarlow, B.D., Pelz, C., Naugler, W.E., Wakefield, L., Wilson, E.M., Finegold, M.J., and Grompe, M. (2014). Bipotential adult liver progenitors are derived from chronically injured mature hepatocytes. Cell Stem Cell *15*, 605–618.

Tatematsu, M., Ho, R.H., Kaku, T., Ekem, J.K., and Farber, E. (1984). Studies on the proliferation and fate of oval cells in the liver of rats treated with 2-acetylaminofluorene and partial hepatectomy. Am. J. Pathol. *114*, 418–430.

Taura, K., De Minicis, S., Seki, E., Hatano, E., Iwaisako, K., Osterreicher, C.H., Kodama, Y., Miura, K., Ikai, I., Uemoto, S., et al. (2008). Hepatic stellate cells secrete angiopoietin 1 that induces angiogenesis in liver fibrosis. Gastroenterology *135*, 1729–1738.

Teichert, M., Milde, L., Holm, A., Stanicek, L., Gengenbacher, N., Savant, S., Ruckdeschel, T., Hasanov, Z., Srivastava, K., Hu, J., et al. (2017). Pericyte-expressed Tie2 controls angiogenesis and vessel maturation. Nat. Commun. *8*, 16106.

Theise, N.D., Saxena, R., Poermann, B.C., Thung, S.N., Yee, H., Chiriboga, L., Kumar, A., and Crawford, J.M. (1999). The canals of Hering and hepatic stem cells in humans. Hepatology *30*, 1425–1433.

Trial, J., Entman, M.L., and Cieslik, K.A. (2016). Mesenchymal stem cell-derived inflammatory fibroblasts mediate interstitial fibrosis in the aging heart. J. Mol. Cell. Cardiol. *91*, 28–34.

vom Dahl, S., Bode, J.G., Reinehr, R., Mönnighoff, I., Kubitz, R., and Häussinger, D. (1999). Release of osmolytes from perfused rat liver on perivascular nerve stimulation: alpha-adrenergic control of osmolyte efflux from parenchymal and nonparenchymal liver cells. Hepatology *29*, 195–204.

Wake, K. (1971). "Sternzellen" in the liver: perisinusoidal cells with special reference to storage of vitamin A. Am. J. Anat. *132*, 429–462.

Wake, K. (1980). Perisinusoidal stellate cells (fat-storing cells, interstitial cells, lipocytes), their related structure in and around the liver sinusoids, and vitamin A-storing cells in extrahepatic organs. Int. Rev. Cytol. *66*, 303–353.

Wang, Y., Yao, H.L., Cui, C.B., Wauthier, E., Barbier, C., Costello, M.J., Moss, N., Yamauchi, M., Sricholpech, M., Gerber, D., et al. (2010). Paracrine signals from mesenchymal cell populations govern the expansion and differentiation of human hepatic stem cells to adult liver fates. Hepatology *52*, 1443–1454.

Wang, B., Zhao, L., Fish, M., Logan, C.Y., and Nusse, R. (2015). Self-renewing diploid Axin2(+) cells fuel homeostatic renewal of the liver. Nature *524*, 180–185.

Wen, Q., Xu, C., Zhou, J., Liu, N.M., Cui, Y.H., Quan, M.F., Cao, J.G., and Ren, K.Q. (2019). 8-bromo-7-methoxychrysin suppress stemness of SMMC-7721 cells induced by co-culture of liver cancer stem-like cells with hepatic stellate cells. BMC Cancer *19*, 224.

Wilson, J.W. and Leduc, E.H. (1958). Role of cholangioles in restoration of the liver of the mouse after dietary injury. J. Pathol. Bacteriol. *76*, 441–449.

Wynn, R.F., Hart, C.A., Corradi-Perini, C., O'Neill, L., Evans, C.A., Wraith, J.E., Fairbairn, L.J., and Bellantuono, I. (2004). A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood *104*, 2643–2645.

Xie, T. and Spradling, A.C. (2000). A niche maintaining germ line stem cells in the *Drosophila* ovary. Science *290*, 328–330.

Yang, C., Zeisberg, M., Mosterman, B., Sudhakar, A., Yerramalla, U., Holthaus, K., Xu, L., Eng, F., Afdhal, N., and Kalluri, R. (2003). Liver fibrosis: insights into migration of hepatic stellate cells in response to extracellular matrix and growth factors. Gastroenterology *124*, 147–159.

Yin, C., Evason, K.J., Maher, J.J., and Stainier, D.Y. (2012). The basic helix-loop-helix transcription factor, heart and neural crest derivatives expressed transcript 2, marks hepatic stellate cells in zebrafish: analysis of stellate cell entry into the developing liver. Hepatology *56*, 1958–1970.

Yokoi, Y., Namihisa, T., Kuroda, H., Komatsu, I., Miyazaki, A., Watanabe, S., and Usui, K. (1984). Immunocytochemical detection of desmin in fat-storing cells (Ito cells). Hepatology *4*, 709–714.

Yoshida, S. (2018). Open niche regulation of mouse spermatogenic stem cells. Dev. Growth Differ. *60*, 542–552.

Zhao, D.C., Lei, J.X., Chen, R., Yu, W.H., Zhang, X.M., Li, S.N., and Xiang, P. (2005). Bone marrow-derived mesenchymal stem cells protect against experimental liver fibrosis in rats. World J. Gastroenterol. *11*, 3431–3440.

Zhao, L., Jin, Y., Donahue, K., Tsui, M., Fish, M., Logan, C.Y., Wang, B., and Nusse, R. (2019). Tissue repair in the mouse liver following acute carbon tetrachloride depends on injury-induced Wnt/β-catenin signaling. Hepatology *69*, 2623–2635.