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# Hepatic stellate cells and their role in the formation of the progenitor cell niche

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**ABSTRACT**

The processes of proliferation and differentiation of progenitor and stem cells in the body are ensured by a specific microenvironment, the stem cell niche. Universal components have been identified for all niches: supporting cells, extracellular matrix, and soluble biological factors. A niche is a dynamic system whose activity depends on regeneration needs.

The review presents data on the structure of the hepatic stem cell niche and one of its main components – stellate cells and their role in pathology.

**Keywords:** stem cell niche, stellate cells, progenitor cells, regeneration

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# Роль звездчатых клеток в формировании ниши прогениторных клеток печени

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**РЕЗЮМЕ**

Процессы пролиферации и дифференцировки прогениторных/стволовых клеток в организме обеспечиваются специфическим микроокружением – нишей стволовых клеток. Для всех ниш определены универсальные компоненты – поддерживающие клетки, внеклеточный матрикс и растворимые биологические факторы. Ниша является динамической системой, активность которой зависит от запросов регенерации.

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В обзоре представлены данные о строении ниши стволовых клеток печени, одном из ее основных компонентов – звездчатых клетках и их роли в патологии.

**Ключевые слова:** ниша стволовой клетки, звездчатые клетки, прогениторные клетки, регенерация

**Конфликт интересов.** Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов при проведении исследования.

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## THE CONCEPT OF A STEM CELL NICHE

For the first time, Wolf and Trentin proposed the concept of the existence of local mechanisms of tissue regulation that provide quantitative control over the structures of hematopoiesis. The concept of hematopoietic inductive microenvironment (HIM) was introduced – certain areas of hematopoietic tissue in which local regulation of blood stem cell maturation in a certain direction is carried out [1]. Later, Schofield proposed using the term "niche" to refer to the microenvironment of hematopoietic stem cells (HSCs), and the first concepts of regulation of the stem / progenitor cell population were formed [2].

According to modern concepts, a niche is a specialized local formation that has histologic and functional characteristics typical of various tissues, in which specific progenitor cells are located [3, 4]. A niche is a dynamic system that ensures tissue homeostasis by controlling the processes of proliferation, differentiation, mobilization and homing of progenitor cells, maintaining a balance between dormancy and self-renewal [5–7].

Thus, the stem cell (SC) niche can be considered an elementary functional unit of the regeneration process [3, 6, 8]. The interaction of neighboring regulatory cells with stem cells is critical for the establishment of the stem cell niche, both through secreted signaling factors and through direct cell – cell interactions [9].

## NICHE TYPES

All SC niches can be divided into two types: stromal and epithelial [10].

The stromal niche. An example of this type of niche is the microenvironment of a hematopoietic stem cell. In the niche, there is a wide stromal zone containing progenitor cells. The interaction between cells is an important feature, as they have a paracrine and autocrine effect on each other [7, 11].

The epithelial niche. This niche type is characterized by cytoarchitectonics when the cells are arranged in the form of certain layers. In this case, stem / progenitor cells form direct contacts with other cells, including daughter cells, and, importantly, with the basement membrane [12].

## NICHE COMPONENTS

In general, a niche is formed by the following components:

1) cells of the microenvironment;

2) extracellular matrix which is a mechanical framework for a niche, as well as a medium for storing and transmitting signaling molecules, hormones, and growth factors;

3) blood vessels;

4) nerve endings.

1. Cells of the microenvironment are represented by various types of cells that directly contact stem cells and also secrete various regulatory factors [3, 13]. The importance of cells in the SC microenvironment was first shown in the works by T.M. Dexter et al., who found that when hematopoietic stem cells are added to stromal non-hematopoietic cells, the lifespan of the HSC culture increases from 1–2 weeks to 14 weeks [2]. Common components of the stem cell niche, characteristic of niches in various organs and tissues, are fibroblasts, endothelial cells, and macrophages [3, 13–16]. These cellular elements determine the proliferation and differentiation status of progenitor cells through the synthesis of cytokines, chemokines, growth factors, other regulatory substances, and components of the extracellular matrix [6, 17]. In the liver, Kupffer cells (liver macrophages) can interact with hepatocyte precursor cells, influencing their proliferation and differentiation either through direct

contacts or through the production of certain humoral factors [16].

2. Extracellular matrix. For a long time, the extracellular matrix was considered a fairly inert component of tissues that does not take special part in the life of cells. However, over the past 25 years, research in this direction has allowed to obtain completely new data [18, 19]. The intercellular substance is a fairly dynamic element of the SC niche, influencing the production, degradation, and remodeling of its own components. Naturally, first of all, the extracellular matrix creates a platform or a framework for the functioning of progenitor cellular elements. The extracellular matrix is specific in biochemical composition for each tissue and reflects the characteristics of the cells present in this tissue [3, 18, 20].

It is known that rigidity is the main property of the extracellular matrix, through which cells sense external influence and respond to environmental changes accordingly. This phenomenon is known as mechanotransduction, which is the conversion of mechanical stimuli into an intracellular biochemical response. Moreover, the interaction between the cell and the extracellular matrix is reciprocal: cells constantly remodel the matrix in their microenvironment, and these dynamic modifications subsequently control cell behavior [18, 21].

## NICHE INNERVATION, NERVE ENDINGS

In addition to the mentioned cellular elements of the SC niche (fibroblasts, macrophages, and endothelial cells), nerve fibers are important elements of the niche. The existence of myelinated and unmyelinated nerve fibers in the bone marrow has been shown, most of which are located next to the arterioles in the hematopoietic tissue [5, 6, 22]. The sympathetic and parasympathetic subsystems of the autonomic nervous system play an important role in regulating the HSC niche.

The release of mediators by terminals affects the production of hematopoietins and the activity of elements of the blood SC microenvironment [3, 19, 22]. The fibers of the sympathetic and parasympathetic nervous systems also end in synapses and various types of liver cells. By stimulating α1B-, α1D-, β1-, and β2-adrenergic receptors, proliferation of hepatic stellate cells and oval cells is activated (both cell types express adrenergic receptors) [23]. Oval cells also carry muscarinic M3 receptors, which, when stimulated by acetylcholine, increase their proliferation [24].

## BLOOD VESSELS

Blood vessels of the microvasculature are an important element of any niche [2, 5]. Endothelial cells and pericytes are of particular importance. In the bone marrow, endothelial cells form a barrier between hematopoietic cells and blood and regulate the migration of blood cells into the bloodstream [25]. The endothelial cells lining the sinusoidal capillaries (sinusoidal endotheliocytes) are the basis of a unique capillary network present in the bone marrow and liver.

These elements contribute to the specialized perivascular microenvironment where the majority of HSCs are located [26]. Endothelial cells participate in the regulation of homeostasis and stimulation of tissue regeneration both through direct interaction with local stem and progenitor cells and through the secretion of angiocrine factors [27]. It is known that in adult animals, sinusoidal endothelial cells of the bone marrow largely ensure the regeneration of hematopoietic tissue [28]. Similar endothelial cells line the capillaries of the liver, with each hepatocyte located in close proximity to a sinusoidal endothelial cell in such a way that their plasma membranes contact. During liver regeneration, endothelial cells create a vascular niche with an instructive role. Through the production of angiocrine factors, it stimulates regenerative processes, similar to factors derived from endothelial cells that support hematopoiesis [29].

## PROGENITOR CELLS OF VARIOUS TISSUES AND ORGANS. COMPOSITION AND FUNCTION OF STEM CELL NICHES IN DIFFERENT TISSUES

Identification and characterization of stem cell niches still remain a serious problem from the point of view of their biology. This is due to the difficulty in identifying cells in certain areas, including the limited number of known markers using which they could be distinguished from other cells of a particular tissue with which they have morphological similarity [3, 6]. To date, SC niches have been identified in hematopoietic tissue [14], skin [30], intestines [31], striated muscles [32], and the central nervous system [15]. The niche of hepatic [33] and pancreatic [34] progenitor cells is being actively studied.

## LIVER

It is known that hepatocytes and cholangiocytes have a high regenerative potential and are able to ensure restoration of liver tissue with moderate cell death and local damage [35]. In addition to hepatocytes

and cholangiocytes, several types of progenitor cells located in different areas of the lobule play an important role in the process of liver regeneration. In cases where hepatocyte proliferation is impaired due to chronic pathology, such as chronic viral hepatitis or non-alcoholic fatty liver disease, hepatocytes cannot effectively mediate parenchymal regeneration [36]. In this case, hepatic progenitor cells are activated, that, as a rule, are sufficient for the regeneration of biliary and hepatocellular epithelium [37].

There are three known populations of progenitor cells in the liver [38]. The first group is located in the canals of Hering, hepatic stem cells (HpSCs, hepatic stem / progenitor cells), which participate in the regeneration of small biliary ducts and the liver parenchyma itself. Hepatic stem cells (HpSCs) are optional bipotent hepatoblast progenitor cells [38; 39]. They express a combination of epithelial cell adhesion molecules (EpCAM), neural cell adhesion molecules (NCAM), cytokeratin-19, albumin and are negative for alpha-fetoprotein (AFP) [37]. Progenitor cells of the biliary tract (BTSCs, biliary tree stem/progenitor cells) can be designated as the second group of hepatocyte precursors. It is a heterogeneous population of cells expressing various transcription factors (SOX9, SOX17 and PDX1), as well as surface (EpCAM, LGR5 and/or CD133) and cytoplasmic markers (CK7, CK19). Cells of this type also support the renewal of cholangiocytes in large intrahepatic and extrahepatic biliary ducts [40]. The third type of progenitor cells is a group of self-renewing Axin2+ hepatocyte cells adjacent to the central vein [38].

## NICHE OF LIVER PROGENITOR CELLS

Like any other niche, the niche of progenitor cells in the liver contains a certain set of cells that directly contact SCs, form intercellular substance, and secrete regulatory factors [41], thus exerting both direct and indirect effects on progenitor elements [33]. SC niches in the liver are formed by different types of cells: hepatocytes; sinusoidal cells [16]; endothelial cells – line the hepatic sinusoids [42]; perisinusoidal cells – stellate cells of the liver (Ito cells) – are located in the space of Disse; leukocytes [43]; as well as connective tissue cells (fibroblasts, mast cells) and angioblasts [36].

All these cell types constantly interact with each other and with hepatocytes through the mediation of the extracellular matrix, constituting a single structural and functional system that ensures homeostasis of hepatic acini and is dependent on complex specialized functions of hepatocytes [44]. Kupffer cells maintain an adequate microenvironment for hepatocytes due to early activation of lysosomal hydrolases in them, activation of the N-acetylglycosamine, mannose and galactose receptor, which can mediate the pinocytosis of some glycoproteins of the extracellular matrix. Kupffer cells also participate in the remodeling of the extracellular matrix, locally secreting collagenase type 4, matrix metalloproteinases (MMP-1, MMP-13), gelatinases, and stromelysin [45].

The precursors of hepatic stellate cells and endothelial cells have almost the same phenotypic characteristics as their mature descendants (stellate cells and endothelial cells), however, there are differences. For example, stellate cell precursors minimally express retinoids, whereas they are found in abundance in mature Ito cells; endothelial cell progenitors do not express CD31 (PECAM), which is a hallmark of mature endothelium.

The products of microenvironment cells, such as fibroblasts and mesenchymal stem cells, include matrix factors (hyaluronans, collagen type III and IV) [42], minimally sulfated proteoglycans, and laminins [46]. These also include soluble signals, such as leukemia inhibitory factor (LIF), hepatocyte growth factor (HGF), and epidermal growth factor (EGF) [47]. In *in vitro* experiments, the addition of any of these factors, as well as hyaluronic acid substrates, to liver cell culture caused the differentiation of HpSCs into hepatoblasts [47, 48]. When the liver is damaged, stellate cells are activated, subsequently producing collagen type I, sulfated proteoglycans, as well as high levels of cytokines and growth factors [49]. In addition to signaling from the niche to stem / progenitor cells, there is also a feedback from stem / progenitor cells to the niche. HpSCs can activate stellate and endothelial cells through the Hedgehog signaling pathway, which leads to the synthesis of certain matrix components (collagen type IV, laminin, syndecans, and glypicans) that are associated with physiological liver regeneration [44].

Hepatic stellate cells (Ito cells, HSCs) were first described in 1876 by Kupffer, who named them “Sternzellen”. In the literature, hepatic stellate cells are found under various names (Ito cells, lipocytes, perisinusoidal cells or parasinusoidal cells, fat storing cells). Currently, the widely accepted and preferred term for these cells is hepatic stellate cells [50; 51]. Like Kupffer cells and liver endothelial cells, stellate cells are non-parenchymal cells located

perisinusoidally in the space of Disse, in the recesses between hepatocytes, limited by the basolateral surface of hepatocytes and the antiluminal side of sinusoidal endothelial cells (SECs) [52].

A series of studies revealed the ability of HSC to deposit retinoids and lipids. Liver stellate cells synthesize proteoglycans, which are the main component of the extracellular matrix of the liver tissue, and their synthesis is 6 times higher than that of hepatocytes. They also the main source of collagen types I, III, IV, V, VI, tenascin, laminin, and fibronectin. This type of cell also synthesizes four types of matrix metalloproteinases [50]. HSCs also closely interact with endothelial cells and nerve endings through their numerous processes passing through the space of Disse.

In the cytosol of stellate cells, there is a rough endoplasmic reticulum, a reduced perinuclear Golgi apparatus, and the cell itself has cytoplasmic processes, some of which are interhepatic, and others are subendothelial [50]. Cell processes have microspikes, with the help of which the Ito cell establishes contacts with hepatocytes, receiving from the latter chemotactic stimuli that cause contraction of the stellate cell [53]. Ito cells contain vacuoles of two types (sap and contractile). Sap vacuoles are cell membrane-bound structures of various sizes that have a diameter of no more than 2 μm, and lysosomes are their precursors. Contractile vacuoles are not connected to the membrane and are larger, exceeding 8 μm [50, 51, 54].

Stellate cells are of two types: resting and activated. Under normal physiological conditions, HSCs are in the so-called inactivated state, and their main function is to accumulate lipids and vitamin A [55]. Due to their plasticity (depending on their functional state) and ability to transdifferentiate, stellate cells perform various functions that are sometimes conflicting. With various types of damage (viral hepatitis, toxic hepatitis), HSCs receive signals from hepatocytes and immunocompetent cells, activate, and transform into myofibroblast-like cells [50, 51]. When activated, HSCs are modified, acquiring a flat shape, and lose their characteristic lipid vacuoles [55]. At the same time, the granular endoplasmic reticulum of the cells increases due to the activation of protein synthesis, and many contractile microfilaments appear in the cytoplasm.

Activation of stellate cells includes two phases: initiation (phase 1) and sustained activation (phase 2) [50]. The first phase is triggered by paracrine stimulation from damaged hepatocytes, Kupffer cells, and endothelial cells. In the second phase of activation, a number of morphofunctional changes occur in the cell: proliferation, chemotaxis, fibrogenesis are activated, contractility appears, matrix degradation and loss of retinoids occur, proinflammatory, profibrogenic, and promitogenic stimuli that act in an autocrine and paracrine manner are released [56].

The assumption about the important role of Ito cells in the process of liver regeneration was first put forward in the works by G. Kent et al. [57]. Their close anatomical location with hepatocytes in the space of Disse and around progenitor cells makes HSC perfect for the role of the main component in the niche of resident stem cells in the liver, as well as a stimulator of hepatocyte proliferation [35, 38, 40, 48].

Ito cells participate in the restoration of the liver parenchyma, both due to the synthesis of growth factors, chemokines, eicosanoids and other small molecules with paracrine, juxtacrine, autocrine functions or chemoattractant activity, and the synthesis of macromolecules of the extracellular matrix, as well as its remodeling [59]. Activated HSCs produce a significant number of cytokines: hepatocyte growth factor (HGF), epidermal growth factor (EGF), erythropoietin, neurotrophin and transforming growth factor alpha (TGFα). TGF-a and EGF act in the same way as autocrine factors, stimulating the proliferation of HSCs. Hepatic stellate cells are the only source of HGF in the liver. Hepatocytes are the main point of application of HGF [60]. When the liver is damaged, activated HSCs proliferate and migrate to areas of inflammation and necrosis of hepatocytes, producing large amounts of extracellular matrix components [50].

## CONCLUSION

Our studies on a model of liver cirrhosis caused by the administration of carbon tetrachloride (CT) and a 5% ethanol solution showed that the content of Ito cells in the organ parenchyma (CD45-CD133+) in this pathology model increases by 267.2% compared to baseline values [61]. According to numerous data, in addition to the liver, stellate cells are present in other organs, including the pancreas [41], kidneys [62], and lungs [63].

Thus, we can conclude that stellate cells are the key elements of the tissue microenvironment and participate in the regulation of liver tissue regeneration. Moreover, there is evidence that stellate cells are

progenitor elements and are capable of differentiating into tissue-specific cells [41, 58, 60, 64].

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