International Journal of Education, Social Science & Humanities.
Finland Academic Research Science Publishers
ISSN: 2945-4492 (online) | (SJIF) = 7.502 Impact factor
Volume-11| Issue-6| 2023 Published: |22-06-2023|

CLINICAL AND CYTOLOGICAL STRUCTURE OF THE LIVER

https://doi.org/10.5281/zenodo.8059658

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One of the most important populations of liver cells are Kupffer cells (KCs, tissue macrophages, shore cells, sinusoid cells, endothelial stellate cells), recognized in mi new medical literature and named after Karl Kupffer, professor of anatomy from Koniggsberg, who first described them in 1876 In Poland, these cells are named after the professor of pathological anatomy at the Jagiellonian University, Tadeusz Brovik (Tadeusz Browicz) [1-3].

KCs are the key cellular components of the intrahepatic innate immune system, play a dominant role in the initial period of inflammation of the liver. KCs is the most important population of a heterogeneous group of liver macrophages, the main function of which is to capture and process old non-functional blood cells. That is why some authors believe that KCs should be treated with special respect [4]. KCs play a central role in maintaining the orderliness of cellular and non-cellular structures and metabolic homeostasis of the liver. They originate from other KCs as a result of mitosis of the latter, as well as from bone marrow cells [5].

KCs - large stellate cells, located inside the hepatic sinusoid capillaries, partly on their bifurcations. Their processes pass between endothelial cells and often cross the lumen of sinusoids (Fig. 1).

KCs are activated during liver intervention by viruses, bacteria, parasites, under the action of toxins, under conditions of ischemia, cholestasis, and other stressful factors. Stimulated KCs secrete biologically active substances, including cytokines, prostanoids, nitric oxide and reactive oxygen species. These factors affect the phenotype of KCs itself, as well as the phenotypes of neighboring cells, such as hepatocytes, Ito stellate cells, endothelial cells and other cells of the immune system [6].

Under the conditions of the inflammatory process, the number of liver macrophages significantly increases (replenishes) due to the constant influx of monocytes from the blood, which, differentiation roaming, turning into tissue macrophages of different degrees of maturity [7]. Resident (permanently present) and free macrophages, related to the system of mononuclear phagocytes of the liver, are different in origin and participation in the inflammatory process. Resident

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macrophages acquire tissue-specific characteristics and maintain their numbers due to in situ proliferation without any involvement of monocytes. These two varieties of macrophages are functionally unique and perform different immunological roles. KCs, related to long-lived tissue macrophages, are activated and act as antigen-presenting cells and regulators of the early immune response. Macrophages of bone marrow origin (inflammatory or infiltrating macrophages) are the main producers of proinflammatory cytokines, play a decisive role in the initiation and progression liver damage, as well as subsequent liver fibrosis and carcinogenesis [8].

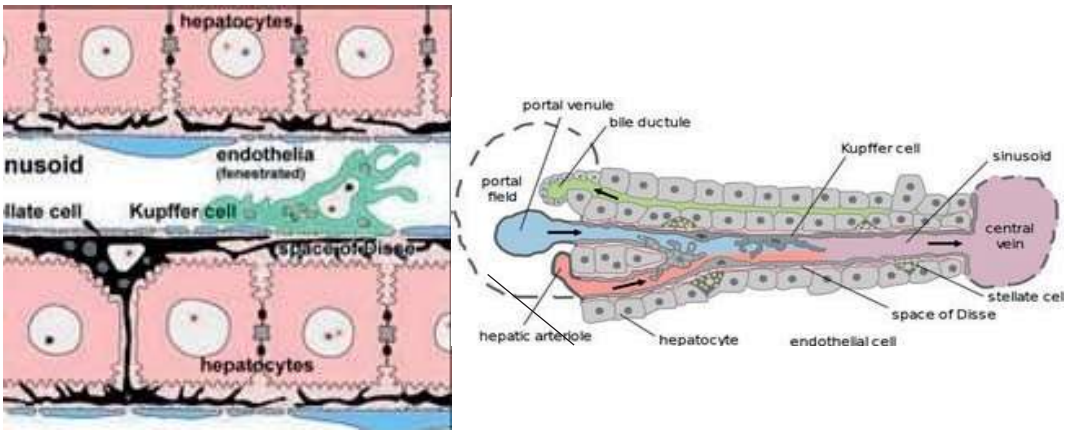

Figure 1. Schematic representation of the KCs among other cells of the suncoud

The mechanisms of activation of phagocytes of both types are fundamentally the same. Activating stimuli can be bacterial products, for example, lipopolysaccharides (LPS), N-formyl peptides and others, complement components (for example, C3 and C5), many cytokines and antitite ela, receptors for which are present on the membranes of phagocytes [9].

Due to the fact that KCS are directly related to the remodeling of the organ and are easily extracted from the liver tissue by enzymatic digestion, they attract close attention as a potential source of cell therapy for liver fibrosis [10].

In recent years, specific diagnostic markers for the detection of KCS in the human liver have been developed, which include CD163L (marker of resident macrophages), CLEC5A (identifier atop of proinflammatory macrophages) and CD68 (non-specific) [11, 12].

The literature mainly provides descriptive information about KCS and insufficiently illustrative data about the structural and functional characteristics of KCs in relation to clinical isc research in various lesions of the liver.

The dimensions of KCs are 20-40 μm. The structure of KCs differs in diversity,

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depending on phagocytic activity, properties of the absorbed material, and localization in the sinusoidal capillary (Fig. 2).

KCs contains an oval nucleus, a different number of mitochondria, a well-developed Golgi complex, short cisterns of the granular endoplasmic reticulum (GER), many lysosomes, dense e residual bodies and rare annular plates (petals), which are considered as a specialized form of granular endoplasmic reticulum.

Intracellular organelles KCs synthesize enzymes for intracellular and extracellular cleavage of foreign material, antibacterial and other biologically active substances (proteases, acid hydrolases, pyrogen, interferon, lysozyme, etc.). The fragocytic of the KCs is a fragment of the Lizocom, which is in the "Cletex", and the fact of the " CHECHIX GP. In the cytoplasm of KCs, a "cellular periphery" is isolated, which provides the macrophage with the ability to move, draw in microprotrusions of the cytoplasm, and carry out endo- and exocytosis. Microtubules and bundles of microfilaments are also observed.

On the surface of KCs there are non-permanent flattened cytoplasmic folds (lamellopodia) or lamellar legs, as well as processes (phylopodia) and microvilli covered with glyco calixom. The plasmalemma forms worm-shaped bodies with a centrally located dense line. These structures may represent condensed glycolic [19].

Small numerous outgrowths of the cytoplasm look like "frills" (ruffles) on clothes (English ruffl); when they close, a small volume of the surrounding "liquid" (micropinocytic vacuoles) enters the cell along with the molecules dissolved in it. KCs also contains large phagolysosomes, which often contain obsolete erythrocytes and foreign substances.

Swelling, KCs act as sphincters of sinusoidal capillaries. In the cytoplasm of KCs, there are many pinocytic and phagocytic vesicles or peculiar tubules, similar to "worms", representing a depot of the cell membrane for fast phagocytic reactions in response to any particles entering the cell. With the help of specific vesicles, receptor-mediated endocytosis is carried out, which in a simplified form is represented by the following stages: receptors in the plasma membrane, transfer being laterally along the cell surface and binding to ligands (macromolecules, some viruses), accumulate in the area of endocytic pits; around such pits and the bubbles formed from them, on the side of the cytoplasm, a reticular sheath is assembled from the clathrin protein; as a result of the fusion of clathrin vesicles, an endosome is formed.

Often there are different variants of cellular cooperation of KCs between themselves, with other sinusoidal cells: Ito cells, lymphocytes, erythrocytes,

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neutrophils.

The population of KCs in the sinusoidal lining of the liver is approximately 15% of the total population of liver cells. At the same time, approximately 43% of KCs is located in the periportal zone of the lobule, 28% in the middle zone and 29% in the central zone. KCs under physiological conditions are long-lived and capable of self-renewal [20]. KCs are capable of amoeboid movement and can enter the lumen of sinusoids. There is evidence that KCs are capable of migrating along sinusoidal walls at an average rate of 4.6 ± 2.6 (HD) mm/min [21].

Depending on the location in the lobule, KCs differ in functions and phenotype, which they adapt to a different microenvironment of signals in the liver [22, 23]. Periportal cells are much larger and exhibit higher phagocytic and lysosomal activity compared to cells of the middle and perivenous zones [24].

There is a number of evidence demonstrating a significant heterogeneity in the activity of liver macrophages, which was classified into two populations - M1 and M2 [25]. M1, or classically activated macrophages, are characterized by increased expression of pro-inflammatory cytokines (TNF-a, IL-b, IL-12 and inducible NO-synthase - iNOS), while M2 or alt natively activated macrophages show low expression of pro-inflammatory cytokines and high expression against - inflammatory mediators (IL-10 and IL-1 [26]. In addition, in the M2 group, significant heterogeneity was noted (M2a, M2b and M2c), in which macrophage subclasses are induced by various regulators and manifest on the surface of cells different marker proteins, as well as different functional activity [27].

Interesting results were obtained in the study of additional phenotypes of resident macrophages in the liver. Macrophages associated with spontaneous resolution of liver fibrosis were named Iredale group [28] scar-associated macrophages (SAM), are Gr-1ni and are associated with increased expression of profibrotic cytokines, transforming growth factor β (TGF-β) and platelet factor growth a [29]. Another specific macrophage phenotype is associated with hepatocarcinoma [30].

KCs, representing very mobile macrophages associated with the endothelium, are formed from blood monocytes and have only a limited ability to divide. It is assumed that the renewal of KCs occurs due to apoptosis and / or migration to other sites - lymph nodes. It has been shown that in response to TH-2 inflammatory signals and an increase in IL-4, resident macrophages, including KCs, can be stimulated to proliferate[31].

KCs phagocytize according to the mechanism of endocytosis (pinocytosis or phagocytosis), which can be receptor-mediated (absorptive) or occur without the

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participation of receptors (liquid-phase). KCs absorb aged cells, foreign particles, tumor cells, bacteria, yeasts, viruses and parasites. They capture and process oxidized atherogenic low density lipoproteins and remove denatured proteins and fibrin in DBC syndrome.

KCs phagocytize various immunogens from the blood flowing from the intestine and delay their entry into the general circulation. The phagocytic function is carried out due to a large number of lysosomes. Liver macrophages are the key agent in iron homeostasis in the blood. At the same time, hemoglobin molecules are destroyed, their globin chains are recycled, and heme is split into iron and bilirubin. With supravital staining, inclusions of hemosiderin or iron can be detected in them. In laboratory rats, each of the macrophages phagocytizes about one erythrocyte per day, without visible harmful effects on the macrophage, but higher erythrophagia (hemo lytic diseases) can lead to damage to macrophages [32].

Metabolites of arachidonic acid, platelet activation factor PAF, g-IFN cause KCS activation. Activation of macrophages is possible only in the presence of specific stimuli (for example, bacterial products, C3b, y-IFN). This feature allows some bacteria, fungi and protozoa to persist in the cytoplasm of non-activated macrophages. The activation of macrophages proceeds rapidly, accompanied by an intensive release of microbicidal substances, as well as cytokines, which regulate the level of the inflammatory reaction and induce the development of the immune about the answer. Activation of KCS by lipopolysaccharides suppresses the uptake of hyaluronic acid by endothelial cells. This effect is possibly mediated by leukotrienes. Activated cells, in turn, produce a complex of biologically active substances, such as oxygen radicals, plasminogen activator, tumor necrosis factor alpha (TNF-a), IL-1, IL-b, transforming growth factor b (TGFb), which can cause toxic damage hepatocytes. Under the influence of IL6, IL-1 and TNF-a, the synthesis of acute-phase proteins begins in the liver, including C-reactive protein, A-amyloid, haptoglobin, factor B of complement and alpha1-antitripcine [33].

It has been established that activated KCs express cytotoxic molecules (TRAIL, phage ligand, granzyme B, ROS, perforin) involved in the lysis of infected hepatocytes. Since cytotoxicity is of a non-specific nature, it is assumed that, along with infected hepatocytes, healthy cells can also undergo lysis [34].

It has been shown that hepatic macrophages (KCs) have a positive antiviral effect in the early phase after infection, but apparently play a role in suppressing antiviral immunity in x ponic infection. In addition to their participation in the modulation of antiviral immunity, KCs is believed to be involved in the

development of fibrosis in chronic viral inflammation. On the other hand, KCs also express multiple matrix metalloproteinases (MMP-9, -12 and -13), which contribute to the degradation of the extracellular matrix and resolve fibrosis [28, 35].

It has been established that KCs become infected at the early stages of HIV infection, which can be in them in a productive and latent state. During latency, HIV does not multiply in KCs; at the productive stage, HIV multiplies and accumulates in the cytoplasm and inclusions in the form of granules they act on liver cells and, by "activating" various signaling pathways, have paracrine effects on other liver cells [36].

Certainly, the functional activity of KCs is affected by processes associated with apoptosis, the intensity of which depends on etiopathogenetic mechanisms. Absence or reduced functional activity of KCs may contribute to pathogen invasion and/or systemic inflammation, on the contrary, activation of KCs in conditions of liver damage does not lead to an uncontrolled inflammatory state in the liver.

Conclusions

KCs have many functions that can affect the inflammatory and fibroplastic process in the liver and which depend on their activity, determined by the existing metabolic and immune conditions. liver functions. KCs, having plasticity, have a large range of polarized phenotypes involved in the resolution of inflammation in the liver with different lesions. Clinical and morphological assessment of the structural and functional state of KCs allows us to clarify the pathogenetic and morphological mechanisms of liver damage. Carrying out morphological studies of liver biopsy specimens with the simultaneous use of different methods of cell identification significantly expands the possibilities of life specific diagnosis of liver damage of various origins.

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