THE KUPFFER CELL

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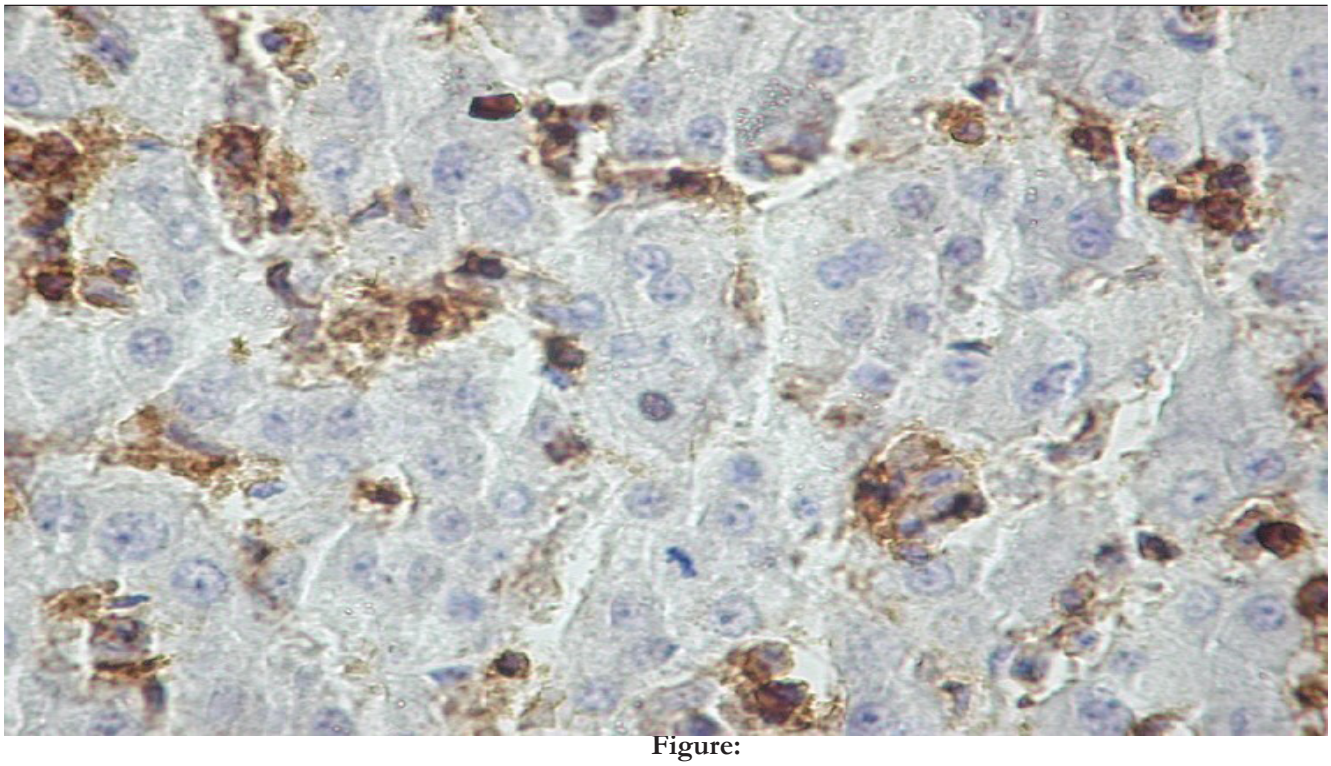

Figure:
CD68 immunoexpression with cytoplasmic pattern in Kupffer cells, CD 68 immunostaining, X400.

The Kupffer cells were first described in 1876 by Karl Wilhelm von Kupffer, who called them "strenzellen", star cells or stellate hepatic cells. He considered that the above mentioned cells belong to a perivascular cell group- the pericytes. In 1898, he reviewed his initial analysis, and stated that these cells are an essential component of the endothelium, capable of phagocytosis of foreign substances. In 1898, Tadeus Browiecz described them as belonging to the macrophage family.

As **origin, differentiation and proliferation**, Kupffer cells appear for the first time, during the development, at the Yolk sac. Then, they migrate into the fetal liver through the umbilical veins and left veins pathways. The active macrophages may be noticed during the second part of the third month (days 75-90) of human development. In the adult life, these macrophages coexist with those of extrahepatic origin. They proliferate and differentiated quickly into the late stages of embryonic development and after birth.

The resident tissue macrophages are a diverse family of cells present in the most organs: the microglia, the liver- Kupffer cell, the lung- alveolar macrophages, the Langerhans cells. The mechanisms responsible for generating diverse types of macrophages in human remain unclear. The mechanisms of KC renewal are unclear. Two hypotheses were proposed: the classic one, in which the Kupffer cells are not capable of cell renewal and they come from monocytes derived from the bone marrow. The second hypothesis argues that Kupffer cells are a population with regenerative capacity that can proliferate as mature cells or that originate from local intrahepatic progenitors. The life of macrophages was described as 3.8 days. In liver transplant patients, donor Kupffer cells persisted for up to one year. The turnover of Kupffer cells is realized by apoptosis and/or migration to lymph nodes. A proliferation increase, induced by IL4 growth, was noticed.

Kupffer cells represent 80-90% of the tissue macrophages, of the monocyte-macrophage or reticuloendothelial system. They are up 15% of the total liver cell population. The displacement speed is 4.6± 2.6 (SD) microns/min. 43% of these cells are localised

in periportal spaces, 28% in the middle area and 29% in the central areas.

The morphology of Kupffer cells in optical microscopy has the following characteristics: a star shape form, an eucromatic nucleus, the cytoplasm exhibits prolongations to the sinusoidal lumen and perisinusoidal space. At the molecular level, human Kupffer cells express CD14, CD68 (figure 1). One of the specific markers of Kupffer cells, highlighting their origin, is the Clec4F gene - type C, LECtina. The molecular model associated with pathogenic events expresses TLRs 2 and 4. These are intracellular sensors that enter in the cell via phagocytosis or pores. The molecular model associated with damage is characterized by the macrophage expression of TLR3, NLR = NOD (oligomerization domain binding oligonucleotide receptors). Their expression is associated with cellular stress. On the surface of macrophages, C1, 3, 4 complement receptors are expressed.

From an **ultrastructural point of view**, Kupffer cells exhibit characteristics microvilli. These, together with cytoplasmic projections, induced invaginations of plasmalema (vermiform bodies) formed by two parallel membranes that give them striated appearance. Kupffer cells present a small, juxtanuclear Golgi complex with numerous mitochondria, vacuoles, lysosomes, lipocrom pigments. Peroxidase reaction can be observed in perinuclear area and REs.

Kupffer cells have many **functions**. They play a role in the elimination and detoxification of micro-organisms, endotoxins, degenerate cells, immune complexes, and toxic agents (ethanol). They are antigen presenting cells responsible for initiating the immune response. Provides host defense by expression and secretion of mediators of soluble inflammation. Kupffer cells are involved in tumor surveillance. The interaction between KC and lipopolysaccharides (LPS) may be the starting point for hepatotoxicity in various types of liver injury, including alcoholic liver disease, ischemia-related disorders; reperfusion, systemic viral infections. They are involved in the processes of liver regeneration.

Activation of Kupffer cell M1 phenotype, with increased proinflammatory cytokines, with the release of TNF-alpha, IL-6, MMP, CXCR, IL-1 beta may have **implications in pathology** and act on stellate hepatic cells in the fibrosis process. It can also influence hepatic steatosis. Another direction is the action on hepatic sinusoidal endothelial cells, with effects on tumor cells, tumor progression, angiogenesis and metastasis. The activation of the Kupffer M2 phenotype is accompanied by the release of PD-L1, IL10, IL12, with the following effects: anti-inflammatory, anti-fibrotic, tumor survival, immune tolerance.

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