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Differentiation, Fine Structure, Function and Clinical Significance of Kupffer Cells

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Abstract

Kupffer cells are the largest aggregations of macrophages in tissue of the body. They are dominantly lining the lumen of liver sinusoids and show endocytic activity against blood-borne materials that entering liver. In the fetal and adult duration, Kupffer cell differentiation are controlled by growth factors especially (Macrophage colony-stimulating factor M-CSF). Kupffer cells (KCs) are essential liver macrophages originating primarily from three waves of embryonic hematopoiesis. The phenotypic and functional heterogeneity of KCs is significant, affecting their response to various liver injuries. KCs have an important role in keeping liver homeostasis, including the clearance of pathogens and apoptotic cells, and regulating inflammation. In acute liver injury, such as acetaminophen overdose, KCs undergo dynamic changes, initially decreasing in number and later recovering via self-renewal. Chronic liver injuries, like NASH, see a depletion of KCs alongside a recruitment of bone marrow-derived macrophages (BM-KCs) to maintain the macrophage pool. The function of KCs varies notably between embryonic-derived KCs and those derived from bone marrow, influencing their responses in inflammation and tissue repair. Strong evidence indicates that KCs may contribute to tissue remodeling and fibrosis in chronic liver diseases by mediating inflammation and extracellular matrix deposition.

Keywords: Histology, Liver, Kupffer Cells, M-CSF, BM-KCs

Introduction

Kupffer cells are specialized macrophages that resudue in the liver that line the walls of hepatic sinusoids, often referred to as “sinusoidal macrophages” or Kupffer–Browicz cells. They represent nearly 80–90% of the total macrophage population in the human body (Chaudhry et al., 2019; Basit et al., 2022). Functionally, they play a central role in innate immunity and take part in the processing and clearance of a wide range of substances. Initially, Kupffer cells were thought to share origins with endothelial cells; however, current evidence

demonstrates that they arise from a distinct macrophage lineage, tracing back to yolk sac progenitors rather than hematopoietic stem cells. (Gomez Perdiguero *et al.*2015; Weiyang Li *et.al*,2022), (fig.1).

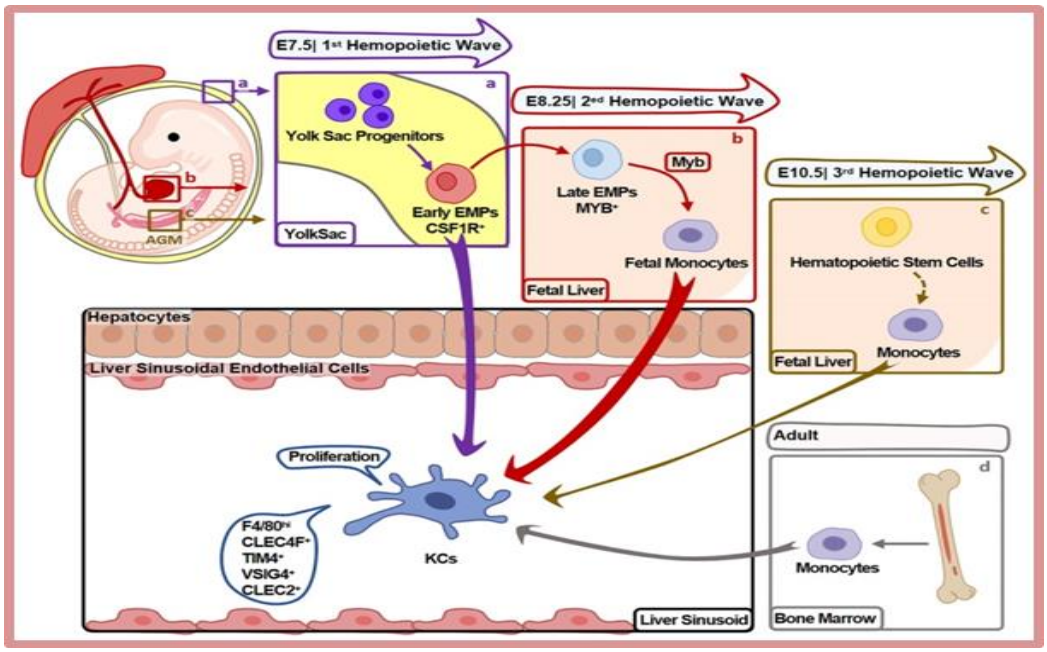

Figure (1): Heterogeneity of KC Origin. Cited from: (Weiyang Li et.al,2022)

Both granulocyte-macrophage colony-stimulating factors (GM-CSFs) and macrophage colony-stimulating factors (M-CSFs), which are found in the hepatic tissue and serum, control the differentiation of Kupffer cells (Yamamoto *et al.* 2008; Li W & He,2021). Although they can be found in the liver's centrilobular and periportal areas, kupffer cells are usually more prevalent in the latter. Nonetheless, specific enzymes, receptors, and subcellular structures may vary between the cells in the two regions (Kolios *et al.*2006).

Cellular Structure:

The hepatic sinusoid contains pit cells, Ito cells, sinusoidal endothelial cells, and specialized macrophages called kupffer cells (Wisse *et al*.1996). Kupffer cells are adhere to the sinusoidal endothelial cells and have an amoeboid morphology (fig.2), (Naito *et al.*2004). They have lamellipodia, pseudopodia, and microvilli on their surface that can protrude in all directions, pseudocodia and microvilli have a role in particle endocytosis. In their cytoplasm, they also have microfilaments, centrioles, ribosomes, microtubules, and the Golgi apparatus (Sichel *et al*.2002). Their nucleus might be divided into lobules and is ovoid or indented. They also express peroxidase action in their annulate lamellae, nuclear membrane, and rough endoplasmic reticulum (Wisse,1974).

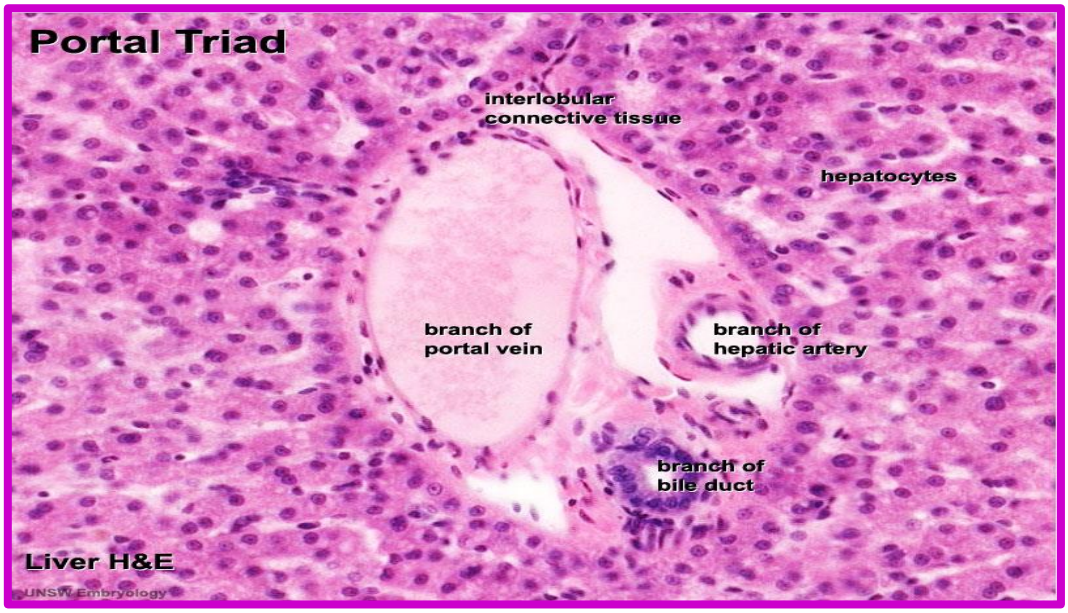

Fig. (2): Histological section in liver,cited from Hill, M.A. (2025, August) Embryology Gastrointestinal Tract - Liver Histology.

Depending on whether they are found in the periportal or centrilobular regions of the hepatic tissue, kupffer cells have different structures and functions. While kupffer cells in the centrilobular regions generate more superoxide anion, those in the periportal regions are often larger, exhibit higher lysosomal enzyme activities, and have greater phagocytic activity (Campion *et al*.2009).

Function

It is believed that a Kupffer cell has a lifespan of 3.8 days (Nguyen-Lefebvre & Horuzsko, 2015). Kupffer cells' main function is to remove foreign objects and waste from the portal system circulation that goes via the liver. Kupffer cells have the ability to pinocytose tiny particles and chemicals and phagocytose big particles. In addition, it has been demonstrated that Kupffer cells have the ability to move to the hepatic lymph nodes and portal sites prior to dying (Hardonk *et al.*1986). Apoptosis controls the steady population of Kupffer cells in the liver, which are phagocytized by nearby Kupffer cells. These cells are able to proliferate, which enables self-regeneration, in contrast to monocyte-derived macrophages that lack this ability. When granulomas form, Kupffer cells become activated in the absence of monocytes and develop into multinuclear giant cells (Yamada *et el.*1990).

The Kupffer cells have a wide range of phagocytic capabilities; they can ingest pathogens by phagocytosis, immunological particles, tumor cells, fat microspheres, liposomes, endotoxins, and other complexes. It is also known that the function of Kupffer cells varies according to their location. They are more active overall in zone 1 (periportal) of the liver lobules than they are in zone 3 (centrilobular) (Campion *et al*.2009). The greater they expose to toxic compounds in zone 1 as opposed to zone 3 is most likely the cause of the activity variation. Kupffer cells are capable of producing oxygen radicals, TNF-alpha, inflammatory cytokines, and proteases in addition to phagocytosis; the generation of these mediators is believed to play a role in the development of liver injury (Roberts *et al.*2007).

Aspects of histochemistry and cytochemistry

Kupffer cells show positive staining for macrophage markers, such as F4/80 in mice and ED1, E2, and Ki-M2R in rats. Their lysosomes have positive acid phosphatase staining. Other tracer materials that aid in their identification, such carbon, India ink, or latex microspheres, can be phagocytized by Kupffer cells (Elchaninov *et al.* 2019 ;Fujita et al.1983)**.**

Light and electron microscopy

Kupffer cells show long cytoplasmic processes and a great variation in the size and shape of the cells. Kupffer cells sit along the endothelial surface of the hepatic sinusoids wherein they make close contact with an enormous miscellany of structures about them. These cells interact not only with endothelial cells but also with collagen fibers, and fat-storing stellate cells in addition

to neighboring Kupffer cells themselves; hence complex cellular networks emerge within the sinusoidal microenvironment (Wisse et al., 1996). In electron microscopic view all macrophages stand located near to the wall of the sinusoid though not based directly onto the basement membrane. Rather, dynamic extensions or pseudopodia often interdigitate with those hepatocyte microvilli that are facing towards the space lying between immune and parenchymal cell signals can be exchanged. With such an arrangement of structure, multifunctionality for Kupffer cells between hepatic immunity and metabolism is indicated (Sichel *et al.*2002).

Pathophysiology

Kupffer cells have a role in the pathogenicity of hepatic injury induced by sepsis. When these cells become activated, they secrete IL-1 and TNF-alpha (Roberts et al.2007) thereby upregulating ICAM-1 on leukocytes and sinusoidal endothelial cells. Proteases, prostanoids, oxygen radicals — as well as other molecules out of leukocytes onto the endothelium — damage tissue. (Gulubova, 1998).

Clinical Importance

The SR-AI/II scavenger receptor present in kupffer cells binds and recognizes the lipid A domain of both lipopolysaccharide (LPS) and lipoteichoic acid. Gram-positive bacteria contain lipoteichoic acid in their cell walls while gram-negative bacteria contain LPS (Van Oosten et al.2001). Mice studies have indicated that those having the SR-AI/II receptor are more sensitive to invasion by gram-positive bacteria hence indicating the role of Kupffer cells in the elimination of microbial poisons from the system (Thomas et al.2000).

Kupffer cells have a crucial function in the pathogenicity of alcoholic liver injury. Many microorganisms able to generate gut-derived endotoxins inhabit the human intestinal tract. Kupffer cells remove gut endotoxins traveling to the liver. Studies have indicated that these endotoxins trigger Kupffer cells (Luedde & Schwabe, 2011). Different mechanisms have explained the relationship between levels of endotoxin and intake of alcohol. For example, chronic ingestion of alcohol reduces the capacity of Kupffer cells to remove endotoxin from the blood efficiently; thus, more endotoxin is present in the blood (Makoto et al.2004). By another pathway, drinking alcohol may increase gut permeability which can result in the increased intestinal absorption of endotoxins. The endotoxin signals the internalization of the lipopolysaccharide (LPS) endotoxin by interaction through both CD14 receptors on Kupffer cells and Toll-like receptor 4 (TLR4) (Ciesielska et al.2021).

The activated kupffer cells begin to release reactive oxygen species like superoxide resulting in oxidative stress in the liver (Ciesielska et al.2021). This, from the other hand, results in triggering of the nuclear factor kappa B (NF-kB) pathway by interleukin-1 receptor-associated kinase (IRAK-1) after TLR4 has been activated. The pathway will then elicit responses that include even more cytokines and superoxides that will contribute to damage in the liver and eventually loss of function of the organ itself through pathology (Luedde & Schwabe, 2011).

Probiotics and antibiotics, TNF-alpha, and IL-1beta are among the regulators used in controlling Kupffer cell activation and in destroying the cytotoxic products of Kupffer cells (Chen et al.2018). Fc, C3, and scavenger receptors help kupffer cells to ingest both labeled and non-labeled material through phagocytosis (Bilzer et al.2006). In addition, scavenger receptors have a role in pathology by enabling the deposition of cholesterol within the arterial walls (Van Oosten et al.1998).

Kupffer cells also remove old erythrocytes from the blood and this is why heme oxygenase becomes active soon after phagocytosis. Heme oxygenase is the enzyme that splits heme molecules found in erythrocytes and is related to the metabolism and synthesis of bilirubin. (Hirano *et al.*2001).

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