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The development and maintenance of the liver tissue with the help of Kupffer cells

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Abstract

Kupffer cells are a group of star-shaped cells in hepatic sinusoids responsible for the formation of the liver and immunological-inflammatory reactions. Macrophages first begin to improve in the yolk sac and mature into kupffer cells during pregnancy. Kupffer cells are a component of the mononuclear phagocytic system, which plays a considerable role in the repair of liver damage by promoting the secretion of cytokines and chemokines involved in the hepatic and systemic response. In case of a disease situation, kupffer cells become pathologically active from the tolerogenic feature, which can lead to hepatocellular damage. Therefore, as in other components of the immune system, the continuity of proper kupffer cell activity has an important role in maintaining the vitality of the organism. A decrease in the number or loss of function of kupffer cells can lead to inflammatory conditions as a result of pathogen invasion of the liver. This brief review study, it is aimed to examine the research evaluating the functions of kupffer cells in liver development and repair.

1. Introduction

The liver is one of the vital organs of the body with endocrine and exocrine hormone functions. Hepatocytes make up 60% of the liver tissue, 40% of the liver consists of the sinusoidal cells, kupffer cells, and stellate cell groups. Kupffer cells were discovered as sternzelle (star cells) by the gold chloride staining method used to stain cells that store fat. In previous studies, kupffer cells were defined as liver macrophages located in portions of the liver sinusoidal space and adjacent to the endothelial cells [1].

Monocytes transferred from adult Medulla Ossea to the peripheral circulation are known as precursors of the tissue macrophages. These monocytes can enter the liver and differentiate into tissue-specific macrophages. The development of kupffer cells is due to macrophage-stimulating factors [2]. Controlled continuity of the kupffer cells in the liver is ensured, but the mechanisms providing this control have not been fully elucidated. Peripheral circulation monocytes enter the lung and liver faster than other tissues. The regeneration time of kupffer cells in the liver is between 14 and 21 days [2]. It is assumed that kupffer cell differentiation occurs due to apoptosis or migration of lymph node cells into different regions. In a study, it was reported that increases in IL-4 in response to inflammatory signals also activate kupffer cells and accelerate macrophage proliferation [3].

According to the results of the mononuclear phagocyte system studies, blood monocytes proliferate and get formed from the precursor cells in the bone marrow, migrate to various tissues, and turn into macrophages [4]. Fetal tissue macrophages develop before bone marrow hematopoiesis. It has been stated that fetal liver macrophages include cytochemical and immunochemical features of the kupffer cells [5]. In this brief review, it is aimed to examine the studies evaluating the functions of kupffer cells in liver growth and repair.

2. Material and Methods

2.1. Development of Kupffer cells

It is known that macrophages originate from hematopoietic tissues. Mammalian macrophages first develop in the Yolk sac [6]. In the second week of pregnancy, blood islets begin to form in the yolk sac mesenchymal region [7]. Primitive erythroblasts and megakaryoblasts are undifferentiated blood cells. While the heart is forming during pregnancy, the cardiovascular system is twisted by the umbilical and vitelline vessels. In this process, mononuclear cells contain F4/80, a type of macrophage antibody found in the vascular wall of the yolk sac [2]. These circular mononuclear cells have large nuclei, numerous polyribosomes, underdeveloped Golgi apparatus, and cytoplasmic organelles to name a few. The transformation of the immature cells with this feature into functional macrophages takes place in as little as one day.

After the 10th day of pregnancy, blood flow to the liver starts from the umbilical and vitelline veins. The umbilical vein and the portal vein come together to form a sinusoidal vein, which forms a network in the fetal liver. In this process, fetal liver erythroblasts hematopoiesis begins. Cells containing F4/80 are not found in the fetal liver. Erythroblasts and mononuclear cells are common in vascular endothelial ducts [7]. Mononuclear cells in the liver have immunophenotypic features of progenitor macrophages located in the yolk sac. It is assumed that these cells are carried by blood vessels in the egg sac during the hematopoiesis and colonized in the fetal liver. While the number of macrophages belonging to the fetus decreases and disappears in the peripheral blood between the 17th and 19th days of the fetus, monocytes begin to appear from the 17th day of the fetus [8].

The number of F4/80 macrophages that start to appear in the fetal liver from the 11th day of pregnancy increases as pregnancy progresses. From the 12th day of pregnancy, macrophages that perform phagocytosis of blood cells rise in number and bind to the cells in the inner part of the liver sinusoid. These macrophages with numerous polyribosomes and enlarged microvilli are compatible with macrophages in the yolk sac. Macrophages in the hepatic sinusoid increase in number proportionally with the duration of pregnancy [9].

As the number of erythropoiesis increases, macrophages and the erythroblasts unite to form islets, and thus macrophages in the fetal liver support hematopoiesis. The development of hepatic hematopoiesis is most evident on the 18th day of pregnancy, increases as the gestation period progresses and disappears immediately after delivery. After the 18th day of pregnancy, hemophagocytosis caused by the macrophages decreases, and after birth, macrophages proliferate and turn into kupffer cells.

2.2. Localization of Kupffer cells in hepatocytes

There are many specialized cell groups in the sinusoidal part of the liver. Liver hepatocytes are considered as the main cell groups that regulate various metabolic events and have toxicological functions. Hepatic sinusoids are covered by special groups of liver cells called fenestra. In addition to T cells, dendritic cells, and natural killer cells are found in the sinusoidal region. It is thought that the function of kupffer cells as the regulators of the liver functions is due to their proximity to liver parenchymal and non-parenchymal cells. Kupffer cells in the healthy liver are tolerogenic to prohibit antigens from intestinal space and dead cells without generating a full blasting inflammatory response [10].

In case of a disease situation, kupffer cells become pathologically active from the tolerogenic feature, which can lead to hepatocellular damage. Therefore, as in other components of the immune system, the continuity of proper kupffer cell activity has an important role in maintaining the vitality of the organism. A decrease in the number or loss of function of kupffer cells can lead to inflammatory conditions as a result of pathogen invasion of the liver.

2.3. Response of the Kupffer cells to the liver injury

Kupffer cells become active in liver damage caused by toxins of pharmacological and chemical agents (endotoxin, galactosamine, acetaminophen). Kupffer cells, which are activated in hepatocellular necrosis when the liver is damaged, activate inflammatory regulators such as cytokines, chemokines, and proteolytic enzymes. When lipopolysaccharide (LPS) and prostaglandins are present in the liver environment, cytokine secretion by hepatic macrophages begins.

Kupffer cells and hepatocytes produce nitric oxide when the liver is damaged, protecting the liver against endotoxemia and hepatic injury. Nitric oxide interacts with reactive oxygen radicals to form peroxynitrite, increasing oxidative stress or activating inflammatory responses for instance interleukins and TNF-α. In liver pathogenesis, activated kupffer cells produce cytokines and chemokines. It has been reported that kupffer cells stimulate TNF-α production in alcohol-related liver injury [11].

In another study, it was shown that Kupfer cells increase MCP1 chemokine production in acetaminophen and CCL_4-induced liver injury. Experimental studies have supported a relationship between the activation rate of kupffer cells and hepatocellular damage and liver destruction [12].

It was reported that while increased liver damage is caused by carbon tetrachloride (CCL_4) in endotoxin treated rats, in low dose endotoxin treated rats CCL_4 had protective role rather than its inflammatory effects [13]. Kupffer cells are involved in the mechanisms of elimination of hepatotoxicity through agents that induce glutathione synthesis and nitric oxide production. Kupffer cells participate in this protection by activating IL-10 and IL-18. Studies have shown that when kupffer cells decrease in the medium, IL-10 and IL-18 also decrease. As a result, in the presence of hepatotoxins in the environment, kupffer cells are actively included in the repair of the liver in case of excessive activation of the liver. Kupffer cells are also very important in the defense against liver infections. In LPS and salmonella treatment, it has been shown that increasing kupffer cell counts improve prognosis [14]. Production of superoxides by kupffer cells increases susceptibility to infection as a result of occlusion of sinusoids in hepatitis and disruption of phagocytic functions [15]. Kupffer cells appear to stimulate the production of TNF-α, IL-6, IL-12, and nitric oxide to inhibit the growth of the microorganisms [16]. In liver tissue fibrosis, the structure and components of the outer membrane matrix of hepatic sinusoid cells are disrupted. The main cell groups of the liver extracellular matrix are Ito and stellate cells. Fibrogenesis in the liver occurs in 2 processes. The first of these is the transformation into myofibroblasts by activating the ito cell. In this process, while Type I and Type III collagen production increases, the expression level of proteolytic enzymes that degrade the extracellular matrix decreases. Thus, there appears to be a problem with the hemostatic mechanisms responsible for the extracellular matrix. Therefore, for the continuation of fibrosis, the production of matrix-associated metalloproteinase enzyme decreases, while the production of metalloproteinase inhibitors (TIMP, alpha-antitrypsin) increases [17]. Kupffer cells are included in the regulation processes of inhibitors of Ito and metalloproteinases. It has been stated that TGF-B1 obtained from kupffer cell regulates Ito cell turnover and regulates collagen and proteoglycan production [18].

2.4. Activation of Kupffer cells after splenectomy

Kupffer cells of monocyte origin have replication capacity in response to traumas in the liver, peritoneal sepsis and splenectomy [19]. Increased Kupffer cell proliferation has been reported in splenectomized rats, especially in cases with monocytopenia for more than four weeks. It has also been reported that Kupffer cell increase in splenectomy rats will be effective on intraperitoneal sepsis [20]. It was observed that giant nucleated cells were formed and kupffer cells multiplied in rats in which granulomas were obtained by using glucan. This was thought to be a sign that kupffer cells were self-renewing. One study suggested that Kupffer cell proliferation prevents aggravation of peritonitis after splenectomy [21].

These effects, which are caused by the effect of endotoxin, are caused by the bacterial translocation in rats, and in cases of organ failure. Sepsis occurs as a result of increased activities of lysozyme and lectin enzymes. In this case, it has been shown that TNFα, IL-6, and Nitric Oxide are synthesized [22]. Swelling of kupffer cells has been reported, especially in multi-organ failure caused by the fecal peritonitis [22].

2.5. The life cycle of Kupffer cells in the liver

It is known that the mammalian liver cells lifespan is 3.8 days. In a study on this subject, it has been reported that liver cell viability is more than 2 weeks and may even extend up to 14 months [2]. In liver transplantations, it has been shown that donor liver cells are found in the transplanted patient for up to 1 year [23]. Two hypotheses have been proposed regarding the mechanisms of liver renewal. The first of these is classical dogma; which assumes that liver cells are not self-renewing but are produced from monocytes in the bone marrow [24-25]. In the second hypothesis, it is assumed that the liver cells are composed of cell groups with self-renewal properties, and proliferate from mature cells and intrahepatic progenitors [26]. In mice with ethanol-induced liver injury, monocytes differentiated into macrophages and became the main population of the liver after 5 days of treatment [27]. Compared to bone marrow-derived macrophages, liver cells provide neutrophil recruitment and protect hepatocytes against bacterial infections [28]. It has been shown that liver cells can migrate from the liver portal area to the hepatic lymph nodes [29].

2.6. Kupffer cell receptors

There are two main recognition receptors (PRR) that regulate innate immunity. These are Toll- and NOD-like receptors involved in the recognition of pathogen-associated and danger-related signals. External molecular models associated with the pathogen are external stimuli, while molecular models associated with danger are internal stress stimuli. While there are many studies on LPS activating TLR4, little is known about the role of PRRs in the liver damage [30-33]. In a study with mice, it was found that ethanol increased mRNA expression for different TLRs (2,4,6,7,8 and 9), and the sensitivity of mice to bacterial ligands increased [34]. It was reported that TLR-7 and 9 expressions were increased in liver samples diagnosed with ALD [35]. Many studies are needed on the effects of complex interactions between kupffer cells and pathogen-associated molecular models and the molecular models resulting from the distress signaling on liver injuries.

3. Conclusion

Kupffer cells are specialized macrophages that form part of the liver reticuloendothelial system. Macrophages first begin to develop in the yolk sac and mature into kupffer cells during pregnancy. Kupffer cells are components of the mononuclear phagocytic system, which plays a crucial role in the repair of liver damage by promoting the secretion of cytokines and chemokines involved in the hepatic and systemic response. Kupffer cells become active in liver damage caused by toxins of pharmacological and chemical agents (endotoxin, galactosamine, acetaminophen). Kupffer cells, which are activated in hepatocellular necrosis in the damaged liver, activate inflammatory regulators such as cytokines, chemokines, and proteolytic enzymes. In addition, when LPS and prostaglandins are present in the medium, they initiate cytokine release by the hepatic macrophages. Kupffer cells and hepatocytes produce nitric oxide when the liver is damaged, protecting the liver against endotoxemia and hepatic injury.

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Author contributions

Harika Topal Önal: Conceptualization, Methodology, Writing original draft **Furkan Ayaz:** Data curation, Editing the original draft

Conflicts of interest

The authors declare no conflicts of interest.

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