IL-6-Mediated Liver Regeneration: Exploring Key Signaling Pathways and Cellular Mechanisms

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Abstract. The liver is a vital organ responsible for a variety of essential functions in the human body, and the growing prevalence of liver damage and disease highlights the need to understand the liver's inherent regenerative capacity. Research into liver regeneration has shown that, among the numerous cytokines involved, interleukin-6 (IL-6) plays a critical and irreplaceable role. Without IL-6, the liver cannot effectively regenerate, underscoring its significance. This review examines IL-6 in detail, including its interaction with its receptor and its involvement in three distinct signaling modes: classical, trans-signaling, and cluster signaling. Additionally, it explores two key pathways activated by IL-6 that drive liver regeneration: the JAK/STAT and Ras/MAPK pathways, both of which are crucial for promoting hepatocyte proliferation and tissue repair. Understanding the precise mechanisms through which IL-6 regulates these signaling pathways, as well as its role in liver regeneration under varying degrees of injury, offers valuable insights that have broad implications for treating liver diseases and improving human health.

Keywords: IL-6; liver regeneration; JAK/STAT; Ras/MAPK.

1. Introduction

The liver is a vital organ for human metabolism and is unique for its remarkable regenerative capacity. Upon injury, toxic exposure, or partial surgical resection, liver cells rapidly undergo division to restore liver mass and function. This regeneration involves various cytokines that facilitate the recovery process, closely correlating with the extent of liver damage. In cases of mild injury, parenchymal hepatocytes initiate regeneration by proliferating. Conversely, in instances of severe damage where hepatocytes fail to transition from the G0 to the G1 phase, liver stem cells known as oval cells begin differentiating into hepatocytes, aiding in the repair and regeneration of the liver.

Liver regeneration occurs in three distinct stages: the priming stage, the proliferation stage, and the termination stage, each characterized by specific cytokine involvement (Fig. 1). During the priming stage, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) induce hepatocytes to progress from the G0 phase to the G1 phase. In the proliferation stage, hepatocytes transition from the G1 to the S phase, driven by growth factors including epidermal growth factor (EGF), hepatocyte growth factor (HGF), and transforming growth factor-α (TGF-α). The termination stage is marked by the cessation of cell growth, primarily mediated by tumor necrosis factor-β (TNF-β) and various cytokines, which inhibit the signaling pathways associated with liver regeneration and activate termination signals [1].

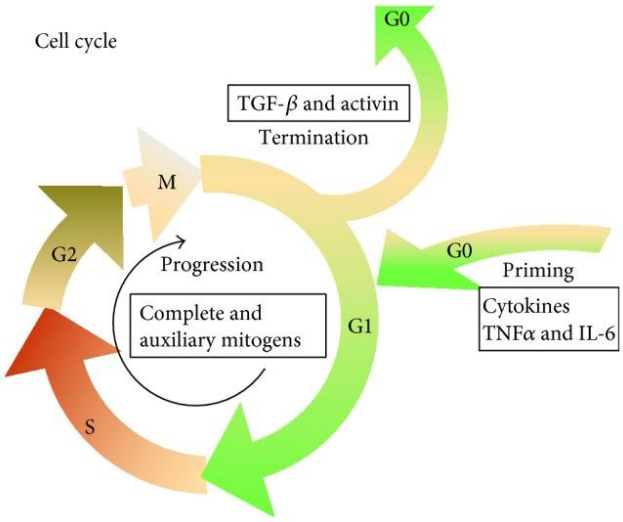

Fig. 1 The process of liver regeneration [2].

Among the cytokines involved in liver regeneration, IL-6 plays a pivotal role due to its diverse biological activities. IL-6 exerts its effects by binding to specific receptors, thereby activating the JAK/STAT and Ras/MAPK signaling pathways. In the JAK/STAT pathway, IL-6 forms a complex with the membrane receptor IL-6R (mIL-6R) and subsequently binds to gp130, leading to the activation of JAK kinases. This activation results in the phosphorylation of signal transducer and activator of transcription (STAT) proteins, which dimerize and translocate to the nucleus to initiate gene transcription that promotes liver regeneration. In the Ras/MAPK pathway, IL-6 engagement with mIL-6R and gp130 activates Ras kinases, which in turn undergo multiple phosphorylation events to form MAPK, driving gene transcription and facilitating liver regeneration.

Thus, IL-6 is essential for the liver regeneration process. This article provides a comprehensive review of IL-6 and its significant role in liver regeneration.

2. IL-6 and Its Receptor

IL-6 is a multifunctional cytokine that regulates both the immune and nervous systems. It is a protein composed of four alpha-helical bundles, with a relative molecular mass of approximately 26 kDa. IL-6 functions in signal transduction through autocrine, paracrine, and endocrine mechanisms [3]. In the liver, IL-6 is primarily secreted by Kupffer cells and endothelial cells, exerting its effects on hepatocytes via paracrine signaling.

The biological activity of IL-6 relies on its binding to a receptor composed of two components: the IL-6 receptor alpha chain (IL-6Rα) and the IL-6 receptor beta chain (IL-6Rβ). IL-6Rα, commonly referred to as IL-6R or gp80 due to its molecular size of approximately 80 kDa, specifically binds IL-6. In contrast, IL-6Rβ, known as gp130, is a signal transduction protein with a molecular size of 130 kDa. While IL-6R does not participate in signal transduction, gp130 plays a crucial role in mediating intracellular signaling pathways. Both IL-6R and gp130 exist in two forms: the membrane-bound form (mIL-6R) and the soluble form (sIL-6R). The soluble form can arise from membrane protein cleavage or alternative mRNA splicing. Gp130 is widely expressed in various tissue cells and is also present in body fluids in its soluble form [4].

3. IL-6 and Its Signal Conduction

The signaling modes of IL-6 can be categorized into three types: classical signaling, trans-signaling, and cluster signaling pathways.

Classical signaling pathway (Fig. 2A): This mode of signal transduction occurs in cells that express both IL-6R and gp130 [5]. In this pathway, IL-6 binds to the membrane-bound IL-6R (mIL-6R) on

the target cell, forming a dimeric complex. This conformational change allows the receptor to associate with at least two gp130 molecules, creating a high-affinity binding site that initiates signal transduction through gp130, activating the JAK/STAT3 pathway [6].

Trans-signaling pathway (Fig. 2B): This signaling mode is observed in cells that express only gp130 and not IL-6R [5]. Here, the soluble IL-6 receptor (sIL-6R) can be generated by the proteolytic cleavage of the membrane receptor by ADAM17 protease or through alternative splicing. IL-6 then binds to sIL-6R, forming a dimer that interacts with gp130, thereby initiating signal transduction [6].

Cluster signaling pathway (Fig. 2C): This signaling mode occurs in cells that only express gp130 and lack IL-6R [5]. In this context, IL-6 binds to mIL-6R on dendritic cells, forming an IL-6/mIL-6R complex. This complex is subsequently presented to gp130 on T cells, facilitating their interaction. Dendritic cells serve as downstream signalers for gp130, activating T cells and initiating the signaling cascade [7].

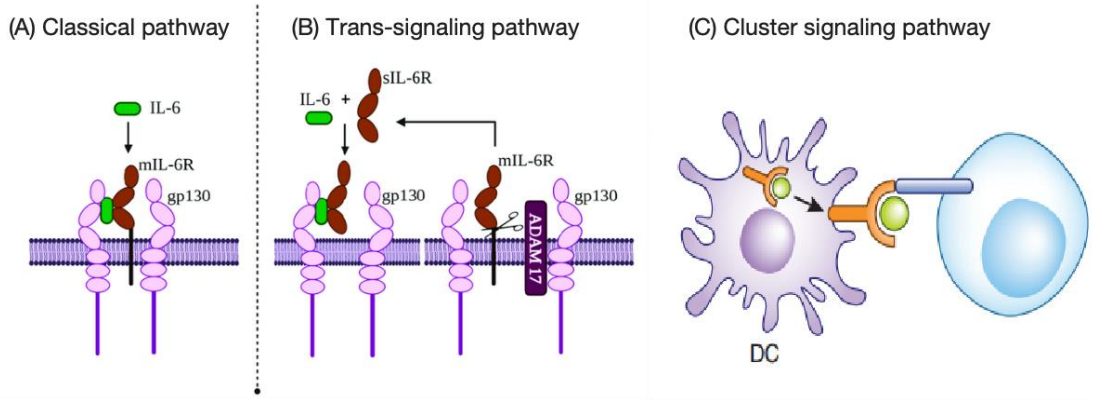

Fig. 2 IL-6 signaling pathways. (A) Classical pathway [8]. (B) Trans-signaling pathway [8]. (C) Cluster signaling pathway [5].

4. Role of IL-6 in Tissue Regeneration

IL-6 is a cytokine with extensive biological activity, playing a critical role in regulating the immune response and facilitating wound healing [9]. Its functions include promoting the proliferation and regeneration of various cell types and tissues.

Wound healing is a tightly regulated process characterized by complex interactions among different tissue types and cells. Initially, platelets and fibrin form an insoluble clot at the wound site. This is followed by an inflammatory phase, during which leukocytes, including neutrophils and macrophages, infiltrate the injury site to clear damaged cells and release a variety of growth factors and cytokines. These factors are essential for triggering the subsequent proliferative phase. Macrophages, in particular, are crucial for tissue remodeling and angiogenesis, making leukocyte infiltration necessary for effective wound healing [10].

In a study by Zi-Qing Lin et al., skin excision experiments were conducted on both IL-6-deficient mice and wild-type control mice to compare their wound healing responses over time [10]. Six days post-injury, wild-type control mice exhibited 50% recovery of the wound area, whereas IL-6-deficient mice demonstrated impaired wound healing. This finding underscores the importance of IL-6 in the wound healing process.

Further analysis of leukocyte infiltration during the inflammatory phase revealed that wild-type control mice had substantial infiltration of neutrophils and macrophages at the wound site. In contrast, IL-6-deficient mice showed significantly reduced levels of these leukocytes, accompanied by decreased expression of various growth factors and cytokines. Overall, the wounds in IL-6-deficient mice displayed delayed macrophage infiltration, impaired fibrin clearance, and reduced wound contraction. Therefore, it is evident that IL-6 plays a pivotal role in facilitating effective wound healing.

5. Role of IL-6 in Liver Regeneration

The process of liver regeneration involves the regulation of various cells and factors in vivo. Recent studies by Farshid Fathi et al. investigated the expression of cytokines such as IL-1α, IL-1β, IL-6, and TNF-α in patients with hepatocellular carcinoma undergoing hepatectomy [11]. The results revealed that following hepatectomy, the expression of IL-6 and TNF-α, as well as their serum levels, increased significantly, while changes in other cytokines were minimal. This underscores the critical roles of IL-6 and TNF-α in liver regeneration. Additional research utilizing gene expression arrays highlighted that genes involved in the G0 to G1 transition and G1 phase progression, including STAT3, were significantly downregulated in IL-6 knockout mice post-hepatectomy. However, administering IL-6 to these knockout mice 20 minutes prior to hepatectomy largely compensated for the loss of gene expression and positively impacted recovery. Moreover, the activation of MAPK was observed earlier in the liver regeneration process of mice with IL-6, while it was significantly delayed in IL-6 knockout mice, further indicating the essential role of IL-6 in liver regeneration.

5.1. IL-6 Activated Signaling Pathway

IL-6 exerts its biological activity primarily through the JAK/STAT and Ras/MAPK signaling pathways to promote liver regeneration.

JAK/STAT pathway: Although gp130 does not contain a tyrosine kinase active domain, it possesses an amino acid residue region with a characteristic sequence that interacts with signaling proteins, allowing it to engage with JAK kinases. Upon binding, JAK kinases become activated and subsequently phosphorylate STAT proteins. STAT contains an SH2 domain that can be activated through tyrosine phosphorylation, leading to the formation of dimers. These dimers translocate to the nucleus, where they bind to specific promoter sequences, initiating the transcription of genes involved in cell growth [4, 12].

Ras/MAPK pathway: Once gp130 is activated, it recruits Src homologue and collagen (Shc), which then associates with growth factor receptor binding protein-2 (Grb2) to form a complex. This complex interacts with guanine nucleotide exchange factor (Sos) to activate Ras proteins. Activated Ras can then trigger downstream signaling proteins, including MAPK, through multiple phosphorylation events. MAPK plays a crucial role in promoting cell growth and liver regeneration [4].

5.2. Activation of IL-6 on Oval Cells

Following liver injury, initial regeneration is primarily mediated by the mitotic proliferation of hepatocytes transitioning from the G0 to the G1 phase. However, if this process is hindered for any reason, oval cells in the liver can differentiate into hepatocytes to facilitate liver reconstruction.

In a study by Zhu Yanliang et al., two-thirds of the rat liver was resected, and 2-acetylaminofluorene was used as an inducer to create a liver regeneration model mediated by oval cells [13]. Compared to hepatocyte-mediated regeneration following two-thirds hepatectomy, they monitored the dynamic changes in IL-6 and TNF-α levels during the regeneration process. The study found that IL-6 can stimulate the differentiation of oval cells, thereby promoting liver regeneration. Similarly, recent findings by YiTong indicated that in mice expressing IL-6, numerous oval cells extended into the liver parenchyma, while IL-6 knockout mice exhibited significantly inhibited activation of these oval cells. Thus, IL-6 is pivotal in the activation of oval cells [14].

In conclusion, IL-6 is a multifunctional cytokine that participates in the acute inflammatory response following liver injury and initiates hepatocyte regeneration. Its importance is evident not only in promoting the transition of hepatocytes from G0 to G1 but also in stimulating the activation of oval cells, thereby facilitating liver regeneration.

6. Conclusion

The liver is a vital organ in the human body, and the prevalence of liver damage and diseases is increasing in today's society. Thus, understanding the liver's regenerative capacity is essential for human health. Among the various cytokines involved in liver regeneration, IL-6 is indispensable; liver regeneration cannot occur without it.

This article has outlined the interaction between IL-6 and its receptor, as well as the three signaling modes through which IL-6 initiates signal transduction. It specifically discusses the two key signaling pathways that IL-6 engages to promote liver regeneration, particularly in cases of mild liver damage: the JAK/STAT and Ras/MAPK pathways. In the JAK/STAT pathway, IL-6 binds to mIL-6R to form the IL-6/mIL-6 complex, which then interacts with gp130, activating JAK kinase. This activation leads to the phosphorylation of STAT, forming dimers that translocate to the nucleus to initiate gene transcription and support liver regeneration. In the Ras/MAPK pathway, Ras kinase, a GTPase, activates MAPK through multiple phosphorylation events. When IL-6 binds to mIL-6R, the IL-6/mIL-6 complex engages with gp130, activating Ras kinase and subsequently MAPK, which also initiates gene transcription to promote liver regeneration.

In cases of severe liver damage, where hepatocytes cannot transition from the G0 to the G1 phase, oval cells can differentiate into hepatocytes to restore damaged tissue, with IL-6 playing a crucial role in activating these oval cells. Thus, IL-6 is fundamental not only in hepatocyte regeneration but also in the activation of oval cells for effective liver recovery.

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