

# Interactions between Myc and Inflammatory Mediators in Chronic Liver Disease

## Abstract

Most Chronic Liver Diseases (CLDs) are characterized by inflammatory processes with abnormal expression of various pro- and anti-inflammatory mediators in the liver. These mediators are the driving force behind many inflammatory disorders of the liver, often leading to fibrosis, cirrhosis, and liver tumorigenesis. c-Myc is involved in many cellular events such as cell growth, proliferation, and differentiation. c-Myc upregulates IL-8, IL-10, TNF- $\alpha$  and TGF- $\beta$ , while IL-1, IL-2, IL-4, TNF- $\alpha$  and TGF- $\beta$  promote the expression of c-Myc. Their interaction plays a central role in fibrosis, cirrhosis, and liver cancer. The molecular interference of their interactions offers a possible therapeutic potential for CLD. In this review, current knowledge on the molecular interactions between c-Myc and various well-known inflammatory mediators will be discussed. Chronic Liver Disease (CLD) is a major cause of morbidity and mortality worldwide. Furthermore, the burden of LTC is expected to increase. Inflammatory cytokines are a group of important regulatory mediators involved in the development of CLD. The development and progression of CLD has been associated with hepatitis B, hepatitis C, alcoholic liver disease, drug-induced liver disease, autoimmune liver disease, Hepato Cellular Carcinoma (HCC), and Cholangio Carcinoma (CCA).

**Keywords:** Autoimmune • Inflammatory • Infections • Mediators • Chronic Liver Disease

## Introduction

c-Myc can be hetero dimerized with Max to trade its target genes by binding the consensus sequence of the E box in the promoter region. c-Myc is involved in the regulation of many biological processes, including cell division, apoptosis, growth, and angiogenesis. We will summarize the interaction of inflammatory mediators with c-Myc in CLD. Although NF- $\kappa$ B and AP-1 are not inflammatory mediators, they play key roles in the interaction of c-Myc and inflammatory mediators. We will also discuss their associations with inflammatory mediators and c-Myc. In addition, we will discuss the involvement of inflammatory mediators and c-Myc in liver disease and to develop anti-CLD strategies. IL-1 is an important upstream pro inflammatory cytokine that affects immunity and hematopoiesis by inducing cytokine cascades. IL-1 mediates inflammation primarily by inducing local cytokine networks, enhancing inflammatory cell infiltration, and increasing expression of adhesion molecules on Endothelial Cells (ECs) and leukocytes demand. IL-1 $\beta$  is a potent inflammatory cytokine mainly produced by macrophages. Toll-Like Receptors (TLRs) play an essential role in innate immune responses. IL-1 $\beta$  production requires stimulation by TLR ligands as well as a second signal such as Muramyl Di Peptide (MDP-)-mediated stimulation of NOD-Like Receptors (NLRs) or P2X7 receptors. IL-1 $\beta$  is associated with nonalcoholic fatty liver disease and alcoholic steatohepatitis [1, 2].

## Discussion

Hepatic Astrocytes (HSCs) play a major role in fibrosis in chronic liver disease. In HSCs, IL-1 $\beta$  mediates up-regulation of the Tissue Fibroblast Inhibitor of Metalloproteinase-1 (TIMP-1) and down-regulation of Bone Morphogenetic Protein and Activin Membrane-Associated Inhibitor

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**Received:** 1-Mar-2023, **Manuscript No.** oarcd-23-91692; **Editor assigned:** 2-Mar-2023, **PreQC No.** oarcd-23-91692(PQ); **Reviewed:** 16-Mar-2023, QC No. oarcd-23-91692; **Revised:** 23-Mar-2023, **Manuscript No.** oarcd-23-91692(R); **Published:** 30-Mar-2023; DOI: 10.37532/rcd.2023.7(2).021-023

(BAMBI). In addition, IL-1 $\beta$  promotes the survival of activated HSCs in mice. Overexpression of IL-1 $\beta$  induces spontaneous liver damage and fibrosis. Several oncogenes, including Myc and Ras, mediate tumorigenesis and activate inflammatory cytokines that establish the pre-invasive tumor microenvironment. Activation of Myc in pancreatic  $\beta$  cells rapidly induces the expression and release of the pro-inflammatory cytokine IL-1 $\beta$ . Inhibition of IL-1 $\beta$  inhibits and significantly retards Myc activation of islet angiogenesis, confirming a key role for IL-1 $\beta$ . IL-1 $\beta$  is the major Myc effector responsible for the rapid initiation of islet angiogenesis. IL-1 $\beta$  directly affects the survival and proliferation of endothelial cells and promotes the generation of other pro-angiogenic factors such as Matrix Metallo Proteinases (MMPs), TGF- $\beta$ , TNF- $\alpha$ , angiopoietin-1, IL-6 and Vascular Endothelial Growth Factor (VEGF). Myc plays an important role in PI3K-mediated VEGF regulation in Neuro Blastoma (NB) cells. c-Myc is essential for angiogenesis and angiogenesis during tumor growth and progression. This effect is partially linked to the requirement for c-Myc in VEGF expression. However, c-Myc is also required for the correct expression of other angiogenic factors, including angiopoietin-1. In a transgenic model of Myc-dependent oncogenesis, such as pancreatic  $\beta$ -cells, IL-1 $\beta$  is both required and sufficient to mediate Myc-induced VEGF release and initiation of small island neoplasia [3, 4].

IL-1 expression is increased in alcoholic hepatitis and cirrhosis. IL-1 $\alpha$  expression is increased in chronic hepatitis B and hepatitis C, whereas IL-1 $\beta$  expression is increased in alcoholic liver injury. IL-1 $\beta$  and IL-1 increased the expression of c-Myc while IL-1 increased the expression of IL-1 $\beta$  mRNA. These EHM's mainly include autoimmune diseases such as CD and Sjögren's syndrome and endocrine diseases such as Auto Immune Thyroid Disorders (AITD) and type 2 diabetes. Hashimoto's thyroiditis or chronic Autoimmune Thyroiditis (AT) is one of the most common thyroid diseases. AT is the most common form of thyroiditis, and its incidence is significantly more common in women and the elderly. The incidence rate in women is 3.5 cases/1000 subjects/year, in men it is lower (0.8 cases/1000 population/year); there is a marked difference depending on different geographical regions. AT is an organ-specific autoimmune disease that is morphologically characterized by chronic lymphocytic infiltration of the

thyroid gland and the presence of circulating auto Antibodies such as Anti Peroxidase (AbTPO) and Anti Thyro Globulin (AbTg). The inflammatory process leads to the destruction of the cyst; indeed, AT is the most common cause of hypothyroidism in iodine-deficient regions. Sometimes, antibodies that block the Thyroid-Stimulating Hormone (TSH) receptor can cause the atrophic form of AT. More rarely, anti-TSH receptor-stimulating antibodies can cause a transient form of hyperthyroidism [5].

In poorly ventilated areas, low NO levels lead to vasoconstriction, which directs blood flow to ventilated areas with high NO concentrations to ensure efficient blood oxygenation. In patients with Pulmonary Arterial Hypertension (PAH), decreased NOS activity compared with controls resulted in inadequate ventilation/perfusion. ADMA as a natural NOS inhibitor is increased in patients with PAH and is associated with unfavorable pulmonary hemodynamics and worsening outcomes in these patients. The underlying mechanism is that a decrease in DDAH-2 expression and activity has been demonstrated in the lungs of patients with Idiopathic Pulmonary Arterial Hypertension (IPAH) as well as in the lungs of monocrotaline-treated rats [6].

## Conclusion

However, increased vasoconstriction in the pulmonary circulation is only one aspect of the complex pathogenesis of PAH. PAH is the result of a combination of pulmonary vasoconstriction, vascular remodeling, local thrombosis, and, in advanced disease, complex vascular lesions (plexiform) resembling neovascularization in these patients with complete obstruction. Besides endothelial damage, invasion of the endothelial layer by fibroblast-like cells and increased matrix deposition, endothelial cell proliferation, are responsible for endothelial changes leading to hypoxemia, which contributes to the progression of PAH. NO is a potent stimulator of endothelial cell proliferation, migration, and angiogenesis. Inhibition of NO generation by ADMA in endothelial cells leads to increased apoptosis. Among the lung Phospho Di Esterase (PDE) isoenzymes, especially PDE-3 and PDE-4, are important regulators of cAMP degradation and are up-regulated in experimental models of PAH. Agents that increase cAMP have been shown to improve EC function, particularly angiogenesis. Treatment of endothelial cells with a conjugated PDE-3/4 inhibitor significantly reduced this

ADMA-induced apoptosis by modulating DDAH-2 activity in a cAMP-dependent manner [7].

Drugs targeting the NO pathway are of great interest in the treatment of PAH. Inhaled NO or NO donors are suitable for short-term use, but due to increasing tolerability, the large number of nonresponders, and the risk of adverse effects, NO and NO donors unsuitable as a long-term treatment. Targeting the NO-sGC-cGMP axis downstream of NO seems more promising. Inhibition of cGMP degradation by inhibiting PDE-5 has been approved for the treatment of PAH. Stimulation of the soluble NO Guanylate Cyclase (sGC) receptor with Riociguat is another therapeutic strategy that works independently of NO levels. Riociguat has shown promising results in clinical trials and may be available soon [8-10].

### Acknowledgement

None

### Conflict of Interest

None

### References

1. Nimmerjahn F, Ravetch JV. Fc-receptors as regulators of immunity. *Adv Immunol.* 96, 179-204 (2007).
2. Nimmerjahn F, Ravetch JV. Fcγ receptors: Old friends and new family members. *Immunity.* 24, 19-28 (2006).
3. Brambell FW. The transmission of immunity from mother to young and the catabolism of immunoglobulins. *Lancet.* 2, 1087-1093 (1966).
4. Pyzik M, Sand KMK, Hubbard JJ *et al.* The Neonatal Fc Receptor (*FcRn*): A Misnomer *Front. Immunol.* 10, 1540 (2019).
5. Andersen JT, Daba MB, Berntzen G *et al.* Cross-species binding analyses of mouse and human neonatal Fc receptor show dramatic differences in immunoglobulin G and albumin binding. *J Biol Chem.* 285, 4826-4836 (2010).
6. Bonati M. Early neonatal drug utilisation in preterm newborns in neonatal intensive care units: Italian collaborative group on preterm delivery. *Dev Pharmacol Ther.* 11, 1-7 (1988).
7. Eriksson M. Neonatal septicemia. *Acta Paediatr. Scand.* 72, 1-8 (1983).
8. Schelonka RL, Infante AJ. Neonatal immunology. *Semin Perinatol.* 22, 2-14 (1998).
9. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics.* 28, 169-181 (1961).
10. Morselli PL, Franco Morselli R. Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. *Clin Pharmacokinet.* 5, 485-527 (1980).