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Review Article

Monocytes, non-alcoholic liver disease crosstalk

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Abstract

With the increasing prevalence of the obesity epidemic, non-alcoholic fatty liver disease (NAFLD) represent the most common liver disease worldwide and one of the important causes of hepatocellular carcinoma development. Also, it is strongly associated with type 2 diabetes mellitus. Metabolic inflammation has been suggested to play a central role in NAFLD progression. Monocytes represent a key player in meta-inflammation. Circulating monocytes, adipose tissue macrophages (ATM), and liver resident macrophages have roles in NAFLD development and progression. Adipose tissue macrophages accumulate as a result of adipose tissue hypoxia, they produce huge amount of cytokines inducing insulin resistance and excess fat accumulation in the liver. In this review, we highlight the burden of NAFLD, its association to metabolic parameters and obesity, with illustration of obesity induced inflammation and pathogenic pathways involved in insulin resistance development. We pointed to the plasticity of circulating monocytes, phenotypic and functional alteration of their subsets in NAFLD, and the therapeutic approaches targeting macrophages and their effects on improvement of insulin resistance and NAFLD progression.

Keywords: NAFLD, Monocytes, Metabolic inflammation.

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a major burden worldwide in a parallel manner with the upgrowing prevalence of obesity[1,2]. 30 -100% of type 2 diabetes mellitus -according to different studies- are estimated to have NAFLD[3,4].

The overall related mortality rate is closely related to the progression of fibrosis[5,6]. Nowadays, NAFLD is considered a component of metabolic syndrome, this is owed to the close association between hepatic fat accumulation and insulin resistance[7]. Many studied pathways seem to be drivers of the development and progression of NAFLD. Of these; chronic metabolic inflammation is considered a major player[8]. Metabolic inflammation or meta-inflammation is characterized by a status of sterile, low-grade chronic inflammation, with monocytes are important regulators of this status. Monocytes produce a plethora of cytokines regulating insulin signaling[9]. Moreover, they are source of cytokines that favor the progression of non-alcoholic steatohepatitis (NASH)[10]. Monocytes are classified into 3 subsets, according their surface expression of CD14 and CD16; classical subset, CD $14^{++}CD16^{-}$, intermediate, $CD14^{++}CD16^{+}$, and non-classic, $CD14^{+}CD16^{++}$. The latter two subsets are called proinflammatory, they are characterized by a pronounced cytokine production[11,12]. Beyond the previously mentioned simple classification; monocytes can respond to different metabolic stimuli by reprogramming that determine their polarization[13,14].

In this review, we will discuss the changes of percentages and polarization of circulating monocytes as well as adipose tissue macrophages, and their contribution to the development and progression of NAFLD.

Obesity induced inflammation and development of insulin resistance

The positive energy balance from overnutrition induce excess fat accumulation within the adipose tissue, this evokes immune response in attempt to restore homeostasis. However, this resp-onse becomes later on maladaptive and promote insulin resistance[15]. The obesity induced inflammation was firstly desc-ribed based on the observation of increased tumor necrosis factor α (TNF α) in obese individuals. TNF α was disco-vered to be driven from adipose tissue macrophages (ATMs)[16]. Adipose tissue hypoxia due to adipose tissue expansion exceeding oxygen supply from angiogenesis is the main cause of ATMs attraction and activation[17]. Being activated, ATMs produce a plethora of cytokines that activate inflammatory pathways such as C-jun N-terminal kinase (JNK) and IκB kinase β (IKK-β). These pathways lead to phosphorylation of insulin receptors and their substrate, hence affecting insulin signaling[18,19].

Many therapeutic approaches target inhibition of ATMs infiltration to adipose tissue as deletion of macrophage chemoa-ttractant protein (MCP-1) or (CCL2), and inhibition of its receptor (CCR2)[20]. These approaches showed promising results in improving insulin resistance. Moreover, it was observed that these approaches ameliorate hepatic inflammation, confir-ming the central role of adipose tissue inflammation, specifically macrophages, in progression of NAFLD[15].

Circulating monocytes and NAFLD

Circulating monocytes are heterogenous and play important roles in host defense and tissue homeostasis. Experimental studies revealed that in setting of liver injury, peripheral monocytes are recruited within the liver driving inflammation and fibrogenesis[21]. Also, many human studies had demonstrated elevated circulating total monocytes percentages in patients with NAFLD[22].

Three functionally and phenotypically different subsets of human monocytes are identified. Classical monocytes CD14++ CD16-, express high level of CCR2 and have high phagocytic capacity. CD16+ monocytes, expressing CX3CR, are called proinflammatory, they include 2 subsets; intermediate CD14++CD16+ which suggested to have a prominent role in inflammation, and non-classical subset CD14+CD16+ which has angiogenic and surveillance function[23].

Many studies had investigated the alteration of different monocytes subsets in patients with NAFLD and revealed that the proinflammatory, CD16+, populations are increased in NAFLD patients[24]. The increased proinflammatory monocytes had been also detected in other comorbid conditions that commonly accompany NAFLD as types 2 diabetes mellitus, dyslipidemia and obesity[25].

These findings augment the prominent role of increased circulating monocytes and alteration of their subsets in the development and progression of NAFLD, also provide another future therapeutic target in controlling NASH progression.

Conclusion

NAFLD is considered nowadays a main component of metabolic syndrome. It is usually associated with many comorbid metabolic derangements such as obesity and insulin resistance. Of the prominent pathophysiologic mechanisms of NAFLD development is metabolic inflammation or meta-inflammation, which is a chronic state of low-grade inflammation that accompanies obesity. Macrophages are considered key regulators of this meta-bolic inflammation, either circulating monocytes, adipose tissue macrophages or liver resident macrophages. They produce a plethora of cytokines that control the state of insulin resistance and influence NASH progression. Thus, further clinical trials of macrophages-targeting therapeutic approaches should be provided. As they will introduce a promising hope for breaking the complex pathophysiological circle of NAFLD, obesity, insulin resistance.

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Conflict of interest
None to declare.

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