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Review

The impact of impaired macrophage functions in cystic fibrosis disease progression

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Abstract

The underlying cause of morbidity in cystic fibrosis (CF) is the decline in lung function, which results in part from chronic inflammation. Inflammation and infection occur early in infancy in CF and the role of innate immune defense in CF has been highlighted in the last years. Once thought simply to be consumers of bacteria, macrophages have emerged as highly sensitive immune cells that are located at the balance point between inflammation and resolution of this inflammation in CF pathophysiology. In order to assess the potential role of macrophage in CF, we review the evidence that: (1) CF macrophage has a dysregulated inflammatory phenotype; (2) CF macrophage presents altered phagocytosis capacity and bacterial killing; and (3) lipid disorders in CF macrophage affect its function. These alterations of macrophage weaken innate defense of CF patients and may be involved in CF disease progression and lung damage.

Keywords: Cystic fibrosis; Macrophage; Inflammation; Lipid homeostasis; Phagocytosis

Contents

Abbreviations: AA, arachidonic acid; AMs, alveolar macrophages; BAL, bronchoalveolar lavage; BM, bone marrow; BMDMs, bone marrow-derived macrophages; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DHA, docosahexaenoic acid; G-CSF, granulocyte-colony stimulating factor; GM-MDMs, granulocyte macrophage-colony stimulating factor monocyte derived macrophages; HETE, hydroxyeicosatetraenoic acid; IFN, interferon; IL, interleukine; KETEs, ketoeicosatetraenoic acids; LOX, lipoxygenase; LPS, lipopolysaccharide; LXR, liver X receptors; MCP, monocyte chemoattractant protein; M-MDMs, macrophage-colony stimulating factor monocyte derived macrophages; PMs, peritoneal macrophages; PPAR, peroxisomal proliferator activated receptors; PRR, pattern recognition receptors; ROS, reactive oxygen species; TLRs, toll-like receptors; TNF, tumor necrosis factor; WT, wild-type.

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1. Introduction

Patients with CF are susceptible to bacterial infections, which induce an intense inflammatory response even in those with only modest pulmonary disease. Impairment of immune cellular defense in CF patients is now commonly accepted, affecting mostly the lungs but also the pancreas, liver and intestine [1]. The ongoing response of immune cells to this chronic infection results in progressive lung destruction and increased disease exacerbations in CF patients, responsible partly for increasing morbidity and mortality. Even in the absence of clinically apparent viral or bacterial infections, inflammation is often present in CF airways, as evidenced by neutrophil/macrophage accumulation and excessive concentrations of interleukin (IL)-8 and proteases in bronchoalveolar lavage (BAL) and sputum [2,3]. Thus, it seems that besides epithelial cells, other CF immune cells, have an inherent altered phenotype that exists without signs of infection. Recruited phagocytes have a role in regulating the innate host response against infection, and resolving inflammation. While the role of macrophages in response to pathogens infection is not completely understood, numerous recent studies have shown an alteration of macrophage function that could contribute to inflammation and to its pathological evolution. In this Review, we summarize the current data on the hyper-inflammatory behavior, reduced scavenger ability, altered phagocytosis capacity and lipid disorders in CF macrophages, in relation to the different tissue origin (alveolar, peritoneal, monocyte-derived, bone marrow-derived) and the species (mice, human).

2. Macrophage is an innate surveillance cellular system impaired in CF

Macrophages are remarkable for the diverse activities in which they engage. Many of these activities appear to be opposing in nature: pro-inflammatory vs anti-inflammatory, immunogenic vs tolerogenic, and tissue destructive vs tissue restorative. The macrophage stands as the guardian of the tissue–blood interface, serving as the front line of cellular defense against pathogens in all organs affected in CF, especially in the lungs. Alveolar macrophages (AMs) are the primary phagocytic cells of the innate immune system present in airways, allowing the clearance of air spaces from infectious, toxic, or allergic particles that were not eliminated by the mechanical defenses of the respiratory tract. Indeed, the roles of macrophages are respectively to phagocytize and to kill toxic organisms within endocytic vacuoles rich in oxygen metabolites, lysozymes, antimicrobial peptides, and proteolytic enzymes, allowing the destruction of the pathogen [4]. Thus, AMs work as regulators of innate alveolar defense against respiratory infections. When facing large amounts of infectious toxins or highly virulent microbes, these macrophages can synthesize and secrete a wide range of cytokines and chemokines such as IL-1, IL-6, tumor necrosis factor (TNF)-α, IL-8, and some arachidonic acid (AA) metabolites such as leukotrienes and prostaglandins. By using these mediators, AMs can initiate inflammatory response and recruit therefore activated neutrophils into the alveolar spaces [5].

In CF, lungs are highly susceptible to environmental toxins and the front-line cellular defense represented by the macrophages has been shown to be defective, allowing the airway invasion by these pathogens. The number of AMs in non-infected CF children has been reported to be elevated compared to non-CF individuals [2,3,6], suggesting an early and constitutive mononuclear inflammation in CF. Besides, the high number of AMs in CF patients BAL was correlated with an increased concentration of the monocyte chemoattractant chemokine (MCP)-1 CCL2 [2,7]. A similar phenotype has been observed in the BAL of several CF mouse models [8,9] suggesting the important role of macrophage in spontaneous lung inflammation.

The adequate activation of an inflammatory response for a subsequent resolution of infection requires the balanced and coordinated activation of macrophage subpopulations with M1 or M2 phenotypes. Classical M1 macrophages are activated by exposure to IFN-γ and GM-CSF, or to bacterial products such as LPS. M1 macrophages produce high levels of the proinflammatory cytokines TNF-α, IL-6, IL-1β, IL-12, IL-23 and CCL2, low levels of IL-10 and increased levels of reactive oxygen species that aid in the clearance of invading pathogens [10]. M2 macrophages are polarized by stimulation with Th2 cytokines such as IL-4 and IL-13, as well as M-CSF , and have upregulated expression of scavenger and mannose receptors, the IL-1 receptor antagonist (IL-1RA) and arginase-1. M2 macrophages are associated with anti-inflammatory and homeostatic functions linked to wound healing and tissue repair. Macrophages are highly plastic and during the progression of inflammatory response the phenotype switching from M1 to M2 enables the dual role of macrophages in orchestrating the onset of inflammation and subsequently promoting healing and repair [11]. Attempts to study macrophage polarization in CF have been