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Review

Could T cells be involved in lung deterioration and hyperglycemia in cystic fibrosis?

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ABSTRACT

Cystic fibrosis-related diabetes (CFRD) is the most frequent complication of cystic fibrosis (CF) and associated with increased mortality. Why patients have an accelerated loss of lung function before the diagnosis of CFRD remains poorly understood. We reported that patients with or without CFRD had increased glucose excursions when compared to healthy peers. Studies have demonstrated that patients with CF have increased glucose fluctuations and hyperglycemia and that this may affect the clinical course of CF and lead to lymphocyte dysfunction. T-helper 17 (Th17) lymphocytes produce and secrete the pro-inflammatory cytokine IL-17. The Th17 pathway is involved in CF lung inflammation, β-cell destruction in type 1 diabetes (T1D) and Th17 cells of patients with type 2 diabetes have increased production of IL-17 when compared to healthy peers. Also, regulatory T-cells (Tregs) have been shown to be dysfunctional and produce IL-17 in T1D. Furthermore, vitamin D can affect inflammation in CF, diabetes and the differentiation of lymphocytes. In this review, we discuss the potential roles of hyperglycemia on Th17 cells, Tregs and IL-17 as a potential cause for accelerated lung function decline before CFRD and how this could be modulated by vitamin D or by directly intervening in the IL-17A pathway.

Contents

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1. Introduction

Cystic fibrosis (CF) is the most common severe autosomal recessive genetic disease among individuals of European descent [1]. First described in North America in 1938 by Dr. Dorothy H. Andersen [2], CF affects one in every 3600 births in Canada [3]. In 1989, researchers discovered that CF is caused by a mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene mainly at position 508 (p.Phe508del) [4]. Since then, over 1900 other mutations have been found in the CFTR gene [5]. The CFTR gene is translated into a chloride channel and its absence or dysfunction causes excess intracellular sodium and water resorption [6]. Consequently, people with CF have an accumulation of thick mucus in various organs such as the lungs and the pancreas, often have recurrent lung infections, exocrine insufficiency and in most cases, ultimately die from lung disease [7,8]. With more aggressive nutritional interventions and antibiotic treatments, the median life expectancy of individuals with CF in Canada has steadily risen to 48,5 years of age in 2011 [3]. This increase led to the emergence of numerous new complications including CF-related diabetes (CFRD) [1,9].

2. CFRD

CFRD is an important complication that affects approximately 20% of adults between 18 and 20 years old with CF in Canada [3]. CFRD is a unique type of diabetes that differs from type 1 (T1D) and type 2 diabetes mellitus (T2D) but shares some common similarities [10]. On one hand, the main cause of death in patients with CFRD is respiratory failure whereas patients with T1D and T2D most often die of cardiovascular disease [10,11]. On the other hand, CFRD is associated to a very significant decrease in insulin secretion [1,12], similar to that observed in T1D [10], caused by a decreased number of β-cells [13,14], atrophy and by important fibrosis and amyloidosis in the pancreas [15]. Similarly to what is observed in T2D, CFRD is preceded by a long phase of glucose intolerance characterized by progressive worsening of postprandial hyperglycemia [1,10]. Its presence in patients with CF is associated with worse lung (*i.e.* FEV_1) and nutritional statuses (*i.e.* body mass index) and with increased mortality [12,16]. CFRD is also associated with an accelerated decline in lung functions years before its diagnosis [3,16]. Both the physiopathology of CFRD and the accelerated lung function decline before CFRD onset are not fully understood but experimental evidence suggests that chronic inflammatory aspects might be involved [17]. In this review, we will discuss the potential roles of T-helper 17 (Th17) and regulatory T (Treg) cells and the pro-inflammatory interleukin-17A (IL-17A) in progressive lung function deterioration and hyperglycemia in CF.

3. Inflammation

The CF inflammatory response in the lungs is dominated by neutrophil activation [18]. Both CF and diabetes are diseases with inflammatory components [7,19]. The thick mucus that accumulates in the lungs of patients with CF is frequently colonized by various bacteria including *Pseudomonas aeruginosa* and *Staphylococcus aureus* [20]. Neutrophils are then attracted by chemotaxis to the site of inflammation by formylated peptides such as formyl-methionine-leucine-phenylalanine produced by bacteria [21] and secrete oxidases and proteases in an attempt to clear the pathogens [18]. This neutrophil response is excessive and contributes to lung tissue damage and eventually contributes to decreased lung function [18].

However, the presence of lymphocytes in the lungs of patients with CF suggests the involvement of adaptive immunity [22,23]. There are two main groups of lymphocytes: T cells and B cells. B cells produce antibodies while T cells are responsible for cellular immunity [24]. T cells are subdivided into cytotoxic T cells that kill intracellular pathogens and helper T cells that assist cytotoxic T cells and B cells by secreting cytokines [25,26].

3.1. *Helper T-cell subsets*

Several T-cell subsets have been identified of which T-helper 1 (Th1), T-helper 2 (Th2) and Th17 cells are the main groups [26]. While on one hand, Th1 lymphocytes are involved in the clearance of intracellular pathogens, on the other hand, Th2 cells play an important role in the humoral response to extracellular pathogens [26].

In CF, in 2001, Hubeau et al. found increased levels of T cells in the airway mucosa of individuals with the disease [22]. Subsequent studies demonstrated that a Th1-dominated inflammatory response was associated with better lung function in patients with CF [27] and that those infected by *Pseudomonas* had elevated levels of Th2 cells, IL-4 and IL-13 in their bronchoalveolar lavage fluids *versus* patients that were

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