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HYPOTHESIZING IMMUNE CELL-BASED POSSIBLE CURATIVE THERAPIES FOR CIGARETTE SMOKE-INDUCED EMPHYSEMA

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ABSTRACT

In Emphysema (EM), one of the diseased states of lung disorder Chronic Obstructive Pulmonary Disease (COPD), the alveoli walls loose shape and or damage leading to the poor exchange of oxygen and carbon dioxide in blood. Such a disorder is accomplished by the activation of enzyme Macrophage elastase (MME) in Macrophage which breaks down the protein elastin in the extracellular matrices of the alveoli walls. The objective of this paper is to hypothesize a possible cure for EM. Because pro-inflammatory cytokine inhibitors have not shown promise in treating EM, I have engineered the therapeutics (against EM) around two of the anti-inflammatory cytokines Interleukin-4 and Interleukin-10. The same Macrophage which exhibits pro-inflammatory activation state can be made to exhibit anti-inflammatory activation state by exposing it to anti-inflammatory cytokines. By assuming that anti-inflammatory activation state of Macrophage can reverse elastin breakdown, and borrowing ideas from chimeric antigen receptor T cell therapy (approved for treating many cancers) I have designed my therapeutics.

INTRODUCTION

Emphysema (EM), one of the diseased state out of the many possible diseased states of the lung disorder Chronic Obstructive Pulmonary Disease (COPD), is characterized by the breakdown of elastic elastin proteins in the extracellular matrices of the walls of alveoli. It is the elastin protein which is responsible for the possible stretch and or flexibility observed in many of the tissues of human body. With stretch lost in the alveoli walls the alveoli disfigure and in most cases even the alveoli walls damage leading to inefficient exchange of oxygen and carbon dioxide in blood. Macrophage elastase (MME) is the enzyme in Macrophage known to degrade elastin apart from a plethora of other activities known to be typical to the MME. In a classic study[1], $MME^{+/+}$ mice developed EM on exposure to cigarette smoke but $MME^{-/-}$ mice did not develop EM on exposure to cigarette smoke. The work[1] also shows that MME can be considered to be responsible for recruiting monocytes to the alveoli extracellular matrices in response to cigarette smoke. It has also been found in the development of EM that macrophage activation leads to the recruitment of neutrophils in alveoli.[2] However, the work[3] finds that the MME and not Neutrophil elastase (NE) is critical in developing EM in lung exposed to cigarette smoke. Another work[4] finds that NE, when activated, acts upstream to inflammatory Macrophage activation, and thereby leads to the production of MME and pro-inflammatory cytokines by Macrophages. CD8+ T cell has also been found to be upstream to the MME activity in EM[5]. In summary the cell which directly degrades elastin in EM is Macrophage, and the molecule within Macrophage which directly degrades elastin in EM is MME. Hence in this paper I focus on Macrophage in developing therapeutic against cigarette smoke-induced EM.

Activation States Of Macrophage In Response To Inflammation

Cigarette smoke comprises of nearly 7,357 chemicals[6], most of which are toxic and inflame the airways in lungs through which they pass. The failure of pro-inflammatory cytokine inhibitors in curing COPD or even alleviating any of the symptoms of COPD[7] shows that the production and activation of MME in Macrophages is either upstream or parallel to the secretion of pro-inflammatory cytokines from immune cells. The presence of pro-inflammatory cytokines in the milieu of Macrophages in lungs is an indication of the Macrophages being in pro-inflammatory activation state CAMΦ. However, when the anti-inflammatory cytokines are present in the milieu of Macrophages (in lungs) the Macrophages are in anti-inflammatory activation state AAMΦ. It has been shown that Macrophages switch between CAMΦ and AAMΦ based on the relative populations of pro-inflammatory and anti-inflammatory cytokines in milieu.[8] The prominent biomarkers associated with AAMΦ are CD163, CD206, CCL18; and the most prominent biomarker associated with CAMΦ is CCL3.[8] Each of these biomarkers is expressed/activated by distinct set of cytokines.

It is a common observation that not all cigarette smokers develop EM. Hence an important question that comes to mind is, "Why do some cigarette smokers not develop EM ?" The likely answer is that the alveoli milieu in cigarette smokers not developing EM is populated with Macrophages in AAMΦ state, and hence these Macrophages have repressed translation of MME gene. There is every likelihood that anti-inflammatory cytokines prevent the production of MME in Macrophages. It has also been suggested in work[9] that the elastin break-down can be reversed by proper therapeutic interference; and I hypothesize in this paper that the possible therapeutic interference against EM could be populating the alveoli milieu with anti-inflammatory cytokines. Out of the 6 anti-inflammatory cytokines studied[8], the cytokines that cause the expression/activation of at least two biomarkers are IL4 and IL10. In next section I propose two novel therapeutics against EM based on the involvement of IL4 and IL10 respectively.

Novel Therapeutics against EM

The Th2 subtype of CD4+ helper T cells (Th) produce IL4.[10] Following infection a variety of immune cells are known to produce IL10 including the Th2 and the Th1 subtype of Th.[11] I propose engineering the Th2 cells as IL4 based therapeutic against EM. And I propose engineering the Th1 cells as IL10 based therapeutic against EM. I am not using Th2 for IL10 based therapeutic against EM because from literature the activation phenotype of Macrophage in the milieu rich in both IL4 and IL10 is not clear. The two proposed therapeutics are as follows.

(1) Isolate Th2 cells from blood; the procedure to do so is given in[12]. Force these Th2 cells to express chimeric antigen receptors (CARs) on their surfaces with the extracellular domain based on immunoglobulin like protein that has complimentarity determining regions recognizing and binding to CCL3 (the main biomarker expressed by Macrophages in CAMΦ sstate). The lentivirus or retrovirus loaded with such a CAR gene can be used to achieve this desired outcome.[13]. Administer these modified Th2 cells intravenously into the blood of EM patient. I call this therapy CAR4-T cell therapy to distinguish it from the conventional CAR-T cell therapy[14] known to be used in treating a variety of cancers.

(2) Isolate Th1 cells from blood; the procedure to do so is given in[15]. Stimulate these Th1 cells with phorbol 12-myristate 13-acetate (PMA) and or Ionomycin so that they produce IL10.[16] After this step rest of the procedure is same as stated (above) in the first proposed therapeutic

against EM. I call this therapy CAR10-T cell therapy to distinguish it from the conventional CAR-T cell therapy, and also to distinguish it from CAR4-T cell therapy

DISCUSSION

The real test of the above two proposed therapeutics against EM would be clinical trials on humans after experiments on rodents. However, following two cares must be observed in using these therapies

(1) These therapies will be harmful in patients with co-morbidities specially if the disease other than EM in such patients necessarily requires an initial phase of inflammation for recovery. Hence, I recommend not to use these therapies in patients with co-morbidities.

(2) Once these therapies have done their work, there must be mechanisms to flush out CAR4-T cells or CAR10-T cells from the patient's blood. Also the recovered patients must quit smoking.

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