Evasion of COPD in smokers. At what price?

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It is clear that smokers are at risk of developing COPD and in some cases severe COPD. Many theories have been proposed to explain the mechanisms and development of the disease, however little attention is being paid to why and how the majority of smokers do not develop or “evade” COPD. Perhaps we should be changing tactics in our approach and start paying more attention to identifying the mechanisms that allow the majority of smokers to evade clinical COPD? Possibly if we could understand the mechanisms of evasion we could more easily understand why some smokers progress toward development of COPD.

An uncontrolled adaptive immune inflammation, triggered by the innate inflammation initiated by smoking, possibly evolves into an autoimmune reaction that destroys the lung causing COPD, particularly severe COPD, in some smokers. An adaptive immune response and autoimmunity could also explain the mechanisms for the evasion of the disease. The initial innate inflammation elicited by the epithelial injury by the smoke exposure is the key factor for the eventual development of the disease because it injures the lung tissue releasing or producing self-antigens with the potential of triggering an adaptive immune reaction involving CD8+ and CD4+ T-cells and B-cells. If not properly controlled, this immune reaction would over time induce the pathological lung abnormalities that are the base of COPD.

WHY SMOKERS EVADE COPD?

The development of an adaptive immune response to a self antigen would depend of the level of tolerance to the antigen: when tolerance is high no adaptive inflammation would result; when there is no tolerance a full adaptive immune reaction and autoimmunity would develop. However tolerance to antigens, especially self-antigens, is not an all or nothing phenomenon. Different degrees of tolerance to self or modified self antigens, could explain the variable responses of the lung to cigarette exposure, the variable number of T-cells in the lung, the wide range of FEV1 observed in smokers and thus the correlation found between the numbers of T-cells and the extent of the disease reported in smokers.

AND HOW IS TOLERANCE LEVEL DETERMINED?

Central thymic tolerance is the first and essential mechanism for immune regulation and immune tolerance. However the backup of the peripheral tolerance system is essential. There is now agreement that the Dendritic Cell (DC), whose role is to present antigens to T-cells, is involved in the initiation of both immunity and peripheral tolerance induction. The ability of DCs to activate T-cells upon antigen presentation depends mainly in the level of inflammation in the microenvironment were the DC resides. In the absence of inflammatory stimuli the DCs would not express the co-stimulatory molecules and cytokines necessary for T-cell stimulation inducing T-cell anergy and/or T regulatory T-cells (Tregs) that would control the effectiveness of activated T-cells contributing to the maintenance of tolerance. In contrast lung inflammation would activate DCs along with the co-stimulatory molecules and cytokines necessary for the activation clonal expansion and migration of T-cells to tissues with active inflammation. For these reasons a coordinated migration and maturation of DCs is considered critical for the final outcome of the immune response. From these arguments it becomes evident that the control of the initial innate inflammatory response, induced in the lung by smoking, could be an essential step in the avoidance or establishment of an adaptive immune response that could lead to COPD. There is ample evidence that “healthy smokers” have milder lung inflammation and mice exposed to smoke that do not develop emphysema have no lung inflammation. Possibly the innate inflammation induced by smoking has been actively suppressed leading the tolerance and evasion from COPD.
HOW COULD THE INFLAMMATION BE SUPPRESSED?

To limit the undesirable effects of excessive inflammation, many stimuli that trigger the transcription and protein translation leading to an inflammatory response simultaneously trigger a complex program in intracellular signaling, the post-transcriptional regulons that actively resolve inflammation by promoting mRNA decay and/or inhibiting protein translation. Also indirectly controlled by posttranscriptional regulatory mechanisms are the lipid mediators that have essential roles in the initiation (such as prostaglandins and leukotrienes) and resolution (such as lipoxins, protectins and resolvins) of inflammation. It is still possible, when the inflammatory stimulus continues as in smokers, that the mechanisms available cannot control the innate inflammatory response, or succeed in only partial control, resulting in a chronic inflammation that will vary in severity. However there are also mechanisms devised to attempt the suppression of the adaptive immune inflammation, and possibly modulate the progression of the disease. The best known mechanism to control the progression of the adaptive immune inflammation is mediated by the CD4+ CD25+ FoxP3+ Tregs. In smokers with normal lung function or mild COPD, Tregs, by controlling the immune reaction, might prevent the development of severe disease. A failure or absence of Tregs might predispose to an uncontrolled adaptive immune reaction with severe lung damage and COPD. The skewing of the classical alveolar macrophage, (AM) M1 pro-inflammatory phenotype toward the M2 phenotype with anti-inflammatory, profibrotic “repairing” properties could be an important factor in the suppression of the inflammatory process. It would then be possible that the suppressive function of the described phenotype, in an attempt to modulate the progression of the inflammation, might result in some degree of immunosuppression, which might have untoward consequences. In fact there is extensive evidence of immune suppressive modification secondary to cigarette smoke affecting the function and proliferation of macrophages, neutrophils and T cells, killed by cytotoxic T cells, and the reduction of serum levels of immunoglobulins in humans. Likely the suppressive effects ought to be variable, effective in smokers without or with mild disease but completely eluded in severe COPD, where a florid adaptive immune reaction drives the lung destruction.

WHAT IS THE PRICE TO PAY FOR COPD EVASION?

Several factors triggered by the chronic exposure to cigarettes would favor the development of cancer in smokers. An important barrier to cancer development is the activity of the immune system, which upon encountering a nascent tumor, can bring about the elimination of the cancer. All things considered it would not be surprising to find that smokers who evade COPD, by suppressing their immune system, would have a higher incidence of lung cancer than smokers who develop COPD, in which a florid adaptive immune response and probably autoimmunity is present. Our recent work showing that smokers with severe COPD had a lower incidence of lung cancer than smokers with mild COPD supports this hypothesis.

In conclusion, it might be worthwhile to start thinking about why smokers evade COPD, rather than why they develop COPD. Dampening inflammation in time is an essential protective mechanism in all types of inflammatory conditions, which also seems to be working in smokers who evade COPD. The failure of the blockade would result in chronic adaptive immune inflammation and, possibly, autoimmunity, as in the case of severe COPD. However, dampening of inflammation can render smokers relatively immunosuppressed, which may carry untoward consequences. Where do we go from here?

References