EVASION OF COPD IN SMOKERS. AT WHAT PRICE?

Manuel G. Cosio¹,² and Marina Saetta².

¹Respiratory Division and Meakins- Christie laboratories Royal Victoria Hospital, Department of Medicine, McGill University, Montreal, Canada.
²Department of Cardiac, Thoracic, and Vascular Sciences, Section of Respiratory Diseases, University of Padua, Italy

Corresponding author:
Manuel G. Cosio MD.
Clinica Pneumologica
Universita' di Padova
Via Giustiniani 3
Padova 35128 Italy
Phone :39 049 8213449
Fax: 39 049 8213110
e-mail: manuel.cosio@mcgill.ca
marina.saetta@unipd.it

Abstract.

Investigations toward the understanding of COPD have been directed, so far, to the study of the mechanisms leading to the disease. We believe that understanding the why about 80% of smokers evade COPD and how this evasion is accomplished might be a fruitful endeavor that could advance the knowledge on the development of the disease. Since the inflammatory infiltrate smokers develop seems to be the key element leading to the lung destruction in COPD the understanding of the possible ways inflammation can be dampened, as well as its consequences, ought to be important. We review here
some of the mechanisms by which inflammation is controlled: by the post-translational regulons, by the mechanisms preventing full activation of dendritic cells and by the Tregulatory cells. The potential role of the M2 alveolar macrophage phenotype and the newly described Myeloid Derived Suppressor Cells (MDSC) is mentioned. We also point out that evasion comes at a price since healthy smokers might be immunosuppressed to some extent and unable to prevent the development of cancer, certainly less so than severe COPD where immunity is heightened. Likely the knowledge of the mechanisms of evasion from COPD could add significantly to the understanding of those leading to the disease.

**Evasion of COPD in smokers. At what price?**

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, or only develop a mild disease. Perhaps we should be changing tactics in our approach to the study of the mechanisms for COPD development and start paying more attention to the other side of the coin, which is what are the mechanisms that allow the majority of smokers to evade COPD? And is there a price to pay for this evasion?

In this Perspective we examined the mechanisms involved in the essential process of limiting or dampening
inflammation, a cardinal feature in the pathogenesis of COPD. These mechanisms are essential in order to evade tissue damage and to allow the initiation of repair processes. Possibly if we could understand the mechanisms of evasion we could more easily understand the why some smokers progress toward the development of COPD.

We have recently proposed that an uncontrolled adaptive immune inflammation, triggered by the innate inflammation initiated by smoking, evolves into an autoimmune reaction that destroys the lung causing COPD, particularly severe COPD, in some smokers.(1) Because the adaptive immune response and autoimmunity could help us to understand not only the mechanisms for the development of the disease, but also the mechanisms for the evasion from the disease, it will be useful looking at the buildup of the adaptive immune response and autoimmunity responsible for the development of the disease first.

The initial innate inflammation elicited by the epithelial injury and chronically maintained by the constant smoke exposure, is the key factor for the eventual development of the disease, unless this inflammatory reaction is controlled and/or minimize. The inflammation is important 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 which, if not properly controlled, would over time induce the pathological lung abnormalities that are the base of COPD. (1)

Thus why so many smokers evade COPD? If inflammation is key in the development of COPD and if an adaptive immune response directed against lung self antigens drives the persistent inflammatory response found in smokers, we have a starting point for our discussion and possibly for the understanding of the evasion phenomenon. The development of an adaptive immune response to a self antigen, along with the eventual development of autoimmunity, 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. (2) Different degrees of tolerance can exist thus different degrees of inflammatory response to an antigenic challenge and hence different degrees of disease severity. Different degrees of failure 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 of smokers, the wide range of FEV1 found in smokers and thus the correlation found between the numbers of T-cells and the extent of the disease reported in smokers. (3, 4)

**And how is tolerance level determined?** Central thymic tolerance, through the elimination of self-reactive T cells and the production of “natural” CD4+ T regulatory cells, is the first and essential mechanism for immune regulation and immune tolerance. (5) However the back up of the peripheral tolerance system is essential. There is now agreement that “professional antigen presenting cells”, of which the Dendritic Cell (DC) is the main player, are involved in the initiation of both immunity and peripheral tolerance induction. (6)

Dendritic cells reside in tissues in direct contact with the environment and their role is to collect potential antigens to be presented to T-cells in order to mount an adaptive immune inflammation against those antigens. 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, the lung in our case. When there is no or low inflammation an immature or semi-mature DC might migrate to local lymph tissue, where presentation of antigens from tissue turnover would take place. However due to the absence of inflammatory stimuli the DCs
would not express costimulatory molecules and cytokines necessary for T-cell stimulation. In this situation self-antigens recognition by T-cells presented by immature DCs will induce T-cell anergy or and T regulatory T-cells (Tregs). Anergic T-cells will be unable to proliferate and produce IL-2 in a subsequent challenge by a competent DC, and the presence of regulatory T-cells (Tregs) would control the effectiveness of possible activated T-cells thus contributing to the maintenance of tolerance. (6,7) In contrast when the lung is inflamed the necessary factors for the recruitment, activation and maturation of the local DCs would be provided along with the costimulatory molecules and cytokines necessary for the activation of T-cells upon antigen presentation. In this situation T-cells would undergo clonal expansion and migrate either to B-cell areas-to assist in antibody production- or to tissues with active inflammation. For these reasons a coordinated migration and maturation of DCs is considered a critical process leading to either tolerance-when the lack of inflammation in the milieu will prevent DC maturation- or immunity-when the strong inflammatory milieu will favor DC maturation- which makes the DC the responsible for the final outcome of the immune response. (6,7)
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 into COPD. There is ample evidence that “healthy smokers” have milder lung inflammation (3,4) and mice exposed to smoke that do not develop emphysema have no lung inflammation.(8) Possibly the innate inflammation induced by smoking is been actively suppressed leading to tolerance and evasion from COPD.

**How could the inflammation be suppressed?** Although inflammation is an essential defensive and repairing component of the innate immune response in multicellular organisms, it can become a double edge sword, as excessive inflammation can exacerbate tissue damage and produce potential antigens.(7) Although many mechanisms for the regulation of different inflammatory factors have been described like: IL-1RA to regulate the effects of IL-1β, the negative regulation of the TLR and NOD receptors(9,10), it is possible that all these mechanisms are controlled by newly described mechanisms that can regulate most of chemokines, cytokines, proteases and other factors involved in the initiation and maintenance of the inflammation.(11) To limit the undesirable effects of excessive
inflammation, many stimuli that trigger the transcription and protein translation leading to an inflammatory response, simultaneously trigger the transcription of mRNA encoding proteins that, through a complex program in intracellular signaling actively resolves inflammation. Furthermore, because long after transcription has ceased transcribed mRNAs can continue to synthesize proinflammatory proteins, a system would be ideally needed to modulate the production of these proteins when not needed. Such systems have been described and consist in a variety of post-transcriptional control mechanisms, the post-transcriptional regulons, that modulate the expression of many proteins involved in the immune mediated inflammation, in most cases by promoting mRNA decay and/or inhibiting protein translation. (11) In this way post-transcriptional dampening of protein expression can actively promote the resolution of inflammation to prevent unintended tissue damage.

It has been found that multiple chemokines and their receptors are downregulated by means of inhibition of protein translation, while cytokines and other inflammatory factors like IL-1β, TNF, INF-y, IL-2, IL-6, among many others, are controlled by accelerating mRNA decay.(11) 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 Resolwins) of inflammation. (11)

In summary the natural resolution of inflammation seems to be driven mainly by 3 different types of processes: (12)

1) Removal of the initial stimulus which is critical. Many chronic ongoing inflammatory conditions are probably driven mostly by persistence of the offending agent or/and autoimmunity. We have a great example of this problem with the continuous use of cigarettes!

2) Decrease of the proinflammatory mediators involved in attracting new inflammatory cells to the lesions and the persistence of the inflammation: Post-transcriptional regulons, by promoting mRNA decay and/or inhibiting protein translation

3) Removal of the inflammatory cells and cell debris to allow the final repair to occur: Alveolar macrophages stimulated by Resolwins and Protectins will clear PMNs and structural cells apoptotic bodies which induces a potent anti-inflammatory response and promote the activation of the anti-inflammatory function of TGB-β. Defects in apoptotic cell recognition and response by alveolar macrophages could make apoptotic debris antigenic promoting chronic inflammation and
even autoimmunity as it has been shown in SLE. (12,13) Some or all of these mechanisms ought to be working in many smokers, likely the 80% that evade COPD, since the inflammatory response in the lung of these smokers seems to be controlled, the degree of their inflammation being very small when compared with smokers with severe COPD. (3,4)

It is still possible, when the inflammatory stimulus continues like in smokers (see point 1 above), that the mechanisms available can’t control the innate inflammatory response, or succeed only at a partial control, resulting in a chronic inflammation that will vary in severity. As a consequence constant but variable degrees of tissue destruction, production of antigens and degrees of stimulation of DCs with variable degrees of adaptive immune inflammation and severity of COPD will follow. Chronic inflammation would have three possible undesirable effects in smokers: progressive tissue destruction which would trigger repair and fibrosis, the development of lung cancer and the possible development of autoimmunity, which are certainly a reality in smokers, at least in some smokers. However there are also available mechanisms devised to suppress, or at least attempt the suppression, of the chronic inflammation, especially 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 Tregulatory cells (Tregs). (14,15) A deficiency of Tregs can impair the immune system tolerance for auto-antigens and lead to autoimmune disease. (15) The behavior of the Treg cells in COPD is of interest and seem to vary with the site in the lung and severity of the population studied. (16) Long term smoking exposure, but not the development of airflow obstruction, increases Tregulatory cell numbers in the lung. (17) As such, when compared with the lungs of nonsmokers, the lungs of smokers with normal lung function and mild functional abnormalities (FEV1 70% predicted) have a greater number of Treg cells in BAL (17) and in lung lymphoid follicles, but not in the lung parenchyma (18). In other studies, the lungs of smokers with COPD and emphysema have been found to have fewer Tregs and less FoxP3 mRNA (19,20) than the lungs of healthy smokers, who had more Tregs than the non smokers. Furthermore smokers with COPD were found to have an upregulation of FOXP3 positive T cells in large airways, but had a downregulation of FOXP3 positive T cells in the small airways, the main site of pathological involvement in COPD, that correlated with airflow limitation. (21) This suggests that in smokers
with normal lung function and 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. Another population of T cells with immunoregulatory properties, the γδCD8+ T cells are increased in smokers with normal lung function but not in smokers with COPD (22). These findings point toward impaired immune regulation in smokers with COPD and to an effective control in smokers with normal lung function. It is worth bringing attention at this point to other type of cells with immunoregulatory function recently described, the M2 phenotype of the alveolar macrophage (AM), and the “Myeloid Derived Suppressor Cells” (MDSC), that might have a potential role in COPD and which could be a target for future investigation in smokers. Alveolar macrophages (AM) in smokers seem to lose their proinflammatory characteristics showing a decrease in phagocytic activity, production of inflammatory mediators and NO production among others. (23) This could reflect the recently described skewing of the classical AM M1 proinflammatory phenotype toward the alternative M2 AM phenotype with anti-inflammatory, profibrotic “repairing” properties in a majority, but
not all, of smokers with COPD. (24,25) This skewing toward the M2 phenotype could possibly be another factor tending to suppress the inflammatory process and even predispose to the development of malignancies in some smokers.

The “Myeloid Derived Suppressor Cells” (MDSC) (26), are a set of cells described first in animal models and patients with advanced stage of cancer and recently found even in patients with early cancer (27,28), which by suppressing the protective immune response to malignant cells, may promote the progression of the tumor and the development of metastasis. (26) However there is strong evidence that these cells are also increased and play a regulatory role in the immune responses in bacterial and parasitic infections, acute and chronic inflammation, autoimmunity, traumatic stress surgical sepsis and transplantation. (29,30,31)

With the idea that MDSCs could conceivably be present also in a chronic inflammatory condition like COPD, we investigated and found in a small group of subjects that smokers with COPD have higher numbers of circulating MDSC than controls (unpublished observation). Although these results are of potential interest, they are preliminary and definitely deserve further investigation.
It would be then conceivable that the different mechanisms described to control or modulate the different steps of the inflammatory response in an attempt to modulate the progression of the disease in smokers, might result in some degree of immunosuppression, which might have untoward consequences.

Are smokers immunosuppressed? There are no available epidemiological studies investigating the immune state of smokers as compared to nonsmokers, possibly because the assessment of immune readiness or level of immunosuppression is not easy to investigate as no easy clear tests are available. However there are numerous studies in mice and humans showing a widespread suppression of many immune functions in smokers.(32,33), These effects include suppression of the effector function PMNs, NK cells and macrophages (34,35,36,37) which have a compromised ability to phagocytose bacteria and apoptotic cells and to sense PAMPs (38,39). Furthermore alveolar macrophages show a skewing of the M1 effector function toward a M2 type immune response with an anti-inflammatory profile and possible tumor promotion (24). A reduced proliferation of Tcells in response to Tcell mitogens and suppression of killing by cytotoxic T cells have also been documented (40,41). Of interest, human smokers have
significant reduction of serum levels of immunoglobulins that might account for the fact that smoking is an important confounding cause for morbidity during an influenza epidemic (32). In support of these observations, mice that were chronically exposed to cigarette smoke were more susceptible to influenza viruses.(32) Furthermore the antibody response to various antigens can be reduced significantly as a consequence of chronic exposure to cigarette smoke.(33) It is not clear at this point if all these effects in the immune system are the direct consequence of the numerous compounds found in cigarette smoke, nicotine is a well known immune suppressor, or of the attempts of the immune system to regulate itself in the presence of a sustained inflammatory challenge as we describe previously. Likely both effects could account for the suppression of different components of the immune response described in smokers, which ought to be variable, i.e. 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?** The association between smoking, COPD and lung cancer has been well demonstrated (42) and it has been shown that
the incidence of cancer is higher in patients with airflow obstruction than in non obstructed smokers. (43) Several factors triggered by the chronic exposure to cigarettes would favor the development of cancer in smokers. Among others, the injury and necrosis of epithelial cells produced by the exposure to cigarette smoke, which are known to release factors like HMGB1, promoting inflammation but also tissue repair (44,45) and potentially favoring the development of malignancies. Interestingly the induction of cancer in animals by dominant oncogenes requires the presence of tissue injury and subsequent regeneration. (46) An essential defense to cancer development is the activity of the immune system which encounter with a nascent tumor can bring about the elimination of the cancer. The increased prevalence of cancers in immunosupressed transplanted patients attests to the importance of the immune system in controlling the development of cancer (47,48) Furthermore the beneficial effect of enhanced immunity has also been shown in a population study in which subjects with high or medium degree of natural cytotoxicity had a significant lower risk of cancer than subjects whose lymphocytes had a low degree of cytotoxicity. (49) In favor of the contribution of the immune system to the development of lung cancer and COPD is the recent
publication by Hemminki et al. (50) These authors examined the associations of autoimmune diseases with COPD and cancer in order to determine the risk of COPD and cancer in persons who had been hospitalized for autoimmune diseases. Their findings showed that a great number of autoimmune diseases, 18/29, were associated with COPD but only a minority had an association with cancer. Furthermore, there was a remarkable lack of excess lung cancer in patients with autoimmune disease who developed COPD, suggesting that the defined autoimmunity might contribute to the development of COPD but also to the suppression of malignancy. All things considered it would not be surprising to find that smokers who evade the development of severe COPD, by suppressing their immune system, would have a higher incidence of lung cancer than smokers who develop severe COPD, in which a florid adaptive immune response and probably autoimmunity is present. Although high immunity would predispose to the development of severe COPD, it could also help preventing the development of cancer in these patients. The opposite could occur with the “evaders”, who would develop lesser COPD, but might have to pay the price of a higher probability for the development of cancer in the lung and possibly other sites. Our recent work showing that smokers with severe COPD had a lower incidence of
lung cancer than smokers with mild COPD, supports this hypothesis.(51)
In conclusion, it might be worthwhile to start thinking on why smokers evade COPD, rather than why they develop COPD. An inflammatory response in the lung to cigarette smoke seems to be the key for the development of COPD thus it is not surprising that those smokers who evade or have milder COPD have a lesser inflammation. Inflammation is necessary, but could be harmful, thus dampening inflammation on time is an essential protective mechanism in all types of inflammatory conditions, that seems to be also working in smokers who evade COPD. The failure of the blockade would result in chronic adaptive immune inflammation and possibly autoimmunity like it is the case in severe COPD. However dampening of inflammation can render smokers relatively immunosuppressed which may carry untoward consequences. Are dampening mechanisms failing in smokers who develop COPD? Why are they failing? A better understanding of this process could improve our knowledge of the immune mediated inflammatory response in smokers and thus the mechanisms underlying the development of COPD.
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