SHORT PERSPECTIVE
Iran J Allergy Asthma Immunol
October 2015; 14(5):472-475.

Are There Any Epigenetic Similarities Between Treatment Unresponsive Sarcoidosis, COPD and Severe Asthma?

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Received: 12 January 2015; Received in revised form: 5 March 2015; Accepted: 5 April 2015

Sarcoidosis is characterized by non-caseating granulomas and several immunological abnormalities in many tissues including the lungs (pulmonary) and others such as skin, bone, heart (extra pulmonary)[1]. The aetiology of the disease is unknown although probably relates to an inflammatory/immune response to an unknown infectious agent.[1] This leads to tissue damage, remodeling of airways, airway hyperactivity and a resultant loss of lung function. Corticosteroids remain the mainstay of first line treatment in sarcoidosis although they are not effective in all patients.[2,3.]Recent evidence suggests that epigenetic mechanisms are involved in the control of inflammation and immune cell function in cancer[1] and in the molecular pathways implicated in other pulmonary disorders such as chronic obstructive lung disease (COPD), severe asthma and interstitial lung disease (IPF).[4] These diseases are all associated with epithelial and mesenchymal cell remodelling within the airways and alveoli associated with altered patterns of growth factor activity and expression; apoptosis; increased oxidative and endoplasmic reticulum stress; altered cellular senescence along with impaired mucociliary clearance and host defense processes in response to environmental agents such as pollution, cigarette smoke or allergens in the case of asthma.[5-7] It is also evident that corticosteroid functions are under the regulation of epigenetic processes.[8]

A range of epigenetic processes such as histone modifications, non-coding RNAs and DNA methylation are associated with the control of gene expression.[9,10] The development and differentiation of most cell types including T cells [11] are reliant upon these mechanisms for efficient tissue- and cell-specific expression of genes. These epigenetic mechanisms do not act independently of each other but act in a co-ordinate manner to regulate the induction and sustained expression of the myriad of epigenetic tags or marks that control gene expression.

The deposition of acetylated histone marks by histone acetyltransferases (HATs) is associated with enhanced expression of immune and inflammatory genes.[7,12,13] Recent evidence indicates that deposition of acetyl tags by HATs is not highly selective whereas removal of these tags by histone deacetylases

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Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

(HDACs), of which there are 18, is more selective.[14] Addition of an acetyl group alters the structure of the local chromatin generally allowing enhanced gene expression[7] which is reversed by the action of HDACs.[12]

An imbalance in HAT/HDAC activity is reported in the airways of patients with severe asthma [15] and in COPD [16] and linked to the reduction in corticosteroid responsiveness in these two diseases[17]. In particular a selective loss of HDAC2 has been implicated in preventing corticosteroid suppression of a number of key inflammatory and immune genes.[18-21] This action is due to both a reduced ability of the activated glucocorticoid receptor (GR) to remove lysing tags from histones at inflammatory gene promoters and due to changes in GR acetylation status preventing interaction with then nuclear factor κappa B (NF-κB) p65.[18] In addition to GR, many other transcription factors such as NF-κB p65 and p53, transcription co-regulators including PGC1, RB and c-Myc, inflammatory signaling pathways such as mitogen activated protein kinases (MAPKs), DNA repair proteins such as Ku 70 and the structural protein β-actin can be acetylated. This acetylation can markedly affect protein and cellular function.[22,23] Complex interactions between acetylated non-histone proteins and HDACs occur, for example, activation of the acetylated transcription factor hypoxia-inducible factor-1α (HIF-1α) which occurs in the lung microenvironment of patients with COPD, decreases HDAC2 expression, resulting in augmented inflammation and steroid resistance.[24]

However, overall little data exists from primary cells/tissues regarding altered histone modifications in this disease. The effects of cigarette smoke on primary human airway epithelial cells which causes corticosteroid insensitivity [5] indicates some changes such as Histone H4K16 and H3K27 acetylation and H3K27 and DNA methylation could be examined preferentially in these patients and linked to gene and protein expression profiles.[25]

There are few published links between the above epigenetic modifications or the expression of the various enzymes involved in depositing or removing these marks with corticosteroid function. This remains an area of intense interest. In contrast, in fibroblasts from patients with idiopathic pulmonary fibrosis (IPF), for example, there have been several studies linking changes in histone methylation and acetylation with alterations in their regulatory enzymes and the control of key genes including cyclooxygenase-2 (COX-2). In addition, the function of transforming growth factor beta (TGF-β) has been associated with several microRNAs (miRNAs) such as miR-218, miR-21, miR-155, miR-20 and let-7d which are differentially expressed in fibroblasts from IPF subjects [25]. Environmental stresses induce alterations in DNA methylation in COPD patients [22] and these can be mimicked in cells exposed to cigarette smoke which suggests that similar changes should be observed in sarcoidosis.[25]

Indeed, the accelerated telomere shortening seen in sarcoidosis has been linked to earlier evidence of subtelomerichypomethylation.[26] In addition, sarcoid patients also demonstrate higher levels of histone H4 in bronchial alveolar lavage (BAL) and histone H2B in plasma compared to healthy controls.[27] Furthermore, there were suggestions that BAL histone H4 proteins were post-translationally modified although this needs to be confirmed. More studies are required in this direction to explore the epigenetic mechanisms underlying sarcoidosis epigenetics in individual response to corticosteroids.

Inflammation in severe asthma, COPD and IPF has also been associated with altered expression of microRNAs and with alterations in DNA and histone methylation[7]. Similar to control of acetylation, methylation at specific residues on histone H3 for example is carefully controlled by the relative activities of histone methyltransferases (HMT)/histone demethylases (HDM) [7,28,29] and it is now clear that DNA methylation is also highly regulated.[30]

Again, there is an interaction between these processes since altered DNA methylation of the miR-17~92 cluster promoter results in the over expression of genes linked to fibroblast proliferation .[31]

Several studies have reported alterations in microRNA expression profiles in severe asthma and COPD[32] including changes in miR-19, -21, -27, -29a, -126 and -146a and some of these have been associated with corticosteroid function including miR-145. [33]

Limited data exists regarding epigenetic processes in sarcoidosisal though miR-92b and miR-206 expression is elevated in both the lung and lymph nodes of sarcoidosis patients. In contrast, miR-20a and miR-302c expression was elevated in lymph nodes but decreased in lung.[34]

In conclusion, there is increasing evidence for

similarities, as well as differences, in epigenetic marks associated with sarcoidosis and with the pathogenesis of other chronic inflammatory airway diseases. Further analysis of epigenetic changes associated with corticosteroid function should be addressed in future. Ideally, blood-based analysis should be performed and methods to allow mathematical deconvolution of the data to enable links to single cell types have been developed.[35] Identification of common epigenetic marks between these diseases or with a lack of corticosteroid responsiveness in association with gene expression data will allow determination of key regulatory modules and delineation of new therapeutic targets[10,36] which is critical for the welfare of these patients.

ACKNOWLEDGEMENTS

Ian M Adcock is supported by the MRC (G1001367/1) and the Welcome Trust (093080/Z/10/Z). Research by IMA is also supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton NHS Foundation Trust and Imperial College London. Esmaeil Mortaz is supported by an ERS Long Term Fellowship (LTRF 2013-2052).

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