Lung Cancer and Idiopathic Pulmonary Fibrosis

From Epigenetics to drug therapy

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Epigenetics is defined as 'the study of mitotically and/or meiotically heritable changes in gene function other than changes in the DNA sequence'. Epigenetic modifications influence gene expression and derive from chemical modifications (methylation, acetylation) of DNA, histone tails or expression of non-coding RNAs (ncRNAs). Epigenetic alterations have now been causally linked to diseases such as autoimmune thyroid disease or asthma, demonstrating that epigenetic modifications convey dynamic information markedly influenced by environmental stimuli. There is evidence that the main risk factor for respiratory diseases, COPD, lung cancer and possibly, idiopathic pulmonary fibrosis –cigarette smoking– is associated with epigenetic changes in the bronchial epithelium, and that epigenetic pathways regulate airway inflammation[1,2].

EPIGENETICS IN LUNG CANCER AND IPF

The main risk factors for the development of lung cancer that have been implicated so far are cigarette smoking, environmental pollution, radiation and exposure to asbestos, however, numerous lung cancer cases have failed to be associated with one of these factors. Although the molecular pathways are yet to be elucidated, microRNA epigenetic aberrations could play an important part in the genesis of the harboring tumor mutations. MicroRNAs, short, non-coding RNA molecules restrict the production of proteins by inhibiting translation from messenger RNAs (mRNAs), or by mediating their degradation. MiR-21 was found overexpressed in six types of cancer, while overexpression of miR-21 was an independent negative prognostic factor for overall survival in NSCLC patients[3].

MicroRNAs have recently been added to gene and proteome expression signatures in the molecular jigsaw of IPF lungs leading to a substantial amount of information regarding the role of microRNAs (miRNAs) in the pathogenesis of IPF. The first report revealing the potential role of miRNAs in IPF demonstrated that 10% of the miRNAs expressed in IPF were were significantly different to control samples. MicroRNAs involved in fibrosis, myofibroblast proliferation and excessive extracellular matrix deposition include miR-21 and members of the mir-29, mir-154 and let-7 families[4]. Mir-21

was found to be upregulated in IPF similarly to tumours enhanced in IPF fibroblasts and epithelial cells[5]. Members of the miR-29 family are considered major regulators in pulmonary fibrosis, their expression is inhibited by TGFβ while they target collagen and other extracellular matrix related mRNAs[6,7]. Let-7d expression is also reduced in IPF lung tissue and this results in the enhanced expression of the transcription factor HMGA2 which in turn regulates proliferation and epithelial to mesenchymal transition through TGFβ-SMAD signaling pathways[8,9].

Merkel cell polyoma virus, initially discovered in Merkel cell carcinoma (MCC) of the skin, has been correlated with hypermethylation of RASSF1A in small cell lung cancer (SCLC), while in non small cell lung cancer (NSCLC) MCPyV has been associated with Human Papilloma Virus (HPV) in 33% of patients[10,11]. We have already shown that deregulation of BRAF and Bcl-2 is associated with MCPyV positive NSCLC patients, implicating for the first time apoptotic pathways with polyomavirus infection in human lung cancer[12]. We are currently investigating the expression of miR-21, miR-376c and miR-145 in MCPyV positive NSCLC identifying significant changes in their expression coupled to deregulation of respective target genes' expression profiles[13].

Recent experimental evidence highlights DNA methylation as an important mechanism involved in IPF[14]. A comparative analysis of global DNA methylation combined with gene expression from IPF and normal samples revealed that both DNA methylation and expression profiles were altered in IPF[15]. Moreover, the expression levels of Dnmt-3a and Dnmt-3b DNA methyltransferases**,** were increased in IPF samples, further supporting the role of DNA methylation in the disease. Another study highlighted an additional epigenetic signature in IPF samples, identifying an intermediate DNA methylation profile, compared to normal and lung cancer samples[16].

IMPLICATIONS FOR THERAPY AND CLINICAL PRACTICE

Idiopathic pulmonary fibrosis (IPF) is a severe, under diagnosed lung disease affecting both daily activity and life expectancy[17], characterized by an irreversible and evolving loss of lung capacity rapidly leading to respiratory failure and dramatic outcomes in terms of mortality[18]. Survival rates from the time of diagnosis are comparable to that of an inoperable pulmonary malignancy[17]. Till recently evidence about the existence of a treatment option that could modify the disease course was lacking[19].

However, current findings of INPULSIS-1, INPULSIS-2[18] and ASCEND trials[20], changed the situation by cultivating new expectations in the management of these IPF patients[19]. Both pirfenidone and nintedanib have been approved for IPF by FDA. Interestigly, highlighting the aforementioned common pathogenetic links between IPF and lung cancer, nintedanib has been approved as second line therapy for lung cancer[21]. Tyrosine kinases are involved in a range of signalling pathways that are essential for cellular homeostasis. However, there is substantial evidence from in vitro studies and animal models that receptor tyrosine kinases, such as the PDGF-R (platelet-derived growth factor receptor), VEGF-R (vascular endothelial growth factor receptor) and FGF-R (fibroblast growth factor receptor), and non-receptor tyrosine kinases, such as the Src family, play critical roles in the pathogenesis of pulmonary fibrosis and lung cancer[22]. Advancements in epigenetic treatments are not only coming from new drugs, but also from modifications or encapsulation of the existing drugs into different formulations leading to greater stability and enhanced delivery to the target site. The epigenome is highly regulated and complex; therefore, it is important that off-target effects of epigenetic drugs be minimized. Epigenetic covalent modifications of DNA and chromatin proteins strongly affect gene expression and cellular activity, and epigenetic misregulation occurs in several diseases, especially cancer. First-generation drugs targeting the relatively promiscuous DNA methylation and histone acetylation modifiers have had successes in the treatment of haematological cancers. Second-generation drug programmes are in the discovery phase, targeting epigenetic enzymes with more tightly defined modes of action[23].

Further research of the role of epigenetic marks will hopefully create exciting possibilities for the understanding of IPF pathogenesis in depth and the improvement in clinical diagnosis and treatment of patients with IPF. The detection of specific miRNAs alterations in serum samples of IPF patients suggests that miRNA could be a non-invasive screening tool for IPF in routine clinical practice. Novel treatment strategies based on epigenetic drugs or exogenous administration of miRNAS could also be proved beneficial for management of IPF patients.

CONFLICT OF INTERESTS

No.

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