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Review

Epigenetics in fibrosis

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ABSTRACT

Fibrosis is a common and important disease. It is a pathological state due to excessive scar formation mediated by an increase in activated fibroblasts that express alpha smooth muscle actin and copious amounts of extracellular matrix molecules. Epigenetics is an area of research that encompasses three main mechanisms: methylation, histone modifications to the tails of histones and also non-coding RNAs including long and short non-coding RNAs. These three mechanisms all seek to regulate gene expression without a change in the underlying DNA sequence. In recent years an explosion of research, aided by deep sequencing technology becoming available, has demonstrated a role for epigenetics in fibrosis, either organ specific like lung fibrosis or more widespread as in systemic sclerosis. While the great majority of epigenetic work in fibrosis is centered on histone codes, more recently the non-coding RNAs have been examined in greater detail. It is known that one modification can affect the other and cross-talk among all three adds a new layer of complexity. This review aims to examine the role of epigenetics in fibrosis, evaluating all three mechanisms, and to suggest possible areas where epigenetics could be targeted therapeutically.

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1. Introduction

Epigenetics refers to alterations of gene expression without a change in the DNA sequence. It is now known that in the human genome there are surprisingly low numbers of genes than predicted, but yet the complexity to determine gene expression in space in time must be regulated by mechanisms above the sequence of DNA; this is termed epigenetics. Each cell is equipped with the same DNA, yet what determines the phenotypes is epigenetic. We now know that epigenetics encompasses three principal mechanisms: DNA methylation, non-coding RNAs and histone modifications, where histone tails are chemically modified (Turner, 2002). All three of these epigenetic modifications are at play at the cellular level and dictate the precise timing and expression of genes, and it is accepted that they are heritable (Oey and Whitelaw, 2014). Epigenetics adds another layer of complexity to the regulation of gene expression by determining precisely gene expression. In the past few years an explosion of data has been generated that has led to a deeper understanding of the epigenome aided by new technologies such as deep sequencing. Methylation is the most studied and understood of the epigenetic machineries, and because of this we now know a great deal of the regulatory networks that facilitate methylation and demethylation and that aberrant methylation is associated with a variety of diseases. However, recently the other epigenetic mechanisms such as histone tail modifications and non-coding RNAs are becoming increasingly understood. Fibrosis is a pathological state in which fibroblasts are secreting copious amounts of extracellular matrix molecules including collagen type I and also fibronectin, and this leads to scar tissue formation and ultimately results in the loss of function of the tissue and organ. Fibrosis, whether organ specific or global, as in the prototypical disease systemic sclerosis, is associated with high morbidity, and it is estimated that 50% of deaths in the Western world have a fibrotic component. In many fibrotic diseases there is no accepted treatment and in diseases such as systemic sclerosis there is a huge clinical variability (Ciechomska et al., 2015). What may underlie this clinical variability is epigenetics rather than genetics as these modifications are malleable. Epigenetics may also underpin the progression or stabilization of disease. There is increasing understanding that fibrosis is a common disease and is an unmet clinical need. This review aims to review the literature on epigenetics in fibrosis and discuss the potential of epigenetic drugs as therapeutic options in what is an intractable disease.

1.1. Fibrosis

Fibrosis is a pathological state in which there is an excessive scar formation, and this hinders tissue and organ function and is associated with a high mortality. Fibrosis is often associated with a chronic inflammatory state in which persistent inflammatory signals and growth factors mediate an acquisition of the myofibroblast phenotype and the subsequent secretion of excess extracellular matrix leading to dense collagen cross-linking (Tomasek et al., 2002). This is part of the normal wound response and the damaged tissue or cells send an 'alarm' signal to the immune system that then triggers a cascade of events that are composed of the infiltration of immune cells to help fight microorganisms and trigger the initiation of the ECM producing cells and the release of various cytokines and chemokines (Wynn and Vannella, 2016). This chronic fibrosis is due to the persistent exposure to the irritant or stimulus initiating the response and essentially termination of the normal wound healing response is lacking regardless of etiology.

2. The myofibroblast

Fibroblasts are a heterogeneous population of cells that function to maintain tissue homeostasis. The myofibroblast is defined as being highly contractile, generated by alpha-smooth muscle actin (α-Sma), and this leads to tissue contracture. Myofibroblasts have a phenotype more closely resembling smooth muscle cells and are generally identified by their high expression of α-Sma. This characteristic not only identifies the cell as a myofibroblast but also endows the cells with a highly contractile phenotype that is important in wound healing. It is now known that the scar tissue is extremely stiff and rigid compared to the adjacent tissue, and this ultimately impedes tissue and organ function (Hinz, 2015). This rigidity is key to the loss of function in organs such as the heart or the liver (Engler et al., 2008).

What is also important is that the myofibroblasts and subsequent mechanical forces generated also then liberate and activate Transforming Growth Factor-β1 to its functional form, leading to a feed forward loop that sustains and amplifies the fibrosis (Wipff et al., 2007). Furthermore, there is often an increase in Tissue Inhibitors of Matrix Metalloproteases (TIMPs) and a reduction in Matrix Metalloproteases (MMPs) and an increase in glycosaminoglycans. It should be noted that although fibroblasts that are activated to become myofibroblasts are identified by the expression of α-Sma in vitro, in vivo they are heterogeneous and not all fibroblasts exposed to the same stimuli will become myofibroblasts (Kalluri and Zeisberg, 2006). It has long been established that the myofibroblasts are the 'effector' cells in fibrosis but their heterogeneity in transdifferentiation capacity is still an unanswered question. Epigenetic modifications are malleable and shaped by the environment and may underpin such heterogeneity. Epigenetic modifications promoting myofibroblast persistence may be important in fibrotic disease regardless of etiology.

3. Histone modifications and fibrosis

The term epigenetics refers to altering gene expression not attributed to DNA base changes and can be heritable. In eukaryotic cells DNA is condensed in chromatin for these must be tightly packed to accommodate such a larger molecule in a small space. The nucleosome is a major part of chromatin and is composed of four different histones that form an octamer (H3, H4, H2A and H2B) (Kouzarides, 2007). This octamer has 146 bp of DNA wound around it, and around 2 m of linear DNA is wrapped around it. The histones are globular in nature except for their tails. It is in the histone 'tails' that they can possess multiple histone modifications of which at least eight are now known. These histone tail modifications include methylation, acetylation, phosphorylation (Banerjee and Chakravarti, 2011), ubiquitination, citrullination, sumoylation and ADP-ribosylation (Wang et al., 2004). Furthermore, there are a family of enzymes that mediate these histone modifications such as the histone acetyltransferases (HATs) which catalyze the addition of an acetyl group from a donor acetyl-CoA. Hyperacetylation of histone tails results in opening up of the DNA and thus permitting access to transcription factors promoting gene expression. These are also enzymes that remove the modifications from the histone tails such as the Histone Deacetylases (HDACs). The HDACs remove the acetyl groups from the histone tails; this leads to a closed chromatin structure and therefore repression of gene expression (Ruijter et al., 2003). Trimethylation of histone lysine 9 of histone H3 or trimethylation of K27me3 are usually associated with transcriptional silencing. Variants of core histones can also alter gene expression.