Scottish Government Health Directorates Chief Scientist Office

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Macrophage Reprogramming in IPF

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Background & Aim. When our lungs become inflamed, the immune system sends white bloods cells to kill any infections and repair the damage. The role of one type of white blood cell, called a macrophage, is particularly important as they ensure that the lung is repaired properly with minimal scarring (termed fibrosis). Excessive fibrosis can reduce the capacity for the lungs to function, which is the central feature of a fatal respiratory condition called Idiopathic Pulmonary Fibrosis (IPF). In IPF, the lungs undergo continual fibrosis causing a sustained decline in their function. It is believed that in IPF, macrophages function incorrectly and fail to prevent the fibrosis. Therefore, a therapeutic strategy for treating IPF is to correct the macrophage function to stop the fibrosis. However, in order to 'correct' macrophage function we must first understand how exactly this 'correct' function occurs. Each macrophage function is dictated by the pattern of internal changes to the cells component protein molecules (termed 'signalling'). This signalling is effectively an internal language used to perform appropriate actions in response to signals that the cell receives; signalling tells the cell to move or release molecules to kill infections or help repair damage. Only when we have a 'blue print' of the correct or normal signalling, can we assess where this may have failed in macrophages from diseases such as IPF.
Our study sought to understand if one of these signalling molecules, called NF-κB, is involved in correct macrophage signalling and then to see if this molecule may also be part of the dysfunctional action of macrophages from IPF lungs.

Project Outline & Methodology. Non-disease macrophages were obtained from healthy volunteer white blood cells isolated from blood donations. These macrophages were mixed with another type of white blood cell called neutrophils. This interaction between macrophages and neutrophils is known to occur normally in health and known to promote correct repair signals in the macrophage. This was therefore the platform from which to study the correct internal NF-κB signalling for repair in macrophages. Disease macrophages from the lungs of IPF and non-IPF patients (patients that have lung inflammtion but do not have progressive fibrosis and for whom the prognosis is much better than IPF) were obtained by a procedure call bronchoalveolar lavage. This is where saline fluid is flushed into the lungs and collected immediately. This lung 'wash' contains the white blood cells including macrophages and neutrophils that are in the deep part of the lung. This enabled us to compare repair signalling and the molecule NF-κB between macrophages from IPF to non-IPF patient lungs and to the correctly signalling macrophages from the study described above.

Key Results. We showed that in normal macrophages, signalling by NF-κB is switched off by neutrophils allowing macrophages to promote correct reparative signalling. However in IPF lung macrophages, NF-κB is not fully switched off and that the repair signal in macrophages is ineffective.

Conclusions. Our study has shown that 1) the regulation of the signalling molecule NF-κB is important for macrophages to adopt a correct repair function and 2) the signalling of NF-κB may not be regulated adequately in IPF macrophages which may contribute to the development of the disease.

What does this study add to the field? This study shows for the first time that a key part of the repair signal in lung macrophages involves the suppression of the molecule NF-κB and that disregulation of this molecule in macrophages may contribute to the development of IPF.

Implications for Practice or Policy. There is no direct implication for medical practice from this study but it does provide important data that can contribute to the development of new and effective therapies for IPF.

Where to next? We will now investigate in detail by what mechanism NF-κB is regulated in macrophages with the aim of identifying the signalling molecules that we can safely modulate with drugs to correct macrophage function.

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