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CCR2 is a critical regulator of fibrocyte recruitment and activation in pulmonary fibrosis

Restoration of injured lung tissue in adults appears to be largely dependent upon adult pulmonary stem cells. Adult bone marrow cells, a known source of stem cells, have the capacity to transform into a variety of pulmonary cells, including tracheal and airway epithelium, type 1 and II pneumocytes, and other cell types that are involved in repair processes such as fibrosis. The transition of stem cells to fibrocytes may involve intermediate cell phenotypes, or may be a direct transition to terminally differentiated fibrogenic cells. The mechanism of transformation of the adult pulmonary stem cells upon lung injury is unclear, but it is generally believed to be a multistep process involving many factors including growth factors and cytokines. Proliferation of pulmonary fibrocytes, fibroblasts or myofibroblasts has been demonstrated in pathologic conditions such as asthma and pulmonary fibrosis. This phenomenon is attributed, at least in part, to the homing of multipotential bone marrow cells to the locally damaged lung tissue, becoming resident for repair. However, the real functional cells in those fibrosing conditions are not known.

Recently, several lines of evidence have pointed to adult pulmonary fibrocytes or fibroblasts as functional cells involved in the repair and regeneration of lungs under both physiological and pathologic conditions. In a report recently published by **Moore et al.**¹ the investigators demonstrated in a mouse model that fibrocytes, either *in situ* or derived from bone marrow, played a critical role in the repair and remodeling of fluorescein isothiocyanate (FITC)-induced alveolar injury. The recruitment of those fibrocytes by soluble monocyte chemoattractant protein 1 (CCL2) released upon alveolar injury appeared to be dependent upon the expression of chemokine receptor 2 (CCR2). Both C57BL/6 and B6/129F2 mice with CCR2^{+/+} background had a significantly higher number of fibrocytes and fibrotic response in the damaged alveolar spaces, compared to the CCR2^{-/-} mice. Transplantation of CCR2^{+/+} bone marrow into CCR2^{-/-} recipients restored recruitment of lung fibrocytes and susceptibility to fibrosis. The fibrotic response of the fibrocytes from CCR2^{+/+} mice was shown to be inducible by CCL2 and TGF- β 1 *in vitro*. The investigators also observed that the CCR2 recruited fibrocytes could transition into fibroblasts with loss of CCR2 expression, while enhancing production of collagen in culture condition. Hence, the loss of

CCR2 may serve to prevent migration of the effector fibroblasts out of the injured lung. The results suggest that CCR2 regulates both recruitment and activation of bone marrow-derived fibrocytes and that blocking CCL2/CCR2 interactions may prevent fibrosis after acute lung injury.

In this issue of *Lab Invest*, **Sabatini et al.**² provided additional evidence that adult human pulmonary fibroblasts had the phenotypic features of mesenchymal stem cells, with multilineage potentialities similar to those of fetal lung fibroblasts and adult bone marrow cells. Adult fibroblasts isolated from the bronchial wall, fetal lung fibroblasts and the adult bone marrow cells all expressed the fibroblast specific CD90 antigen, as well as mesenchymal stem/progenitor cell specific markers including CD73, CD105 and CD166. The findings suggest that the adult lung fibroblasts are closely related to the mesenchymal stem cells in the lung. Both studies advance understanding of the mechanisms of fibrogenesis in some pulmonary fibrosing conditions, with potential therapeutic implications.

Ruliang Xu, MD, PhD

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Exacerbation of mitotic defects in p53-deficient transdifferentiating pancreatic acinar cells

Studies have shown that acinar cells may contribute to the histogenesis of pancreatic carcinoma through acinar-to-ductal metaplasia, also known as acinar-ductal transdifferentiation. In this process, acinar cells exhibit increased proliferation and changes in nuclearity and polyploidy. These in turn may cause genomic instability and lead to polyploidy and aneuploidy, thereby recapitulating the processes contributing to genomic instability in pancreatic carcinoma. p53, as a tumor suppressor gene, is mutated in more than 50% of pancreatic carcinomas and its deficiency alone is sufficient to promote genomic instability in animal models.

In a recently published study, **Sphyrin and Harrison**¹ showed that p53 deficiency indeed exacerbated the mitotic defects in transdifferentiating acinar cells. In culture of acinar cells deficient in p53, the cells rapidly descend into aneuploidy

with increased S-phase entry, giant nuclei, multinucleation, multipolar mitoses and centrosome hyperamplification. The p53-deficient pancreatic acinar–ductal transdifferentiating cells also showed overexpression of mdm2, which is known to inactivate p53 gene, and could conceivably interfere with endogenous checkpoint functions. This would predispose proliferating cells to spontaneous mitotic abnormalities and polyploidization. Also noted was the accumulation of p21 and p27 in these cells, genes which either suppress or promote polyploid progression. This *in vitro* model may recapitulate the genomic instability in pancreatic carcinoma *in vivo* and attest the importance of p53-dependent polyploidy checkpoint.

In this issue, **Lee *et al*²** created an *in vitro* system to study pancreatic carcinomas by developing immortal primary human pancreas cells with properties of intermediary cells that are formed during acinar-to-ductal metaplasia. These properties in-

clude undifferentiated phenotype, expression of Nestin, active Notch signaling and most importantly the ability to differentiate to pancreatic ductal cells.

Both studies support the mounting evidence that acinar-to-ductal metaplasia plays a vital role in the initiation of pancreatic cancer development.

Arief Suriawinata, MD

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