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04 | 2023

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WHAT'S NEW

Vaccination-based immunotherapy to target profibrotic cells in liver and lung

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The present work was performed by researchers in the team of principal investigator Christian Stockmann, in collaboration with the Distler, Sommer and Werner labs. The shared first authors received the SKINTEGRITY.CH Young Investigator Award for their work.

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Jing Chen, Michal Sobecki, Ewelina Krzywinska. Fibrosis is a common endpoint of many chronic diseases that can affect various organs such as the liver and lungs, regardless of their underlying cause. Despite tissue-specific features, fibrotic disease is characterized across organs by common hallmark features, including the expression of α-smooth muscle actin (αSMA) by activated fibroblasts and the excessive accumulation of extracellular matrix (ECM). However, the availability of therapies that selectively target profibrotic cells while sparing healthy tissues is limited.
A recent study from Prof. Christian Stockmann`s group introduces a novel vaccination-based immunotherapy for the prevention and treatment of liver and lung fibrosis [1]. The study, published in Cell Stem Cell, demonstrates that targeting genes specifically activated (e.g., ADAM12, GLI1) in profibrotic cells can ablate fibroblasts and reduce fibrosis in the liver and lungs of mice. During fibrogenesis, certain genes, such as the disintegrin metalloprotease ADAM12, and the transcriptional factor GLI1, that are active during embryonic development but silenced afterwards become transiently reactivated in profibrotic cells *(Figure 1)*. In silico epitope prediction indicates that ADAM12 and GLI1 give rise to peptides that can be recognized by MHC I, and, hence, represent potential endogenous «antigens».

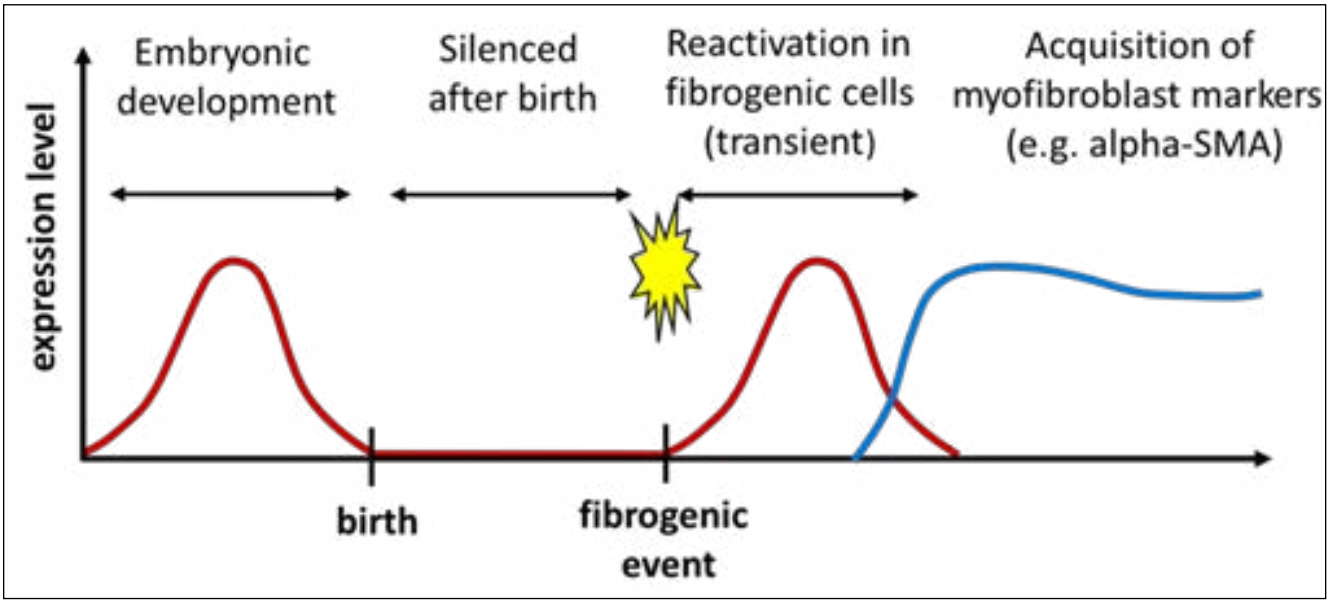

Figure 1: Graphical abstract. During fibrosis, certain genes that are active during embryonic development but silenced afterward become reactivated exclusively in fibrogenic progenitors that give rise to fibroblasts. Examples of these genes include the disintegrin ADAM12 and the transcriptional factor GLI1. These genes are transiently upregulated in profibrotic cells before the subsequent acquisition expression of a myofibroblast phenotype and the expression of platelet-derived growth factor receptor alpha (PDGFR-Œ±) and the myofibroblast marker alpha-smooth muscle actin (Œ±-SMA). Although there is not a feasible approach in a clinical therapeutic setting, it suggests that such reactivated genes specifically «tag» fibrogenic cells and therefore represent potential therapeutic targets.

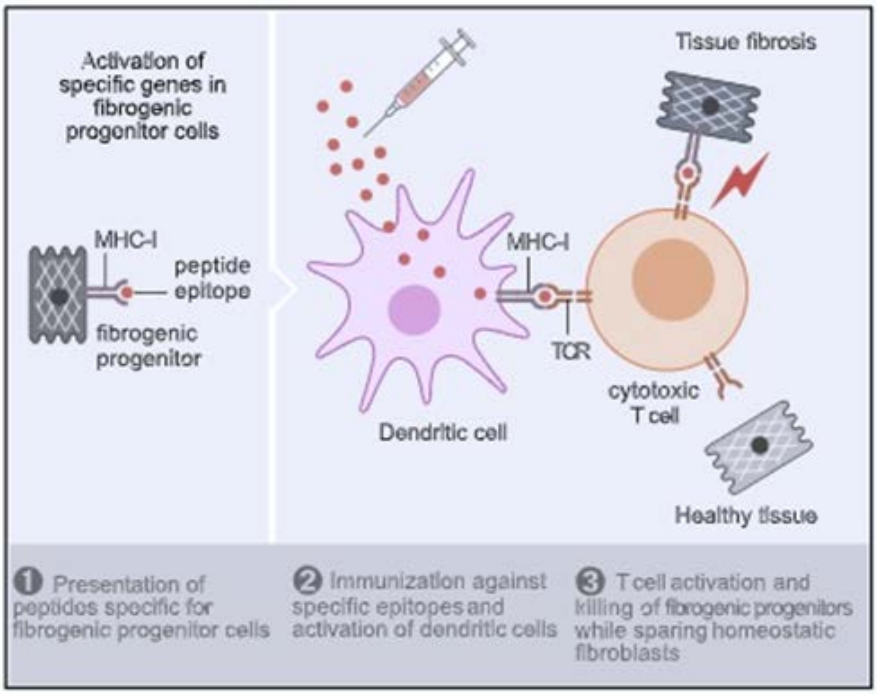

Figure 2: A scheme illustrating vaccination-based immunotherapy to target fibrosis. Antigen-presenting cells, such as dendritic cells (DCs), present the complex of MHC class I and the epitope peptide of targeted genes to naive CD8+ T cells. Along with co-stimulatory signals and cytokine stimulation, CD8+ T cells are activated and possess cytotoxic functions. Activated CD8+ T cells target and kill profibrotic cells that express ADAM12 or GLI1, but the resting fibroblasts in healthy tissues will not be targeted.

Based on this, the authors developed an ADAM12 and GLI1 vaccine to stimulate a specific cytotoxic CD8+ T cell response, which eliminates ADAM12+ and GLI1+ profibrotic cells in the fibrotic liver or lungs, while leaving fibroblasts in non-fibrotic organs undamaged *(Fig. 2)*. The authors demonstrate the efficacy of the ADAM12 vaccine in prophylactic and therapeutic vaccination schemes. Moreover, the efficacy of the vaccine relies on CD8+ T cells, as depletion of CD8+ T cells abolishes its antifibrotic effect. Finally, a series of safety studies shows that the ADAM12 vaccine and GLI1 vaccine do not negatively affect tissue integrity of major organs, or physiological wound healing processes.

In summary, this preclinical study highlights the substantial potential of vaccination-based immunotherapy for organ fibrosis, one of the leading causes of mortality worldwide.

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Reference

Sobecki, M. et al. Vaccination-based immunotherapy to target profibrotic cells in liver and lung. Cell Stem Cell 29, 1459-1474.e9 (2022).