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Reducing harmful extracellular collagen deposits in fibrosis

Researchers have developed a novel strategy to control cellular processes with the help of peptides, which could lead to new therapies for fibrotic diseases that are still difficult to treat / publication in 'Nature Communications'

Researchers at the University of Cologne and the Centre for Genomic Regulation (CRG) in Barcelona (Spain) have developed an experimental strategy that uses peptides as inhibitors to reduce the effects of excessive connective tissue secretion. Peptides are chains of amino acids and the 'little sisters' of proteins. The results from experiments with patient cells and animal studies showed that the new approach is effective and non-toxic. The results of the study 'TANGO1 inhibitors reduce collagen secretion and limit tissue scarring' have been published in Nature Communications.

The extracellular matrix (ECM) is a substance that fills the space between cells, the so-called intercellular space. If proteins such as collagen are secreted into the ECM in an uncontrolled manner, this can lead to scarring and fibrosis, often as a result of a chronic inflammatory process in the affected organs. In fibrosis, proteins of the ECM, including collagen, are overproduced by fibroblasts. The consequence is an uncontrolled wound healing process or incomplete regeneration with loss of function of the affected tissue. To date, there are no satisfactory treatment options.

The research team explored whether it would be possible to control collagen secretion. The secretion mechanism of very large proteins such as collagen from the endoplasmic reticulum (ER) - a transport system of our cells in which proteins are folded - was only recently understood at the molecular level. Researchers also discovered the proteins of the so-called TANGO1 family, including TANGO1 and the closely related cTAGE5. The interaction between these two proteins is one of the key steps in the organization of the 'exit route' for collagen from the ER into the tissue. The research groups cooperated closely to develop peptides that can enter the cells and specifically control a protein-protein interaction between TANGO1 and cTAGE5. The peptides can regulate how much collagen is secreted and enters the tissue.

The peptides were tested in fibroblasts, a certain type of skin cell, from patients with scleroderma, a complex autoimmune disease. This disease is characterized by fibrosis of the skin and many other organs. "In fact, treatment with the peptides led to a significant reduction in collagen secretion in the cultured cells. This suggests that these peptides successfully suppress the TANGO1/cTAGE5 interaction and thus normalize the activity of the fibroblasts," said Professor Dr Ines Neundorf from the University of Cologne's Institute of Biochemistry. Further studies in zebrafish, a common model organism used to study tissue development and wound healing, also showed a visible reduction in collagen in the affected areas.

Overall, the study showed that the activity of the two proteins TANGO1 and cTAGE5 can be specifically controlled by precisely targeting them with peptides. In addition, the ER export of specific proteins of the extracellular matrix can be controlled with the help of the cell-penetrating peptides. Professor Neundorf sees great potential in this approach: "The results of this study are fundamental for the development of future therapeutic interventions in difficult-to-treat fibrotic diseases characterized by the excessive protein production of the extracellular matrix."

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