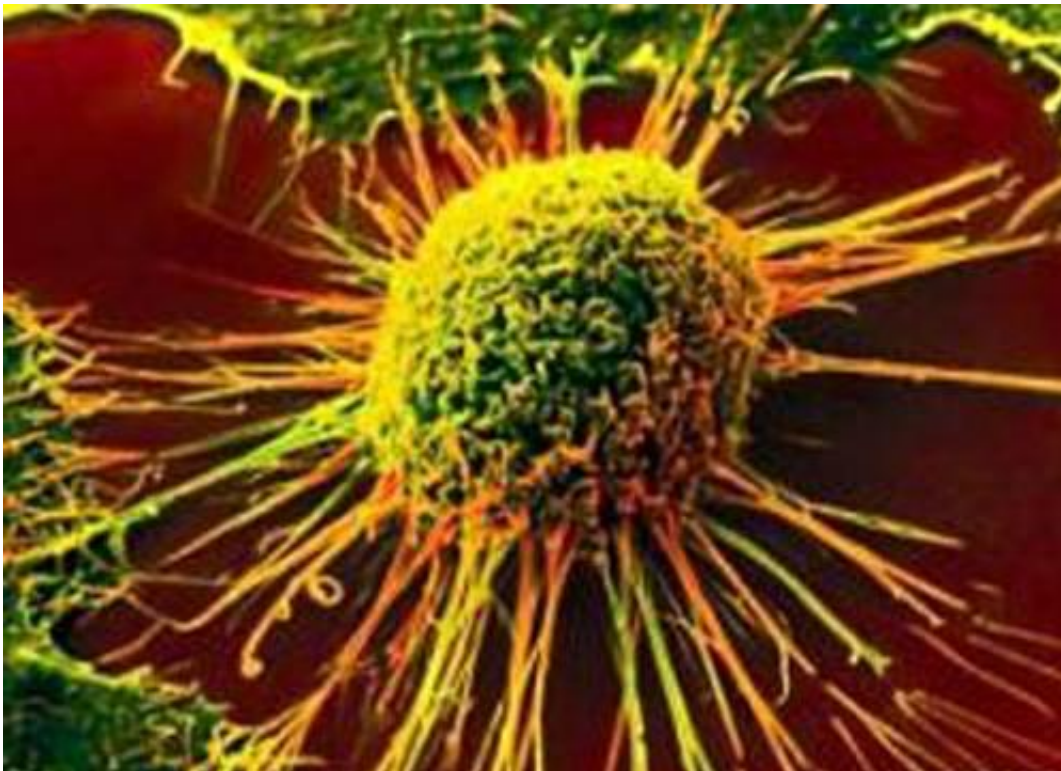


Collagen plays protective role during pancreatic cancer development

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Contrary to long-held beliefs, Type I collagen produced by cancer-associated fibroblasts does not promote cancer development but instead plays a protective role in controlling pancreatic cancer progression, reports a new study from researchers at The University of Texas MD Anderson Cancer Center. This new understanding supports novel

therapeutic approaches that bolster collagen rather than suppress it.

The study finds that [collagen](#) works in the [tumor microenvironment](#) to stop the production of immune signals, called chemokines, that lead to suppression of the anti-[tumor immune response](#). When collagen is lost, chemokine levels increase, and the [cancer](#) is allowed to grow more rapidly. The research was published today in *Cancer Cell*.

"Collagen has been the most highly studied component of the tumor microenvironment for decades, but its precise role has remained unclear," said senior author Raghu Kalluri, M.D., Ph.D., chair of Cancer Biology. "Now, we understand that it is part of a cancer defensive strategy of the body. If we can better understand that strategy, even if it may be suboptimal, we can work to shore up our body's natural defenses to have therapeutic impact."

Collagen, the most abundant protein in the human body, is produced by a class of [cells](#) called fibroblasts and is found mostly in bones, tendons and skin. The protein also tends to accumulate in and around tumors during [cancer development](#) and growth, leading researchers to hypothesize that it helps promote tumor growth, metastasis or drug resistance, Kalluri explained.

To investigate these possibilities and clarify the role of collagen, the research team created a mouse model in which collagen is not produced by cancer-associated fibroblasts during pancreatic cancer development. After genetically deleting collagen from these cells, called myofibroblasts, more than 50% of the total collagen was absent in the tumor microenvironment.

With collagen reduced, pancreatic cancer growth accelerated, and the overall survival of the mice significantly decreased, suggesting that collagen plays an important role in blocking cancer progression.

The researchers looked further to understand how collagen was impacting tumor development. In tumors with reduced collagen, the [cancer cells](#) produced higher levels of chemokines known to attract myeloid-derived suppressor cells (MDSCs), a type of immune cell that dampens anti-tumor immune response.

Indeed, the researchers found that collagen-deficient tumors had more MDSCs present and fewer immune cells, such as T cells and B cells, that could mount an effective anti-tumor response. Interestingly, blocking chemokine signaling activity with targeted therapies reversed the immune profile in these tumors and slowed tumor progression, bringing it back to a level similar to that of controls.

"This was somewhat surprising because we think of pancreatic cancer as a cancer with poor immune surveillance—with an immunosuppressive tumor microenvironment," Kalluri said. "However, this study shows that the immune system actually is controlling pancreatic [tumor growth](#) to some extent, and we see an even more detrimental immune suppressive tumor microenvironment when collagen is lost."

Noting that pancreatic cancer is one of the most aggressive tumor types with poor outcomes overall, Kalluri acknowledged that collagen by itself may not be a particularly effective defense mechanism, but it shows that our bodies are doing what they can to control cancer development.

He likens the body's response to a car with faulty brakes. The car cannot stop as efficiently as it might with good brakes, but it is better than a car with no brakes at all.

The challenge now, Kalluri explained, is to identify a therapeutic strategy to fix those brakes, by increasing collagen levels or boosting collagen's downstream effects to further strengthen the anti-tumor response. Exploring these strategies will be the focus of future work by

Kalluri's team.

Provided by University of Texas M. D. Anderson Cancer Center

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