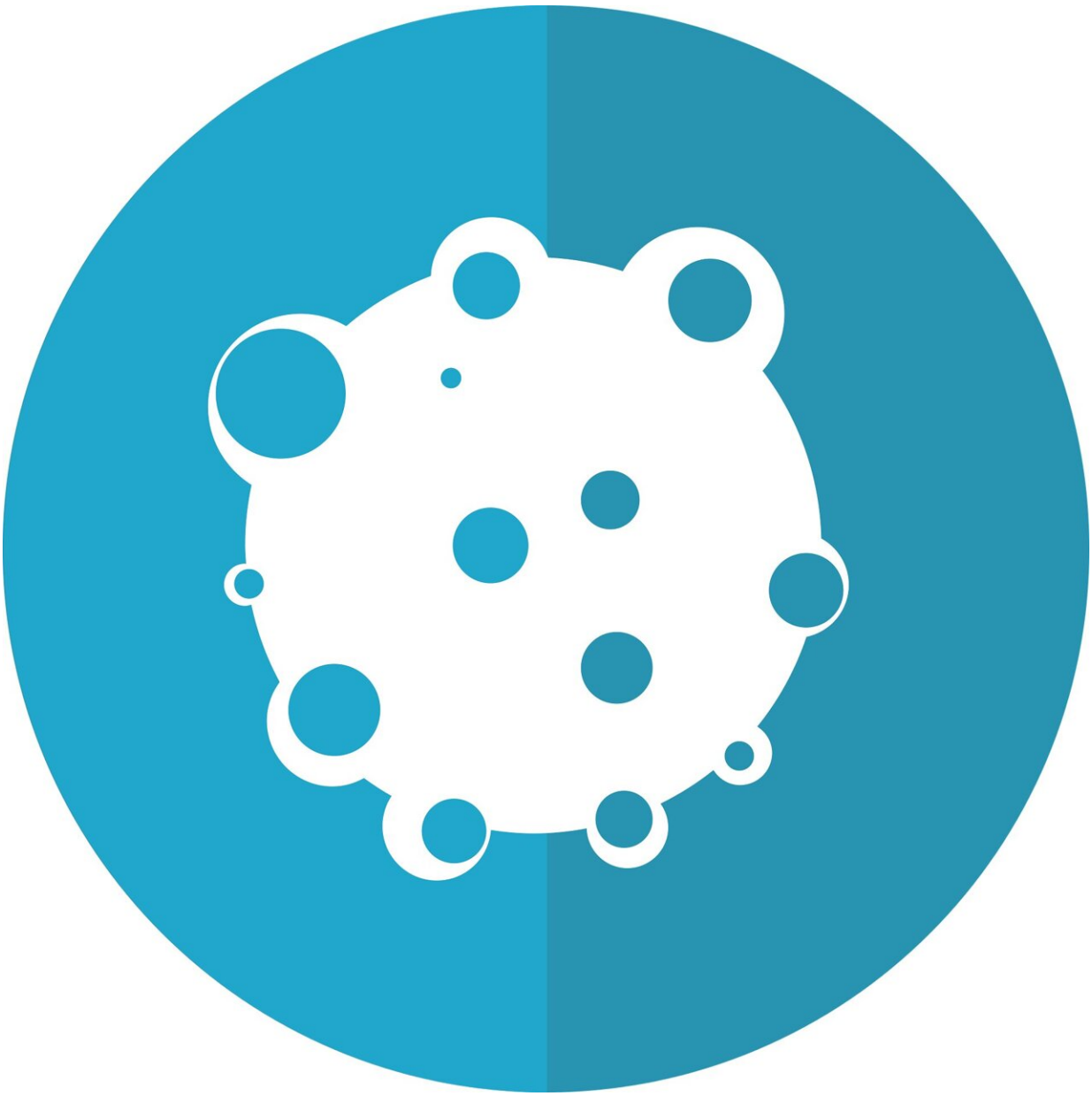
Distinct classes of fibroblasts in tumors play opposing roles, promoting or restraining pancreatic cancer growth

March 29 2022



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Researchers at The University of Texas MD Anderson Cancer Center have discovered that two distinct classes of cancer-associated fibroblasts (CAFs) accumulate in the pancreatic tumor microenvironment and play opposing roles to promote and restrain pancreatic cancer development.

The preclinical findings suggest that appropriately targeting these unique CAF populations may offer strategies to improve the use of other treatments, such as chemotherapy and immunotherapy. The results were published today in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Cancer-associated fibroblasts are known to regulate cancer progression, but targeting these cells in pancreatic cancer has largely failed to improve patient outcomes and has, in some cases, worsened response," said lead author Kathleen McAndrews, Ph.D., postdoctoral fellow in Cancer Biology. "Our findings provide the first evidence of the functional heterogeneity of CAFs in pancreatic cancer that may explain the variations in patient outcomes."

Fibroblasts, a type of cell found in connective tissue, are involved in important biological processes, such as wound repair. Cancer-associated fibroblasts are those that accumulate in tumors. These cells can be found in large numbers in pancreatic cancers, but their precise role in cancer development had remained unclear.

The researchers performed single-cell RNA sequencing to analyze gene expression and clarify the types of CAFs present in pancreatic tumors.

They identified two distinct subsets of CAFs marked by expression of fibroblast activation protein (FAP) and alpha-smooth muscle actin (αSMA).

Interestingly, the researchers found that expression of these proteins in treatment-naïve human tumor samples correlated with eventual outcomes. Increased expression of αSMA was associated with significantly improved overall survival (OS), whereas elevated FAP levels were associated with significantly decreased OS.

Using novel mouse models, the researchers demonstrated that FAP+ and αSMA+ CAFs play distinct and opposing roles in the tumor microenvironment. Loss of FAP+ cells suppressed tumor progression and improved OS, suggesting these cells act to promote tumor development.

Conversely, loss of αSMA+ fibroblasts resulted in more aggressive tumors and shorter OS, indicating that these cells work to block pancreatic cancer progression.

Loss of FAP+ vs. αSMA+ cells resulted in distinct gene expression changes in the tumor, resulting in altered regulation of various cancer-associated pathways and different accumulation of immune cells in the tumor microenvironment.

To clarify the distinct roles of FAP+ and αSMA+ cells, the research team also analyzed secreted proteins that may affect the tumor and surrounding cells. The immune signaling protein interleukin 6 (IL-6) is produced by both classes of CAFs. Loss of IL-6 in αSMA+ cells, but not FAP+ cells, improved responses to chemotherapy and immunotherapy with significantly improved OS.

These results are indicative of the complex and heterogeneous roles of

these different classes of CAFs, explained senior author Raghu Kalluri, M.D., Ph.D., professor and chair of Cancer Biology.

"This is a new discovery that helps move the field forward, with a new appreciation of the biology of pancreatic cancer and possible strategies for therapeutic interventions," Kalluri said. "Our next steps are to identify therapies that can target the tumor promoting fibroblasts while sparing the sum beneficial responses of our body in its effort to fight cancer."

McAndrews led the study together with Yang Chen, Ph.D., and J. Kebbeh Darpolor, Ph.D.

More information: Identification of Functional Heterogeneity of Carcinoma-Associated Fibroblasts with Distinct IL-6 Mediated Therapy Resistance in Pancreatic Cancer, *Cancer Discovery* (2022). aacrjournals.org/cancerdiscove … 2159-8290.CD-20-1484

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