National Cancer Institute
Division of Cancer Biology

Meeting Summary

Fibrosis at the Crossroads of Tissue Homeostasis and Cancer

Dates: June 8-9, 2026
Sponsor: National Cancer Institute (NCI), Division of Cancer Biology
Format: NCI scientific workshop

Workshop Information

The National Cancer Institute (NCI), Division of Cancer Biology, convened the workshop **"Fibrosis at the Crossroads of Tissue Homeostasis and Cancer"** on June 8-9, 2026. The workshop brought together academic investigators and NCI staff with expertise in cancer biology, fibrosis, extracellular matrix (ECM) biology, immunology, metabolism, regenerative medicine, pathology, engineering, and computational and spatial biology.

The workshop included six scientific sessions and discussion periods.

Background

The workshop was convened in response to a growing recognition that chronic disease-linked fibrosis and cancer-associated ECM plays a pivotal role in tumor initiation, progression, and response to therapy. Fibrosis is not simply a consequence of tissue injury or tumor growth, but a dynamic biological process that influences tissue repair, immune regulation, metabolism, mechanics, tumor initiation, progression, metastasis, and treatment response.

Despite the link between fibrosis and cancer, much of its tumor suppressive and/or promoting functions remain ill-defined and are difficult to target. Related to this, the mechanisms that underlie how fibrosis suppresses or promotes cancer, and the role of specific ECM components/configurations and specific cell types, e.g. tumor cells, fibroblasts, cancer associated fibroblasts (CAFs), diverse immune cell types, endothelial cells, adipocytes, in these processes – and how these change/shift during disease progression – are not well understood.

The goal of the workshop was to synthesize and discuss the current state of the science, identify conceptual and technical gaps, and consider how advances from fibrosis biology,

cancer biology, and related disciplines including systemic/systems biology might be integrated to accelerate progress.

Major Topics of Discussion

1. Tissue Homeostasis, Fibrosis and Cancer

Speakers presented data showing that mesenchymal and stromal populations provide instructive signals that regulate epithelial identity during development, homeostasis, wound healing, and cancer. Participants discussed the heterogeneity of fibroblasts and related stromal cells across organs and anatomical niches, and the importance of both lineage and local context in determining function. Particular attention was given to the idea that fibroblast populations can exert divergent effects—some promoting regeneration or differentiation, others supporting inflammation, fibrosis, or tumor progression.

The session also highlighted the extracellular matrix as a major determinant of tissue behavior and stressed that matrix composition, matrix organization, and matrix-associated factors need to be distinguished more carefully across health and disease. Speakers noted that fibrotic matrix is not the same across different disease settings or organs and emphasized the need for better tools to define matrix composition, the cells that produce it, as well as matrix-driven pathways that ultimately influence epithelial cells/tissue outcomes.

Engineering models were presented as an approach to study immune-stromal networks, local and distal tissue responses, and communication among fibroblasts, immune cells, matrix, and vasculature. Adipose tissue was also discussed as an active tissue component in fibrosis and inflammation rather than a passive bystander. Across the discussion, themes that emerged were temporal dynamics, spatial organization, and the need to understand how local tissue context shapes stromal and epithelial responses.

2. Cancers as wounds that never heal-the underlying biology of fibrosis

This session focused on how fibrosis, tissue injury, and tumor development intersect over time. Presentations centered on fibroblast activation, stromal evolution, and the ways fibrotic tissue environments may restrain or promote tumor growth depending on context. Pancreatic cancer as a highly desmoplastic disease was used as a model to show how stromal compartments evolve with tumor progression, how early lesions can already display tumor-like profiles but have drastically different microenvironments, as well as how fibroblasts in different spatial neighborhoods may differ in lineage, transcriptional state,

and function. Speakers mentioned that fibroblasts are heterogeneous and that both tissue of origin and local environment contribute to the behavior of cancer-associated fibroblasts.

A theme of the session was that fibrosis itself can create conditions that support cancer and metastatic dissemination. Fibrosis can have systemic effects, induce vascular remodeling, and drive organ-specific metastasis. Session participants also discussed fibroblast persistence through the concepts of mechanical memory and cell-cell communication, including the importance of direct contact between fibroblasts and macrophages in shaping cell state. In liver, the link between advanced fibrosis and hepatocellular carcinoma risk was discussed, as was hepatic stellate cells as a heterogeneous population with a role in fibrosis resolution, and studies aimed at identifying new targets/approaches for targeting fibrosis. Discussion topics in this session included similarities and differences between wound healing, fibrosis, and tumor-associated stromal responses and the need to understand when fibrosis is protective, when it becomes detrimental, and how these changes develop over time.

3. Tissue mechanics in fibrosis and tumorigenesis

This session focused on tissue mechanics as a central feature of fibrosis and tumorigenesis, with speakers highlighting the importance of looking at diverse mechanical properties of fibrotic tissues and tumors beyond just stiffness- including, for example, porosity, viscoelasticity, and solid stress. Notably, the need to better connect tissue mechanics as an integral facet of cancer biology was emphasized. Speakers described how these physical features influence cell properties (nuclear deformation, DNA damage, altered chromatin organization, cell migration/invasion) as well as the microenvironment (immune cells, soluble factors). Participants discussed how confinement and matrix organization can change the mode of invasion and alter the behavior of both tumor and immune cells, underscoring the need to understand tissue mechanics as a set of interacting properties.

The session also discussed how fibrosis changes the mechanical environment of tissues and how those changes may contribute to cancer development. Speakers described the effects of fibrosis on stiffness, viscosity, viscoelasticity, solid stress, and fluid flow and how they lead to changes in cell-cell and cell-matrix signaling, and tumor progression. Speakers emphasized that these properties are difficult to measure at relevant spatial scales and that current methods often capture only part of the picture. The need to translate mechanical measurements into clinically useful trait profiles was presented as a way to connect local tissue mechanics with clinically relevant fibrotic states.

4. Immune mechanisms and impact of fibrosis in cancer

This session was focused on the reciprocal relationship between fibrosis and the immune system in cancer. Speakers noted that the fibrotic tumor microenvironment can support immune suppression but may also support immune activation depending on context. This duality was discussed in relation to ECM composition, CAF states, and the types of immune cells present in different fibrotic environments. Participants highlighted that fibrosis affects not only whether immune cells enter a tissue, but also how those immune cells function once they are present. A translational framework was presented for thinking about how to target the fibrotic microenvironment in cancer, and challenges related to the need for better understanding of the underlying biology of fibrosis (i.e., beyond its physical barrier properties and functions), tumor/stromal resistance pathways, and the need for improved models and biomarkers.

The session also focused on fibroblast-immune cell crosstalk as contributing to ECM remodeling and fibrotic niche formation. Speakers presented data on fibroblast subsets interacting with different immune populations and that inflammatory fibroblast and myofibroblast states may have distinct immune consequences. The need for better genetic tools to study fibroblast heterogeneity and function was emphasized. Neutrophils and neutrophil extracellular traps were presented as active participants in remodeling matrix, stimulating macrophages, and helping create fibrotic niches that support metastasis. Also, cytokine signaling was discussed as a pathway linking inflammation, myeloid cells, hepatocytes, and fibrosis in liver disease, with examples extending from mechanistic studies to a clinical trial. Across the discussion, participants highlighted that fibrosis affects not only whether immune cells enter a tissue, but also how those immune cells function once they are present.

5. Metabolism and fibrosis: a reciprocal dynamic

The session explored the role of metabolism in fibrosis and cancer, highlighting metabolic reprogramming across various fibrotic tissues and tumors, including the complexity of metabolic pathways involved and the heterogeneity of cell types contributing to these processes. The use of mass spectrometry (MS) technologies to study metabolism in tissue samples was discussed, focusing on fibroblast metabolic states in tumors, as well as the use of deep visual proteomics for single-cell analysis, the potential of MS imaging to map metabolic gradients and activities in tissues, and how fibroblast metabolism could potentially provide targets and non-invasive readouts. Also discussed was the impact of

metabolic disease and matrix remodeling on cancer progression, focusing on liver fibrosis and cirrhosis, in particular findings related to altered collagen architecture, mechanical properties, and their influence on tumor invasion and metabolic adaptation.

Another area of focus was mitochondrial metabolic reprogramming in tumor-associated macrophages (TAMs) and their role in fibrosis and immune suppression. Discussions were held on how macrophages adapt metabolically to produce proline for collagen synthesis, contributing to tumor fibrosis and T cell exclusion. The session concluded with added discussions linking fibrosis, inflammation, and metabolism to cancer risk, particularly in breast tissue with high mammographic density and hereditary predispositions/germline mutation carrier. It was highlighted that tissue stiffness drives inflammatory infiltrates, lipid peroxidation, DNA damage, and mutational burden, supporting creation of a pro-tumor microenvironment. Across the session, participants emphasized that understanding metabolism in fibrosis will require integrating spatial approaches, protein-level measurements, functional tracing, and imaging methods that can be translated to the clinic.

6. Chronic diseases and cancer – the tipping points between protective and detrimental fibrosis

This session focused on chronic disease states and how fibrosis can be a risk factor for cancer across multiple organs. The organ-specific diversity of fibroblasts and their homeostatic functions, dual roles of fibrosis in pre-malignant and tumor microenvironments, and the impact of fibrosis/fibroblasts on cancer progression and therapy resistance were discussed. Potential pathways involved in pro- versus anti-tumor effects of fibrosis and premalignant environment (PME) fibrosis as a tipping point for cancer were also highlighted.

Obesity was raised as a clinically important chronic condition that alters mammary gland tissue, leading to chronic inflammation, macrophage recruitment, extracellular matrix remodeling, and tumor progression. It was presented that obesity changes the tissue microenvironment before tumors arise and that some of these changes persist after weight loss, raising questions about obesity memory, matrix remodeling, and long-term cancer risk. Participants also discussed that matrix remodeling in bone can occur as a consequence of fibrosis and that this supports the formation of osteogenic niches and metastasis, and the importance of mineralization of the bone matrix (which can be affected by pathological conditions) and its impact on tumor cell phenotypes.

The convergence of fibroblast phenotypes in organ fibrosis and tumors was presented, focusing on the role of senescent fibroblasts in promoting epithelial cell subsets with plastic tumor cell states. Therapeutic targeting of senescent fibroblasts suggests shared stromal vulnerabilities in chronic fibrosis and cancer. Across the session, participants returned to the idea of “tipping points” and stressed that chronic disease, aging, obesity, senescence, and therapy all shape whether fibrosis remains protective, becomes unresolved, or supports cancer development and progression.