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Incendiary by nature: connecting inflammation and cancer complexity

By Alexander Burik
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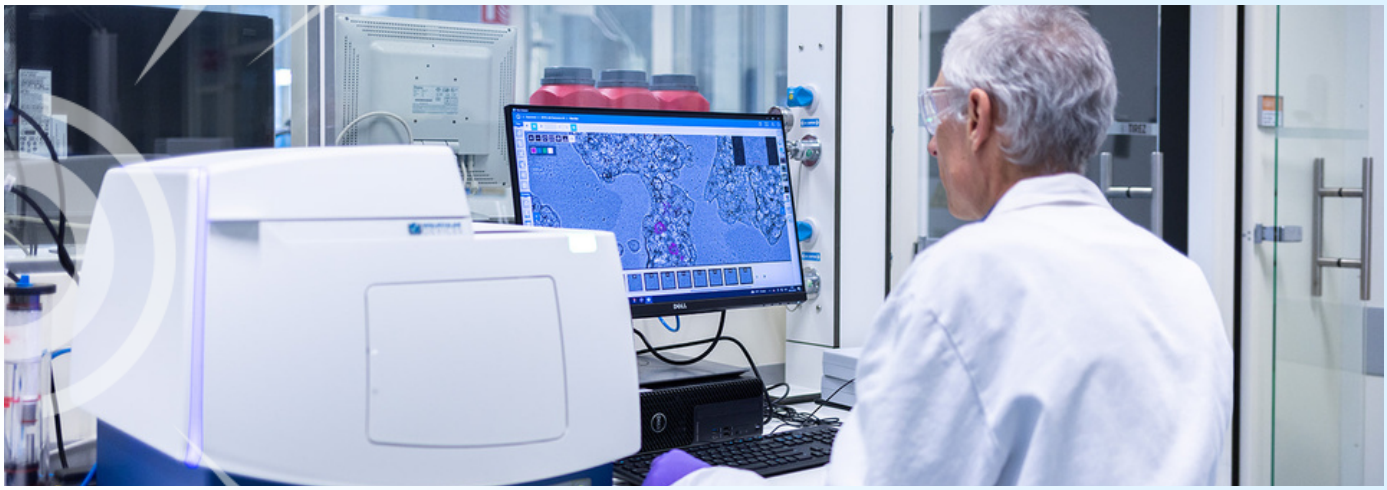


In most cases, chronic inflammation is known to lead to cancer, however, the mechanisms behind this are not fully understood. Preclinical models in immuno-oncology are the first step towards a better understanding of cancer mechanisms, improved treatments and prevention of cancer caused by inflammation.

Inflammation is the immune system's natural response to bacterial, viral, and parasitic infections, as well as external or environmental factors like allergens, toxins, and injury. A healthy inflammatory response leads to the repair of damaged tissue and the growth of healthy new cells. If the underlying causes persist or the control mechanisms regulating the immune response fail, however, inflammation can become chronic.

Chronic inflammation and cancer complexity

It is now known that cancer results from molecular and genetic abnormalities arising in the body's cells. Moreover, it is well-established today that chronic inflammation may be at the root of up to 25% of cancer cases. Inflammatory bowel disease, chronic obstructive pulmonary disease (COPD) and sepsis, for example, are types of inflammation known to increase the risk of cancer.

The steps leading from chronic inflammation to cancer are intricate. Inflammation increases the risk of developing cancer by accumulating double-strand breaks in genomic DNA within the nuclei of cells. If left unrepaired, these mutations, along with pro-inflammatory cellular signaling molecules, can disrupt the genetic control mechanisms of cellular growth. Eventually, this can lead to the initiation of cancer.

"Chronic inflammation, such as colitis, or fibrosis in the kidney, bladder, lung and liver, can arise in many different tissues and organs. All types of chronic inflammation highly increase the risk of developing cancer," says Olivier Duchamp, head of Translational Pharmacology at Oncodesign Services, a preclinical pharmacology contract research organization (CRO) based in Dijon, France.

While cancer can occur anywhere in the body, a tumor resulting from chronic inflammation is usually first localized in the inflamed tissue. Initiating treatment at this early phase, before the cancer spreads to other organs, remains a key challenge.

“We need more non-surgical solutions for treating early stage cancers,” Duchamp elaborates. “Identifying these cancer patients as soon as possible, just before or right at the beginning of the tumor appearance, will make it easier to treat them.”

However, the cellular processes leading from inflammation to genetic mutations and cancer are complex and still not fully understood. A clearer understanding could help identify cancer sooner and create more effective treatments and prevention methods in the future.

The power of a model

In order to better understand how inflammation results in cancer, researchers use experimental models that mimic the types of inflammation and cancer seen in humans.

To study the mechanisms of cancer development, an inflammatory response can be exogenously elicited in mice or rats using viruses, bacteria or chemical agents. Alternatively, transgenic and humanized models genetically alter or introduce specific cell types into mice or rats to induce inflammation.

Oncodesign Services has long-standing expertise in immuno oncology, and offers a range of in vitro, in vivo models, including humanized models. Each type of model comes with its own advantages, but they also have limitations. Therefore, researchers must find the combination of models best-suited to their needs.

To study cancer initiation, Oncodesign Services uses immuno-competent models. These models generate a high grade of exogenously induced inflammation in selected organs of mice or rats. The inflammatory response lasts for at least 3 to 6 months in these models.

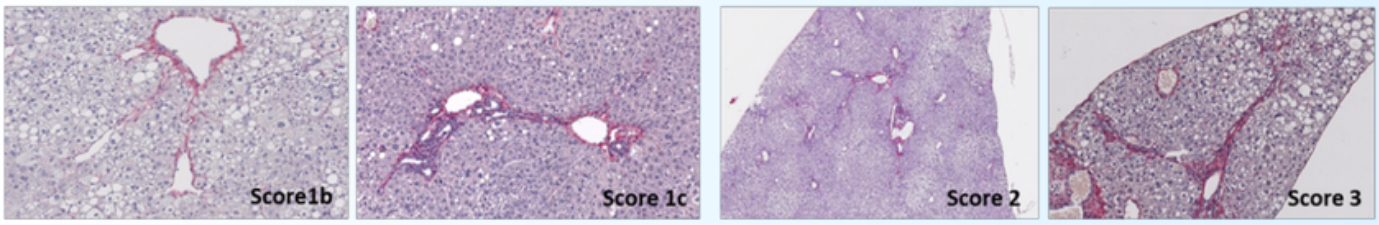
The company's model of DMBA-induced breast tumors in rats can mimic the different phases and grades of the human breast cancer pathology more closely than mouse models. In rats, the tumor innervates more closely with connective tissues, allowing for improved reuptake of drugs and tracers. Additionally, experimental drug doses in rats are closer to human dosages.

Oncodesign Services also offers a powerful bacteria/DSS/chemo-induced colitis-colon cancer model in mice. First, the inflammatory agent dextran sodium sulfate (DSS) is used to induce colitis. Following this, the carcinogen azoxymethane (AOM) is added, which decreases the time required to generate tumors. Finally, the addition of bacteria increases the prevalence and severity of tumors. This model allows researchers to generate a high number of mutations and observe the cancer for 3 to 6 months.

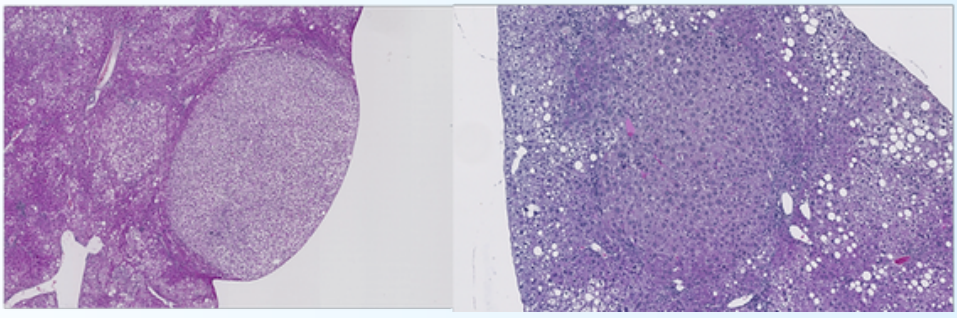
Excitingly, another one of Oncodesign Services' current models shows how liver cancer arises from nonalcoholic steatohepatitis (NASH), the most severe form of non-alcoholic fatty liver disease. Patients with NASH develop inflammation after excessive fat accumulates in the liver. NASH leads to fibrosis, which can result in liver cancer.

"*All the mice develop tumors in the liver after fibrosis, after NASH. We treat the animals at different stages of the pathology, either at the fibrosis or the tumor when it's detected," Duchamp clarifies. "From this, we know that treating fibrosis reduces the number of mice developing tumors*."

But, these murine models differ from the human immune system. Now, researchers are developing more "human" models in order to better mimic the clinical situation. These humanized models may also lead to a better understanding of the mechanisms by which inflammation leads to cancer initiation.



Fibrosis score in NASH-HCC model



Liver tumor in NASH-HCC model

A humanized touch

Humanized models insert immune cells into a murine host organism in order for it to resemble the human body more closely. Oncodesign Services offers chronic inflammation models, including colitis, fibrosis, or graft-versus-host disease (GvHD) in immune-humanized mouse models.

"However, even when we succeed in inducing chronic inflammation in immune humanized mice, we have yet to see tumor appearance following the inflammatory phase," adds Duchamp. *"This is probably a field of new technology development in the next decade."*

Treating to target

The connections between chronic inflammation and cancer are complex, and point towards multiple avenues for improving cancer treatments.

For example, an improved understanding of cancer initiation will facilitate the discovery of novel targets for new cancer detection and treatment strategies. Moreover, anti-inflammatory treatments for chronic inflammation may reduce the initial risk of tumor development. Last but not least, in cases where inflammation plays a harmful role in the tumor microenvironment, targeted anti-inflammatory treatments could become potent adjuvants to the cancer treatments themselves.

"*Once we understand the mechanism of tumor initiation after chronic inflammation more fully, we will be able to know what types of immune cells are involved,"* Duchamp predicts. *"This knowledge can be incorporated into our experimental models, which will probably become very helpful in understanding and modeling tumor initiation."*

Cancer's Achilles heel

Regarding the mechanisms underlying cancer initiation, early studies suggest stem cells, which usually replicate infrequently, could be involved. After being exposed to physical and chemical carcinogens, as well as certain viruses, these stem cells increasingly transform into cancer cells.

Moreover, stem cells driving tumor initiation and growth may also be responsible for treatment resistant cancers. This may be why current treatments, which target the proliferating cells within a cancer, often fail. Therefore, it has been suggested that directly targeting the stem cell progenitors of a tumor may be the most curative potential method for treating cancer.

To explain the initiation and progression of cancer more fully, novel evidence-based models are needed to enhance the current body of knowledge. In the future, this should improve not only our understanding of the healthy mechanisms of human gene regulation, but also our ability to identify the true initiators and drivers of oncogenic and inflammatory processes.

For instance, some driver oncogenes have already been identified as playing a symbiotic role in both inflammation and tumor progression: the NF-κB family of transcription factors performs essential roles in inflammation and innate immunity, and is increasingly recognized as a key player in cancer initiation and progression. New experimental models will continue to elucidate a growing number of vital oncogene targets and expose cancer cells' Achilles heel.

For life science companies who strive to innovate the treatment of chronic inflammation and cancer, Oncodesign Services can help pave the way to preclinical success and lay the foundation for truly personalized cancer therapies.

See how Oncodesign Services can help clients bring insight and innovation closer to your lab today!

Oncodesign services

Image courtesy: Oncodesign Services and Antoine Martel