Cancer-causing mutations rewire growth signaling in prostate cancer model

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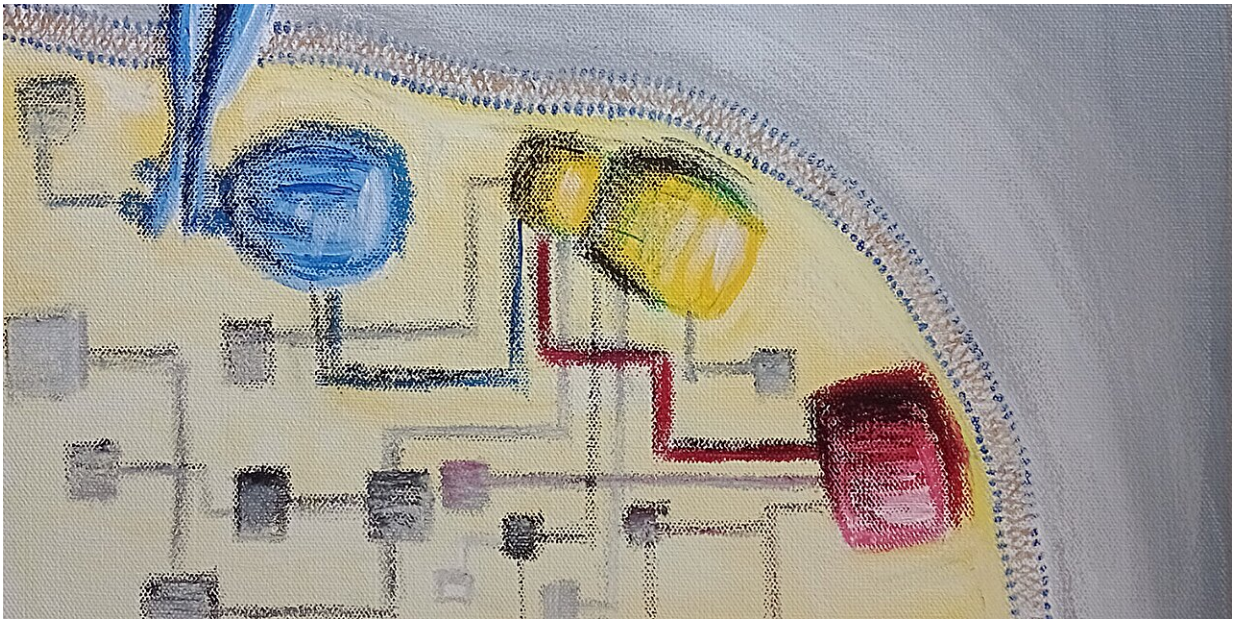

A section of a painting by lead researcher, Tamara Chessa, representing the research findings described in Chessa et al. PI3K signaling is represented as an electric circuit, with the nodes representing proteins. In PTEN-null tumors, a decrease in signaling to PI3K (depicted in yellow) is represented by blue wires. PLEKHS1, depicted in red, becomes the dominant driver of PI3K signaling and tumor progression in PTEN-null tissue. Credit: Babraham Institute

Experts in cell signaling at the Babraham Institute have identified how prostate cancer cells achieve cell growth free from the usual growth cues and regulators. This discovery has implications for potential therapeutics

in prostate cancer and other cancer types as understanding more about this network remodeling and the drivers of cellular growth provides molecular targets for drugs to stop tumor progression.

The PI3K signaling pathway is critical for normal cell function, controlling many aspects of cell biology and metabolism needed for cell growth and survival. The pathway is typically inactive until stimulated by external growth cues, such as insulin. Genetic mutations causing hyperactivation of this pathway are a common feature of many cancers and drive cancer progression.

One of the most common mechanisms that drives deregulated cell growth is mutations that inactivate the tumor suppressor PTEN. In healthy cells, the PTEN enzyme turns the pathway off, and the loss of PTEN leads to hyperactive PI3K signaling.

Using mouse models of prostate cancer, researchers from the Institute's Signaling research program found that pathway hyperactivation due to loss of PTEN not only causes a sustained increase in pathway activity but also a dramatic rebuild of the pathway in terms of its components and their organization. The new pathway architecture reduces its dependence on extracellular growth factors and introduces a self-sustaining, positive-feedback loop that means it can be active with minimal requirement for external cues.

Importantly, what was seen in the prostate cells from the mouse models correlates with PI3K activity in human prostate cancers.

"Surprisingly, we found that the PI3K signaling network was not simply hyperactivated but remodeled in different tumor contexts. This means that the activators of the PI3K signaling pathway in cancer are distinct to those in healthy tissue," explained Dr. Tamara Chessa, who led the study.

"This suggests there are potential targets in the pathway that are preferentially active in cancer cells, offering the opportunity to create drugs that target cancer cells and not healthy neighbors. Traditional, direct inhibitors of PI3Ks inhibit the PI3K pathway in both cancerous and healthy cells, limiting their benefits."

During their research, the scientists looked for the direct activators of PI3K signaling in normal mouse prostate and prostate in which PI3K signaling had been chronically activated by loss of the tumor suppressor PTEN, leading to the slow emergence of prostate cancer.

In their analysis of the tumor cells in the PTEN-lacking mice, the researchers noticed something remarkable. As expected by what is known about PI3K pathway regulation, hyperactive PI3K signaling triggered a negative feedback mechanism to suppress pathway activation by growth factor signals.

This negative feedback mechanism kicked in as expected and shut down normal growth factor driven activation of PI3K signaling. However, another growth-driving mechanism, centered around a virtually unstudied protein called PLEKHS1, was identified. PLEKHS1 is unaffected by this feedback and creates a self-sustaining positive-feedback loop driving growth. This represents a key event in prostate cancer progression.

"We were surprised to find PLEKHS1, a protein with previously largely unknown function, to be a major driver of PI3K activation and cancer growth and progression in the mouse model for prostate cancer. Not only that but the properties of PLEKHS1 are very unusual in that it is capable of both stimulating the PI3K network and being stimulated by the PI3K network, allowing positive feedback. We then wanted to find out if this remodeling could be found in other models of cancer," Dr. Len Stephens, group leader in the Signaling research program, explains.

To explore this, the researchers examined two further models (in mice) of tumor progression driven by genetic activation of the PI3K network: a model that also slowly develops prostate cancer but is caused by a distinct type of mutation, and an ovarian tumor model. Using these models, the researchers found that PLEKHS1 does not have a uniform role in remodeling PI3K networks in the absence of PTEN and that other PI3K activators may take on more important roles in other tissues.

For example, the researchers found that another protein member of the PI3K signaling network, AFAP1L2, can also contribute to pathway remodeling.

Dr. Phill Hawkins, group leader in the Signaling research program, is hopeful for the future of this research. "Our analysis of human datasets supports our findings in the mouse models, and strongly suggest that PI3K pathway rewiring is relevant in human cancers. We now have a potential new avenue for therapeutic targeting of the PI3K signaling pathway in human cancers, via PLEKHS1 and potentially its upstream activating kinase, with minimal predicted toxicity."

The findings also have important implications for understanding of the mechanisms that cause aging. Many studies have shown that excess PI3K network activity accelerates aging and loss of PI3K activity decelerates aging but the mechanistic details are unclear.

Based on this recent finding, the research team are now exploring whether there is a similar but distinct rewiring event during normal aging that might lead to loss of sensitivity to growth factors like insulin and support excessive autonomous PI3K network signaling leading to loss of normal metabolic balance and possibly the emergence of age-related inflammation.

The paper is published in the journal *Molecular Cell*.

More information: Tamara A.M. Chessa et al, PLEKHS1 drives PI3Ks and remodels pathway homeostasis in PTEN-null prostate, *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.07.015

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