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Study identifies a role for the metabolism regulator PPAR-gamma in liver cancer

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Liver cancers are a major cause of cancer-related deaths. Large-scale genetic analyses have associated liver cancer with dysregulation of numerous molecular pathways, but disruptions in insulin signaling pathways appear to have a particularly important contribution to liver tumor formation. Obesity is a major risk factor for developing liver cancer, and the nuclear receptor PPARγ critically controls fat uptake and storage in the liver by regulating the transcription of metabolism-associated genes. However, whether PPARγ also plays a role in promoting the growth of liver tumors is not clear.

This week in the *JCI*, research led by Ganna Panasyuk at INSERM examined the link between PPARγ and liver tumor formation. The findings identify a metabolic pathway with pro-tumor effects that can be suppressed by selectively blocking PPARγ.

Researchers initially observed that increases in PPARγ expression and activity in human liver tumors were associated with loss-of-function of the transcription factor hepatocyte nuclear factor 1α (HNF1α). In a mouse model, they determined that loss of HNF1α led to abnormal increases in PPARγ expression that in turn led to increased tumorigenesis.

Pharmacological activation of PPARγ in a mouse model of liver cancer exacerbated tumor formation; in contrast, treatment with a PPARγ inhibitor had positive therapeutic effects.

Taken together, these findings demonstrate a role for PPARγ in the metabolic pathway disturbances that promote liver tumorigenesis and reveal that PPARγ is a potential target for anti-tumor therapies to treat liver cancers.

More information: Cecilia Patitucci et al, Hepatocyte nuclear factor 1α suppresses steatosis-associated liver cancer by inhibiting PPARγ transcription, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI90327