TECHNIQUE

A new mouse biosensor to monitor Akt activity in live tissues

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The PI3K/AKT signaling pathway has essential roles in multiple normal cellular processes, including cell growth, survival, metabolism and motility. Aberrant activation of this pathway is observed in various human cancers, and has been linked to obesity and type 2 diabetes mellitus. Despite the AKT pathway being a target for therapy for decades, most drugs targeting this pathway alone have so far been ineffective as therapeutics. In a study published in *Science Advances*, investigators report the development of a new biosensor mouse model to monitor Akt activation status in vivo in real time. This new preclinical tool could help identify optimal therapeutic strategies for subsequent clinical trials.

The researchers optimized a previously described Förster resonance energy transfer (FRET) biosensor for Akt activity to generate mice that can either ubiquitously express the Akt-FRET biosensor or conditionally express the biosensor in selected tissues of interest. Upon phosphorylation by active Akt at a specific consensus sequence, the Akt-FRET biosensor undergoes a conformational change, resulting in an increase in the FRET efficiency, which can be measured by fluorescence lifetime imaging microscopy (FLIM).

First, the investigators used their novel Akt-FRET biosensor mouse to measure and map Akt activity in several genetically engineered mouse models of cancer, including PTEN loss–driven pancreatic ductal adenocarcinoma (PDAC), prostate and breast cancer models. FLIM-FRET analysis revealed an upregulation of Akt activity in all cancer mouse models tested, confirming findings from previous studies that used standard approaches to monitor Akt kinase activity in PDAC, prostate and mammary carcinomas driven by PTEN loss.

Next, the investigators confirmed the suitability of their biosensor to monitor Akt activity in response to drug targeting the AKT pathway in spheroid, organotypic cancer models as well as in a mouse model of breast cancer using intravital imaging in conjunction with image stabilization and a mammary imaging window.

Finally, the team used Akt-FRET biosensor mice engrafted with optical imaging windows to longitudinally measure Akt activity in pancreatic islets and adipose tissue upon glucose or insulin challenge.

Altogether, these findings suggest that the Akt-FRET biosensor mouse will be useful to monitor AKT activity in several malignant and metabolic disease contexts, guiding the development of improved therapies.

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