Metabolic- and Malignancy-mediated Akt signaling revealed by Akt-FRET biosensor mouse

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Abstract

Aberrant AKT activation occurs in a number of cancers, metabolic syndrome and immune disorders making it an important target for the treatment of many diseases. To monitor spatial and temporal AKT activity in a live setting we generated an Akt-FRET-biosensor mouse which allows longitudinal assessment of AKT action using intravital imaging in conjunction with image stabilization and optical windows technology. We demonstrate the sensitivity of the Akt-FRET biosensor mouse using various cancer models and verify its suitability to monitor response to drug targeting in spheroid and organotypic models. Elevated levels of AKT activity were observed in the pancreatic cancer models driven by mutant *KRas*$^{G12D/+}$ and *KRas*$^{G12D/+}$;*p53*$^{R172H/+}$, including PTEN loss driven PDAC and AKT activity mapped over the course of disease progression. Whole body *PTEN*$^{G129E/+}$ mutation or PTEN loss (*PTEN*$^{floxed/+}$) mice were also crossed to the Akt-FRET biosensor mouse and AKT activity quantified in several cancers such as lymphomas, adrenal, mammary and prostate cancer. We also show that the dynamics of AKT activation can be monitored in real-time in diverse tissues during homeostasis and metabolic diseases, including in individual beta-islets of the pancreas, the brown and white adipose tissue, as well as in the skeletal muscle. Thus, the Akt-FRET biosensor mouse provides a new and important tool to study AKT dynamics in live tissue contexts and has broad pre-clinical applications.