Biomedical Data Mining

Extended Abstract

Calcium-mediated KRAS allosteric modulation: Implications in cancer drug discovery

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Abstract

For quite a long time, KRAS, a little GTPase, has been ensnared in malignancy research. Many have endeavored to orchestrate little atom inhibitors that have the ability to interfere with the constitutively dynamic, GTP-bound province of KRAS which causes an overstimulated oncogenic pathway. Burhman (2015) tackled the KRAS X-beam structure within the sight of calcium, an advancement recommending the presence of allosterically-intervened changes not recently theorized. Later in vitro measures that will be introduced uncover calciummediated underlying soundness changes, the help of SOS-catalyzed nucleotide trade, and the assistance of KRASGTP characteristic and GAP-catalyzed hydrolysis. KRAS-calcium primary and utilitarian regulation is an original finding that can add to the clarification of the genuine intracellular conduct of KRAS, introducing new potential in disease drug revelation by the union of highaffinity KRAS-restricting mixtures that advance dynamic site hindrance of calcium-intervened KRAS, which is profoundly present in the cell.

K-Ras4B is a highly oncogenic Ras isoform and is the only isoform associated with initiation of adenocarcinomas. Mechanistic insight into why and how K-Ras4B mediates ductal adenocarcinomas, particularly of the pancreas, is vastly important for its therapeutics. The current review points out the overlooked but critical role of calmodulin (CaM) which selectively binds to GTP-bound K-Ras4B; but not to its isoforms. Cell proliferation and growth require the MAPK (Ras/Raf/MEK/ERK) and PI3K/Akt signaling pathways. We propose how Ca^{2+}/CaM promotes PI3K/Akt signaling and how Ca^{2+}/CaM involvement explains enigmatic observations like the elevated calcium levels in adenocarcinomas. We hypothesize that CaM recruits and activates PI3K at the membrane, and that this is the likely reason for Ca^{2+}/CaM-dependence in adenocarcinomas. CaM contributes to initiation and progression of many ductal cancers (e.g., pancreatic, colorectal, lung) via both PI3Kα/Akt and Raf/MEK/ERK pathways. Therefore, blocking the K-Ras/MAPK pathway and CaM/PI3Kα binding in a K-Ras4B/CaM/PI3Kα heterotrimeric complex has promising clinical potential as an adenocarcinoma-specific therapeutic strategy.

RAS signaling cascades are still not entirely understood. Cell decisions are temporal, and functions typically involve more than one pathway. Growth and proliferation, which require both the mitogen-activated Ras/Raf/MEK/ERK (MAPK) and the phosphatidylinositide-3-kinase (PI3K)/Akt pathways, provide a compelling example. Under normal physiological conditions, PI3Kα is recruited to the membrane by activated tyrosine kinase receptors (RTKs) such as the epidermal growth factor receptor (EGFR) or adaptor proteins. When K-Ras4B is constitutively activated by mutations, calmodulin (CaM) can act to accomplish the *full* activation of the PI3K/Akt pathway role. K-Ras4B is the only Ras isoform or splice variant to bind CaM; we propose that by activating the PI3Kα/Akt pathway in the absence of a growth cue, CaM plays a critical role in adenocarcinomas, particularly pancreatic cancer. The high calcium levels observed in adenocarcinomas may explain CaM's involvement in recruiting and activating PI3Kα through interaction with its n/cSH2 domains as well as K-Ras, and why K-Ras4B specifically is

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a key player in these cancers. CaM's role in recruiting PI3Kα essentially makes it act as a Ca^{2+}-regulated scaffolding protein. Based on genetically-engineered mouse models, even in the absence of RTK signal, oncogenic mutations in K-Ras can lead to oncogene-induced senescence (OIS) or to proliferation and differentiation; however, on their own, oncogenic mutations in K-Ras4B are unable to achieve full PI3Kα activation. Thus, a compelling question is whether in addition to the mutations, there exists another factor. Possible factors include elevated levels of CaM/Ca^{2+}, a redundant pathway, bypassing PI3Kα-dependent growth, and PI3Kα mutations. The first two can be cell/tissue-specific. A K-Ras4B/CaM/PI3Kα trimer fits available experimental and clinical data, is able to explain the high frequency of oncogenic K-Ras4B in adenocarcinomas, particularly in pancreatic cancer, and is a promising, highly specific therapeutic venue for adenocarcinoma.

Here we suggest that in PDAC, colorectal cancer (CRC) and lung adenocarcinomas, CaM/Ca^{2+} can regulate two major pathways, MAPK and PI3K/Akt. CaM/Ca^{2+} temporally down-regulates MAPK; it is required for *full* activation of PI3Kα by K-Ras4B. GTPase homologs activate PI3K through direct and indirect feedback processes; direct interaction of Ras with RBD-p110α is an absolute requirement for in vivo Ras-driven tumor formation. Endogenous oncogenic $K\text{-}Ras^{G12V}$ triggers senescence alone, in the absence of RTK signaling. These facts indicate that different from physiological conditions, in cancer a fully activated PI3K pathway is required for cellular growth and proliferation.

This leads us to reason that in adenocarcinomas, cell-specific up-regulation of CaM/Ca^{2+} expression may substitute for the missing phosphopeptide ^{p}YXXM signal from RTKs. CaM/Ca^{2+} can play two distinct activation roles: as an activator when bound to nSH2-p85α, or as an adaptor when bound to cSH2-p85α. For the first, the prediction of CaM/Ca^{2+} interacting with nSH2-p85α by PRISM suggests that CaM/Ca^{2+} can achieve full PI3Kα activation by relieving the p110α autoinhibition exerted by nSH2-p85α, via a steric hindrance mechanism similar to that induced by the ^{p}YXXM peptide. For the second, CaM has been shown capable of dissociating K-Ras4B, but not its H-Ras or N-Ras isoforms, from membranes in a Ca^{2+}-dependent manner, with CaM's C-terminal domain binding its farnesylated HVR. Our modeling suggests that even when K-Ras4B dissociates from the membrane, CaM can fully activate PI3Kα via an allosteric mechanism. PRISM models a trimer, K-Ras4B-GTP/CaM/PI3Kα, with an interaction between CaM and cSH2-p85α. CaM can act as an adaptor protein to increase the likelihood of K-Ras4B-GTP binding to RBD-p110α. In turn, the increase in membrane binding capability via an enhanced Ras binding environment allows PI3Kα to remain close to the plasma membrane without relying on K-Ras4B being anchored to membrane. In short, CaM can provide the critical missing link in K-Ras4B initiation and progression of pancreatic, colorectal and lung cancers.

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