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Perspective

Clinical Signalling Pathway of *KRAS* Mutant Pancreatic Cancer

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DESCRIPTION

Pancreatic cancer is a difficult cancer to treat, with one of the lowest 5-year survival rates. The presence of oncogenic mutations in the *KRAS* gene is a defining feature of pancreatic cancer. The KRAS oncogene is important in the initiation and progression of pancreatic tumors, and its signalling network is a major target for therapeutic intervention. Several inhibitors of kinase effectors in signalling pathways have been developed. However, their clinical activity has been disappointing thus far. Covalent inhibitors of the *KRASG12C* oncoprotein have recently been developed. In early clinical trials, these inhibitors demonstrated promising activity in *KRASG12C* mutant pancreatic cancer, allowing us to gain a better understanding of mutant *KRAS* function in pancreatic cancer and discuss therapeutic strategies that target oncogenic *KRAS* signalling in this disease.

In patients, *KRAS* plays a critical role in modulating the tumor microenvironment. Furthermore, *KRAS* can control metabolic changes in PDAC cells in a variety of ways. Although previously has shown that KRAS mutation detection can be used for early diagnosis and prognosis prediction in patients, and many pathways to suppress *KRAS* effects have been proposed, there is still no single pathway that leads to effective treatment of *KRAS*-mutant PDAC. As one of the four main driver genes in PDAC (*KRAS, TP53, CDKN2A, and SMAD4*), the *KRAS* gene is a member of the RAS gene family and encodes the *KRAS* protein (21 kDa), which has GTPase activity and thus binds GTP in the activated state and GDP in the deactivated state.

Signalling pathway

Ras controls cell proliferation, differentiation, and apoptosis by activating a variety of signalling pathways, including the RAF/MEK/ERK, PI3K/AKT/mTOR, PLC/PKC, and RAL pathways. PDAC contains *KRAS* mutations at codons 12, 13, 60, and 61, which cause the *KRAS* protein to remain, activated in the absence of signal stimulation, resulting in an uncontrollable functional status. Furthermore, *KRAS* causes metabolic changes that alter the production of mitochondrial reactive oxygen species (ROS). PDAC cells develop several mechanisms to combat high ROS levels, which are harmful to tumour cells. As a result, cancer cells can reduce the cellular damage caused by ROS. *KRAS* mutation is currently thought to activate Nuclear Factor-Erythroid 2-Related Factor 2 (Nrf2) to initiate the antioxidant mechanism, which activates a number of antioxidant genes. Nrf2 has been shown to regulate over 100 genes, including NADPH regulators, drug efflux pumps, and growth factors. The inhibitor KEAP1 strictly controls Nrf2 levels by binding to Nrf2 and mediating Nrf2 ubiquitination; thus, Nrf2 levels remain low under normal conditions. According to one study, mutant *KRAS* primarily signals *via* the Mek-Erk-Jun pathway to promote Nrf2 nuclear localization and antioxidative gene expression. Initially, non-cancerous metabolic disorders were treated with selective, synthetic PPAR agonists that were clinically tested. Large pharmaceutical companies, however, abandoned the development of PPAR agonists due to concerns about their carcinogenic effects.

CONCLUSION

Nonetheless, PPAR agonists like GW501516 are still being sold illegally to athletes to improve muscle endurance *via* websites that claim a lack of evidence for harmful effects. Given the availability and uncertainty surrounding these PPAR agonists, there is an urgent need to clarify PPAR's role in carcinogenesis. Pancreatic cancer remains one of the most difficult clinical oncology problems. The majority of human pancreatic cancers are caused by a mutated *KRAS* oncogene. We have attempted to meet this challenge by developing a therapeutic platform for local and prolonged siRNA delivery. PDAC with *KRAS* mutations may represent a distinct molecular subtype of pancreatic cancer. The presence of an activated MAPK, MSI/dMMR, and kinase-fusion genes in varying proportions are the genetic hallmarks of this category. Unlike conventional PDAC, these special PDAC subtypes can be treated with specific therapeutic strategies if appropriately selected based on their individual genomic and molecular features.

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