

Review

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Seminars in Cancer Biology



Inhibition of Akt and other AGC kinases: A target for clinical cancer therapy?

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ABSTRACT

AGC kinases have been identified to contribute to cancer development and progression. Currently, most AGC inhibitors in clinical development are Akt inhibitors such as MK-2206 or GDC-0068, which are known to promote cell growth arrest and to sensitize cancer cells to radiotherapy. Response rates in clinical trials with single agent Akt inhibitors are typically low. The observed adverse events are within the expected limits for compounds inhibiting the P13K-mTOR axis. Preclinical and early clinical data for combination therapies are accumulating. Based on these data, several Akt inhibitors are about to enter phase 3 trials. Besides drugs that target Akt, p70S6K inhibitors have entered clinical development. Again, the response rates were rather low. In addition, relevant toxicities were identified, including a risk for coagulopathies with these compounds. Multi-AGC kinase inhibitors are also in early clinical development but the data is not sufficient yet to draw conclusions regarding their efficacy. More trials with isoform-specific PKC inhibitors are expected. Taken together, therapies with AGC kinase inhibitors as single agents are unlikely to meet success. However, combination therapies and a precise stratification of patients according to the activation of signaling axes may increase the probability to see relevant efficacy with these compounds. The emergence of onco-immunotherapies holds some new challenges for these agents.

1. The rationale for AGC kinase-directed therapy in clinical cancer care

AGC kinases are a subgroup of Ser/Thr protein kinases. Based on the structure of their catalytic kinase domain, kinases are related to cAMP-dependent protein kinase 1 (PKA), cGMP-dependent protein kinase (PKG) and protein kinase C (PKC), building the acronym AGC [1]. The AGC family contains 60 of the 518 humain protein kinases and 42 possess functional domains other than the kinase core, which are mostly involved in regulating kinase activity and localization [2].

Recent studies have identified around 1100 cancer drivers, both oncogenes and tumor suppressor genes. Roughly 10% of those cancer drivers correspond to protein kinases, making this group of enzymes a prime target for cancer therapy. Although some of these kinases are mutated at high frequency (> 10% in a given cancer entity), the mutation rate of most cancer drivers is low. The most common genetic aberration of protein kinases are somatic mutations, followed by copy number aberrations and gene fusions. Of the eight main classes of kinases, by far the most frequent genomic aberrations have been

identified in tyrosine kinases (TK), followed by tyrosine-like kinases (TLK) and homologues of yeast sterile 7 (STE).

Cancer driving genomic alterations of AGC kinases are less frequent. However, a number of AGC kinases have been identified to contribute to cancer development and progression, including Akt 1, Akt 3, PRKCI, PRKCZ, RPS6KB1, and SGK1 [3]. The role of those kinases in tumorigenesis and cancer progression depends on the context in which a mutation occurs. In cervical cancer for example, tumor cells only become dependent from SGK2 upon loss of p53 [4]. This has implications for the development of clinical biomarkers.

2. Predictive biomarkers in oncology

True predictive markers are able to estimate the likelihood of clinical benefit of a specific therapy in an individual. Predictive markers can be genetic by nature but markers based on RNA arrays or protein expression have been validated in the clinic as well. Examples for predictive markers in oncology include Her2 amplification as well as the expression of the estrogen and progesterone receptor in breast

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