Topics in mTOR pathway and its inhibitors

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Abstract

PI3K/AKT/mTOR is a cell signalling pathway that plays a major role in regulation of apoptosis, cell growth and cell cycle. This pathway is often deregulated in human cancers, and constitutes an interesting target for antitumor therapy. Rapamycin is an inhibitor of mTOR that has first been developed for its immunosuppressive characteristics, as a preventive treatment of graft rejection. More recently, three rapamycin analogs have been developed, resulting in interesting results in preclinical studies on cancer cell lines: temsirolimus, everolimus, and deforolimus. These molecules are being tested in clinical studies, and both temsirolimus and everolimus have demonstrated efficacy in metastatic renal cancers. In contrast, perfosin, an AKT inhibitor, did not prove to be active in clinical studies. Many ongoing studies explore next indications of these drugs, given alone or in combination with chemotherapy or with other targeted therapy. Identification of predictive factors for sensibility to treatment represents another way of research.
Picking the Point of Inhibition: A Comparative Review of PI3K/AKT/mTOR Pathway Inhibitors. Rodrigo Dienstmann, Jordi Rodon, Violeta Serra and Josep Tabernero. Rodrigo Dienstmann. The frequent activation of the PI3K/AKT/mTOR pathway in cancer, and its crucial role in cell growth and survival, has made it a much desired target for pharmacologic intervention. Following the regulatory approval of the rapamycin analogs everolimus and temsirolimus, recent years have seen an explosion in the number of phosphoinositide 3-kinase (PI3K) pathway inhibitors under clinical investigation. Mammalian target of rapamycin (mTOR) is a key downstream molecule of PI3K/Akt pathway. It integrates input signals from growth factors, nutrients and energy to regulate cell growth and proliferation via different cellular processes. Gene mutations of mTOR pathway-related proteins are very common in many carcinomas. Abnormal expression of these related proteins can result in aberrant hyperactivity of mTOR pathway. Therefore, mTOR-targeted therapy has shown promising role in the management of various cancers. This article reviewed the current status of researches on mTOR and its inhibitors in an. These results open the way for the design of direct inhibitors of protein synthesis as novel acute myeloid leukemia therapies and also for the development of second generation mTOR inhibitors (the TORKinhits). Introduction. This review focuses on the class IA PI3K/AKT and mTOR signaling pathways and on recent data concerning their role, mechanisms of activation and interactions in AML biology. General biology of the class IA PI3K and mTOR signaling pathways. Given its reported PDK2 activity, the mTORC2 complex is likely to be activated in primary AML cells and might control AKT Ser473 phosphorylation.