An Isogenic Cell Panel Identifies Compounds That Inhibit Proliferation of mTOR-Pathway Addicted Cells by Different Mechanisms

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The mTOR pathway is a critical integrator of nutrient and growth factor signaling. Once activated, mTOR promotes cell growth and proliferation. Several components of the mTOR pathway are frequently deregulated in tumors, leading to constitutive activation of the pathway and thus contribute to uncontrolled cell growth. We performed a high-throughput screen with an isogenic cell line system to identify compounds specifically inhibiting proliferation of PTEN/mTOR-pathway addicted cells. We show here the characterization and mode of action of two such compound classes. One compound class inhibits components of the PTEN/mTOR signaling pathway, such as S6 ribosomal protein phosphorylation, and leads to cyclin D3 downregulation. These compounds are not adenosine triphosphate competitive inhibitors for kinases in the pathway, nor do they require FKBP12 for activity like rapamycin. The other compound class turned out to be a farnesylation inhibitor, blocking the activity of GTPases, as well as an inducer of oxidative stress. Our results demonstrate that an isogenic cell system with few specific mutations in oncogenes and tumor suppressor genes can identify different classes of compounds selectively inhibiting proliferation of PTEN/mTOR pathway-addicted isogenic clones. The identified mechanisms are in line with the known cellular signaling networks activated by the altered oncogenes and suppressor genes in the isogenic system.

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