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ABSTRACTS

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Signaling Pathways of Survival—What Can They Teach Us?

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Background: Major signaling pathways that control cell replication are deregulated in cancer. Growth-promoting pathways show a gain of function; growth-suppressive signals suffer a loss of function. Emerging targeted cancer therapy is directed toward gain-of-function signaling pathways. Among these, the phosphoinositide 3-kinase (PI3K) pathway is the most promising.

Methods: Studies with human tumor material in cell culture and in animal model systems show that PI3K signaling is upregulated in most cancers. These studies involve gene sequencing and determining the expression and activity levels of individual signaling components.

Results: Cancer-specific somatic mutations have been identified in p110α, a catalytic subunit of class I PI3Ks. The mutations induce a gain of function in enzymatic and signaling activity and confer oncogenic properties onto the mutated protein. Most of the mutations map to three hot-spots in the coding sequence of p110α. The three other isoforms of class I PI3K, p110β, p110 γ and p110δ, do not show cancer-specific mutations but are often overexpressed in cancer. They have oncogenic potential as wild-type proteins. p110 has therefore emerged as an extremely attractive drug target, and candidate inhibitor compounds are in clinical trials. Among other components of the PI3K pathway, the TOR (target of rapamycin) kinase stands out as an important integrator of metabolic and growth-regulatory signals. The traditional TOR inhibitor, rapamycin, is being replaced by a new generation of compounds that are ATP-competitive and interfere with all known TOR activities.

Conclusions: The PI3K pathway is a prominent cancer target. New inhibitors are being introduced. They will generate novel therapeutic options for several types of cancer, including cancers of the gastrointestinal system.