Research Tools

Model System for Identifying Anti-Cancer Agents

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in a model system for the high throughput screening of compounds that interfere with Gli2 dependent tumorigenesis, thereby identifying anticancer agents.

Overview

The Hedgehog (Hh) signaling pathway is conserved in animals as diverse as fruit flies and humans. This pathway is involved in embryological development, and activation of the pathway in adult tissues has been implicated in tumorgenesis. The Hh pathway is one of the most studied signaling pathways and many of the upstream steps in the pathway are well characterized. A signal outside of the cell triggers the binding of the protein ligand sonic hedgehog (in vertebrates) to a cellular protein receptor, PTCH. This event stimulates a signal cascade resulting in the activation o f a family of transcription factors called, GLI. Gli2 appears to be the major nuclear effector of Hh signaling. Gli1 has also been implicated in genetic activation while Gli3 has been identified as a repressor of a variety of genes.

The Invention

UW-Madison researchers have identified a specific point mutation that confers added stability and activated the protein independent of upstream Hh signaling. A Gli2 protein have an S662A point mutation that interferes with binding by the ubiquitin-ligase beta-TriCP. The mutation inhibits ubiquitination of Gli2, which is the first step in degradation of the protein. Gli2 stability and half-life are increased in the host cell resulting in an increase in Gli2-dependent transcription and concomitant neoplasia and tumorigenesis. Assays using the stabilized protein can be screened to identify novel inhibitors of the Hh signaling and may be used as disease models where over expression of Gli2 or activation of the Hh pathway is indicative of a disease state.

Applications

- Provides a tool for screening for compounds that affect the Hh signaling pathway
- Provides assays to explore the mechanism of activity of compounds on the pathway

Key Benefits

- This mutant form of the protein has not been reported before
- Discloses a mechanism of activation of Gli, which has not been previously reported
- Expression of greater levels and greater activity of the mutant protein in two cell lines, HEK293 (human kidney cells) and HeLa (human cervical adenocarcinoma), as compared to the wild type protein

Stage of Development

The researchers have confirmed the mechanism of activation of the mutant protein (interruption of a specific ubiquitin ligase activity on the Gli2 protein).

Tech Fields

- Research Tools : Other research tools

For current licensing status, please contact Jennifer Gottwald at jennifer@warf.org or 608-960-9854