Blocking a protein in a critical signaling pathway could offer a new way to combat tumors

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Cancer drugs that block a cell-signaling pathway called Hedgehog have shown promise in recent years in treating patients with skin cancer, leukemia and other types of tumors. But the available treatments mostly target the same protein in the Hedgehog pathway, and tumors often develop resistance to these drugs.

Researchers at the A*STAR Institute of Molecular and Cell Biology have now discovered an alternative potential drug target that, when disrupted, completely negates the ability of cells to respond to Hedgehog signaling.

Inhibiting this protein's activity "could provide an effective way of blocking Hedgehog activity in tumor cells," says Philip Ingham, a developmental geneticist at A*STAR and the Lee Kong Chian School of Medicine in Singapore, who led the work. Plus, he adds, "using a combination of drugs against different targets should reduce the probability" of resistance developing against any particular agent.

The Hedgehog pathway is vital for cell growth and differentiation in the developing embryo, but in adult tissues its activity can lead to cancer. The two drugs vismodegib and sonidegib—both of which target a protein called Smoothened, a key component of the Hedgehog pathway—are currently approved to treat a common kind of skin cancer called basal cell carcinoma. And, while drugs directed at other targets have been pursued, still more are needed. Especially sought are drugs that act downstream of Smoothened, undermining a tumor's resistance to Smoothened-directed agents.

Along with researchers at Stanford University, USA, Ingham and his team focused on one possible target; the G-protein-coupled receptor kinase 2, or GRK2. They generated zebrafish embryos lacking a functioning copy of GRK2 and observed a complete loss of responsiveness to Hedgehog or Smoothened activity.

Previously, scientists had only partially and transiently knocked down the activity of GRK2, revealing much more subtle effects on Hedgehog signaling. "Our study emphasizes the importance of making stable transmissible mutant alleles to study gene function," Ingham says.

Ingham says he is still "puzzled" by how exactly GRK2 regulates Hedgehog activity—it was previously thought to work by chemically modifying Smoothened through a process called phosphorylation, but Ingham's team showed this probably is not the case. Ingham now suspects that GRK2 works through some other protein intermediary.

Even without understanding of the mechanistic details, Ingham is optimistic about GRK2's chances as a potential drug target. Nonetheless, "GRK2 is not specific to the Hedgehog pathway," he cautions, "so blocking its activity could cause unwanted side-effects."

More information: Zhonghua Zhao et al. An essential role for Grk2 in Hedgehog signalling downstream of Smoothened, *EMBO reports* (2016). DOI: 10.15252/embr.201541532

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