Arf6 wins the MVP award
The mevalonate pathway drives cancer metastasis and drug resistance by promoting the activation of Arf6.

The biosynthetic mevalonate pathway (MVP) produces the building blocks for a wide range of biological molecules, from cholesterol to the long-chain prenyl groups that mediate the membrane association of Ras family GTPases (1). Mutations in the tumor suppressor p53 can up-regulate the MVP, a phenomenon that enhances the invasiveness of certain breast cancer cell lines by an unknown mechanism (2). Hashimoto et al. reveal that the MVP drives cancer cell invasion by promoting the activation of the GTPase Arf6, suggesting that MVP inhibitors may be effective treatments for breast cancer patients whose tumors express high levels of Arf6 signaling components (3).

MVP components and Arf6 signaling proteins. “Thus, we hypothesized that mutant p53 and the MVP utilize Arf6 signaling to promote invasiveness,” Sabe says.

Arf6 is acylated, not prenylated, so it can’t be a direct target of the MVP or GGT-II,” Sabe explains.

Instead, the researchers thought, GGT-II might prenylate a Rab family GTPase responsible for delivering Arf6 to the plasma membrane. Hashimoto et al. found that knocking down the endosomal Rab protein Rab11b blocked the plasma membrane recruitment and activation of Arf6. Moreover, MDA-MB-231 cells lacking Rab11b were less invasive in vitro and were no longer able to metastasize when injected into nude mice, suggesting that the MVP enhances Arf6 signaling by promoting the prenylation and membrane trafficking activity of Rab11b. “But abnormal overexpression of every component of the Arf6 pathway is necessary to substantially promote invasion and metastasis,” Sabe says, explaining why MDA-MB-468 cells do not become more invasive upon MVP up-regulation.

The Arf6 pathway may also boost the drug resistance of breast cancer cells. Hashimoto et al. found that knocking down GGT-II, Rab11b, or Arf6’s downstream effector EPB41L5, increased the sensitivity of MDA-MB-231 cells to two different cytotoxic compounds. “We are very interested in understanding how Arf6 and EPB41L5 promote drug resistance,” Sabe says.

Statins, which inhibit the MVP’s rate limiting enzyme HMG-CoA reductase, have been investigated as potential anticancer drugs due to their ability to block the prenylation of Ras. Clinical trials have so far produced mixed results, but Hashimoto et al.’s data suggest that future efforts might focus on breast cancer patients whose tumors express high levels of Arf6 signaling components, and which could therefore be susceptible to a reduction in Rab11 prenylation. Indeed, the researchers found that simvastatin increased the drug sensitivity of MDA-MB-231 cells, and inhibited the cells’ ability to metastasize in vivo. “Blocking the MVP might effectively kill cancer cells that overexpress the Arf6 pathway, especially in combination with other drugs,” Sabe says. Developing this therapeutic approach could be crucial, because the researchers found that patients whose tumors expressed high levels of both MVP components and Arf6 signaling proteins showed poor long-term survival rates.

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