

Arf6 wins the MVP award

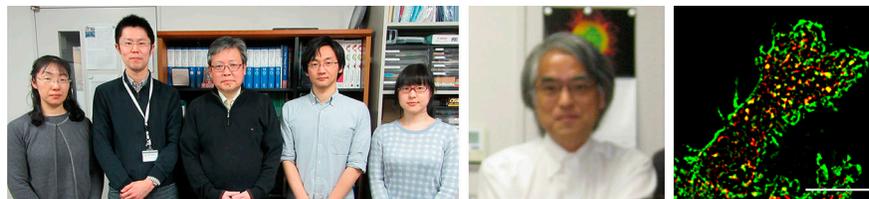
The mevalonate pathway drives cancer metastasis and drug resistance by promoting the activation of Arf6.

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).

Mutations in p53 up-regulate the MVP in both MDA-MB-231 and MDA-MB-468 breast cancer cell lines, but only MDA-MB-231 cells show an increased tendency to invade their surroundings (2). Hisataka Sabe and colleagues at Hokkaido University Graduate School of Medicine in Sapporo, Japan, noticed that MDA-MB-231 cells overexpress Arf6 and its downstream effector proteins, components of a signaling pathway that enhances cancer cell invasion and metastasis by promoting the cells' transition to a more mesenchymal phenotype (4). MDA-MB-468 cells, in contrast, do not overexpress Arf6 signaling proteins. "Thus, we hypothesized that mutant p53 and the MVP utilize Arf6 signaling to promote invasiveness," Sabe says.

Sabe and colleagues, led by assistant professor Ari Hashimoto, first determined that the cytokine TGF β 1 activates Arf6 signaling and MDA-MB-231 cell invasion through the receptor tyrosine kinase c-Met (3). But silencing mutant p53, or inhibiting the MVP, blocked Arf6 activation and invasion. Knocking down mutant p53 prevented Arf6's recruitment to the plasma membrane, a critical step in the GTPase's activation by receptor tyrosine kinases.

"Blocking the MVP might effectively kill cancer cells that overexpress the Arf6 pathway."



(Left to right) Ari Hashimoto, Tsukasa Oikawa, Shigeru Hashimoto, Yasuhito Onodera, Yukari Kado, Hisataka Sabe, and colleagues investigate how the metabolic mevalonate pathway enhances the invasiveness of some, but not all, breast cancer cell lines. The researchers find that the pathway promotes the prenylation and membrane trafficking activity of Rab11b (red), which delivers the Arf6 GTPase (green) to the plasma membrane where it can be activated to promote cancer cell invasion and drug resistance. The mevalonate pathway only enhances the invasiveness of cell lines that overexpress Arf6 signaling proteins, but patients whose tumors show up-regulation of both Arf6 and mevalonate pathway components have poor long-term survival rates.

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Hashimoto et al. found that silencing the enzyme geranylgeranyl transferase II (GGT-II) also inhibited Arf6's plasma membrane recruitment and activation. GGT-II promotes the membrane association of certain GTPases by modifying them with prenyl groups generated by the MVP.

"But 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 anti-cancer 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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