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“When a normal cell runs low on energy, it won’t divide, but in some cases, cancer cells can override the built-in shutoff. The same cellular brake helps cells and organisms adapt their glucose metabolism. I am particularly interested in understanding the molecular link between cancer and metabolism since it embodies a critical intervention point for future therapeutics.”

People with Peutz-Jeghers syndrome, a rare inherited cancer syndrome caused by a mutation in the tumor suppressor LKB1, develop gastrointestinal polyps and are predisposed to colon cancer. Currently there is no treatment for Peutz-Jeghers; patients must undergo continual surgeries to remove the polyps and tumors as they arise. During earlier work, Shaw had discovered that LKB1 activates a metabolic master switch known as AMPK. If a cell runs on empty, LKB1 turns on AMPK, which puts a damper on cell growth and proliferation. When LKB1 is absent or disabled, cells facing starvation never get the message and continue to divide. AMPK operates via the mTOR pathway, short for “mammalian target of rapamycin.” Rapamycin is a powerful immunosuppressant that binds and inactivates mTOR.

Since a loss of LKB1 results in a hyperactive mTOR signal, Shaw and his team hypothesized that rapamycin could be used to treat the tumors that arise as a result of Peutz-Jeghers. When administered to mice that had intestinal polyps because of an LKB1 mutation, rapamycin shrank their polyps and in

most cases eliminated them altogether. The researchers then wondered whether they could visualize the drug’s effectiveness using a technique called FDG-PET, which reveals the uptake of radioactively labeled glucose into cells. Normally, heart cells are the most ravenous consumers of glucose, but in patients with cancer, tumors light up. Most people assumed that polyps weren’t far enough along on the road to malignancy to be visible on an FDG-PET scan, but Shaw’s experiments revealed that the LKB1 mutation resulted in altered glucose metabolism in cells and tumors, allowing even benign LKB1 polyps to be clearly visible.

Their findings suggest that FDG-PET could be used to detect when polyps arise in people with Peutz-Jeghers syndrome, but also to monitor the therapeutic response to treatment. These findings also suggest that the subset of human lung cancers harboring alterations in the LKB1 gene may show altered glucose uptake, perhaps allowing for their early diagnosis and helping to dictate their therapeutic treatment.

For more information, please visit
salk.edu/faculty/shaw.html

Left to right:

Front row: David Shackelford, Dana Gwinn, Annabelle Mery,
Debbie Vasquez, Laurie Gerken, Reuben Shaw

Back row: Pierre-Damien Denechaud, Dan Egan,
Maria Mihaylova, Rebecca Kohnz, Jonathan Goodwin

