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“The goal of our group is to elucidate signal transduction mechanisms utilizing protein phosphorylation/dephosphorylation, ubiquitination, and sumoylation and to investigate how these processes regulate cell proliferation, growth control, and the cell cycle. Ultimately, we want to use this information to uncover how dysregulation of such posttranslational modifications is involved in cancer.”

Cell cycle checkpoints act like molecular tripwires for damaged cells, forcing them to pause and take stock. The DNA damage checkpoint, for example, is triggered by DNA damage and blocked replication—the process that copies DNA—buying time to repair damage and recover from stalled or collapsed replication forks. If not repaired, these errors can either kill a cell when it attempts to divide or lead to genomic instability and eventually cancer. A key role in this process is played by the checkpoint protein Chk1, which responds to stressful conditions induced by hypoxia, DNA damage—inducing cancer drugs, and irradiation. These same conditions set the protein up for eventual degradation, which allows the cell to resume cell cycle progression after the damage has been repaired. But just how the cellular protein degradation machinery knows that it is time to dispose of activated Chk1 had been unclear.

In their experiments, Hunter and his team discovered that activation of Chk1 exposes a so-called degron, a specific string of amino acids that attracts the attention of a protein known as Fbx6, short for F box protein 6. Fbx6, in turn, brings in an

enzyme complex that flags Chk1 proteins for degradation, allowing the cell to get rid of the activated checkpoint protein. Once Chk1 is eliminated, cells can exit the checkpoint or, in the prolonged presence of replication stress, undergo programmed cell death. Yet some cancer cells keep dividing even in the presence of irreparable damage. A closer look at some cancer cell lines resistant to camptothecin, an FDA-approved cancer drug that induces replication stress, pinpointed defects in the Chk1 destruction machinery as the underlying cause. As a result, the checkpoint tripwire stays in place longer, allowing cells to recover and press on regardless of the damage.

A better understanding of this crucial process may lead to the identification of biological markers that predict patients' responsiveness to chemotherapy drugs such as irinotecan, platinum compounds, and gemcitabine, as well as the development of new cancer drugs with fewer side effects.

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

Left to right:

Front row: Andrea Carrano, Nguyen Nguyen, Hui Ma, Jill Meisenhelder, Tony Hunter, Susie Simon, Lorena Puto, Wei Zhu, Xinde Zheng

Back row: John Brognard, Aaron Aslanian, Justin Zimmermann, Hidenori Matsuzaki, Huaiyu Sun, Mike French, Liz Baun, Jeremy Copp

