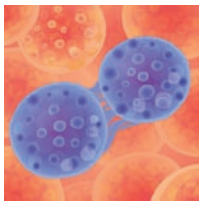
Cell Division

Major finding: *CCND1* and p53 transmitted to daughter cells in mitosis determine if cells are proliferative or quiescent.

Concept: Daughter cells utilize memory of mitogen and stress signaling to control cell-cycle entry.

Impact: Mutations that disrupt the competition between cyclin D1 and p21 may promote cancer progression.

MITOGEN AND STRESS SIGNAL MEMORY REGULATES DAUGHTER CELL PROLIFERATION



After the completion of mitosis, daughter cells can enter the next cell cycle immediately or exit to a quiescent state, but it is unknown what drives the selection between proliferative and quiescent states. Yang and colleagues used a live-cell reporter of cyclin-dependent kinase 2 (CDK2) activity to investigate the choice between cell-cycle paths. After mitosis, daughter cells could increase CDK2 activity to proliferate ($CDK2^{inc}$), or decrease CDK2 activity to enter a persistent ($CDK2^{low}$) or transient ($CDK2^{delay}$) quiescent state. MEK inhibition or removal of mitogens in mother cells suppressed cell-cycle entry in daughter cells. ERK activity was elevated in the mother cells of $CDK2^{inc}$ daughter cells, and ERK signaling promoted cyclin D–CDK4 activity in daughter cells to promote the $CDK2^{inc}$ path. However, ERK activity was not sufficient to fully predict CDK2 path selection. The DNA damage/p53 signaling pathway was investigated as a potential additional regulatory mechanism, as high levels of p53-regulated p21 are associated with cell-cycle exit. Live-cell analysis of cells with endogenously tagged p53 and p21 revealed that expression of p53 and p21 was higher even before mitosis in cells on the $CDK2^{low}$ and $CDK2^{delay}$ paths compared with the $CDK2^{inc}$ path. This indicates that, along with ERK signaling, DNA damage and p53 signaling in mother cells influence the cell-cycle decision in daughter cells. Further, DNA damage–induced p53 signaling competed with mitogen/ERK signaling in mother cells to determine the $CDK2^{inc}$ path selection. Stress and mitogen signaling originating in daughter cells then continued to regulate the path selection between $CDK2^{delay}$ and $CDK2^{low}$. Stoichiometric inhibition of cyclin D1–CDK4 activity by p21 resulted in ultrasensitive control of the retinoblastoma and E2F transcriptional programs to determine CDK2 path selection. These findings reveal a mechanism by which daughter cells undergo proliferation or quiescence based on variable mitogen and stress signals in the mother cell, and suggest that mutations affecting the competition between regulators of cyclin D1 and p21 may affect cancer progression. ■

Yang HW, Chung M, Kudo T, Meyer T. Competing memories of mitogen and p53 signalling control cell-cycle entry. Nature 2017 Sep 6 [Epub ahead of print].

Melanoma

Major finding: Talimogene laherparepvec plus pembrolizumab achieved responses in 62% of patients with melanoma.

Concept: Oncolytic virotherapy using talimogene laherparepvec increases tumor-infiltrating $CD8^+$ T-cell density.

Impact: Oncolytic virotherapy plus anti–PD-1 may be beneficial even in patients with low T-cell infiltration.

TALIMOGENE LAHERPAREPVEC ENHANCES THE EFFICACY OF PD-1 BLOCKADE

Checkpoint blockade therapies targeting PD-1 or PD-L1 achieve durable responses in a subset of patients with cancer, but tumors lacking infiltrating $CD8^+$ T cells do not respond well to checkpoint blockade, suggesting that combination immunotherapy aimed at attracting $CD8^+$ T cells to the tumor might enhance the antitumor activity of PD-1 blockade. The oncolytic virotherapy talimogene laherparepvec has been FDA approved for the treatment of melanoma and was designed to selectively replicate in tumors and to produce GM-CSF to promote antitumor immune responses. Thus, Ribas and colleagues performed a phase Ib trial evaluating the combination of talimogene laherparepvec and the anti–PD-1 antibody pembrolizumab in 21 patients with advanced melanoma. A run-in period with single-agent talimogene laherparepvec allowed for investigation of its effects on the tumor microenvironment before the commencement of combination therapy. Combination therapy did not result in increased toxicities compared to single-agent therapy. Responses were observed in 61.9% of patients, with complete responses occurring in 33.3% of patients. The talimogene laherparepvec run-in enhanced $CD8^+$ T-cell infiltration in patients who responded to combination therapy, and responses were observed even in patients who had low baseline density of $CD8^+$ T cells, lacked PD-L1 expression, or lacked the IFNγ gene expression signature (a marker of PD-L1 induction, as IFNγ stimulates PD-L1). Further, talimogene laherparepvec increased tumor-infiltrating lymphocyte density, the number of circulating T cells, and PD-L1 expression, suggesting a potential resistance mechanism that might be overcome by the addition of anti–PD-1. In addition to suggesting that combination therapy with talimogene laherparepvec plus pembrolizumab has antitumor activity in patients with advanced melanoma, these findings suggest that oncolytic virotherapy may modulate the tumor microenvironment, promoting T-cell infiltration to enhance the efficacy of PD-1 blockade. ■

Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RH, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell 2017;170:1109–1119.e10.