Breaking Advances
Highlights from Recent Cancer Literature

Skp2 as a Modulator of Rb and p53

Skp2 is an E3 ligase and Rb target that functions as an oncogene and is frequently overexpressed in cancers. Wang and colleagues analyzed mice with mutations at both *Rb* and *Skp2* and found that *Skp2* was required for pituitary tumor formation, due to apoptosis observed in the absence of Skp2. In a related paper, Lin and colleagues demonstrated that adrenal tumors arising in $Pten^{+/-}$ mice were partially blocked by loss of *Skp2*, due in this setting to induction of senescence rather than apoptosis. These findings suggest a role for *Skp2* as a therapeutic target in cancer.

Wang G, Lin HK, Chen Z, et al. Skp2 targeting suppresses tumorigenesis by Arf-p53-independent cellular senescence. Nature 2010;464:374–9.

Wang H, Bauzon F, Ji P, et al. Skp2 is required for survival of aberrantly proliferating Rb1-deficient cells and for tumorigenesis in Rb1+/– mice. Nat Genet 2010;42:83–8.

Improved Safety for Thalidomide Derivatives

Thalidomide, developed as a sedative for use during pregnancy, was found to be teratogenic, that is, to cause multiple defects in the limbs of the newborn. Although thalidomide continues to show effectiveness in the treatment of several cancers, the basis for its teratogenicity has remained unknown. Now Ito and colleagues have found that thalidomide binds cereblon, an E3 ligase that is important for limb outgrowth. Although the relationship between this mechanism and the immunomodulatory and antiangiogenic effects of thalidomide remains uncertain, these findings may make it possible to identify derivatives of thalidomide in which its teratogenic effects are diminished.

Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. Science 2010;327:1345–50.

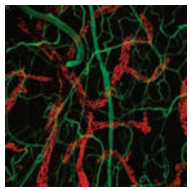
MTORC1/2 Kinase Inhibitors in Cancer Therapy

The mammalian target of rapamycin (mTOR) kinase is present in two complexes, mTORC1 and mTORC2. Allosteric inhibitors of mTORC1 (rapalogues) are already in use in the clinic, and ATP-competitive inhibitors of mTORC1/2 kinase are in clinical development. Inhibitors of mTORC kinase are more effective than rapamycin; however, their activity has been traced not to improved inhibition of mTORC2 but, surprisingly, to improved inhibition of mTORC1. The mTORC1 complex regulates translational control through two primary outputs, S6 and 4EBP1 kinases. The authors of two recent papers explain this observation. Whereas rapamycin and inhibitors of mTORC1/2 both blocked S6 kinase, inhibitors of mTORC1/2 were more efficient than rapamycin in blocking 4EBP1. Inhibitors of mTORC1/2 also showed activity in preclinical models of both leukemia and solid tumors, suggesting the promise of these agents in cancer therapy.

Hsieh AC, Costa M, Zollo O, et al. Genetic dissection of the oncogenic mTOR pathway reveals druggable addiction to translational control via 4EBP-eIF4E. Cancer Cell 2010;17:249–61.

Janes MR, Limon JJ, So L, et al. Effective and selective targeting of leukemia cells using a TORC1/2 kinase inhibitor. Nat Med 2010;16:205–13.

Integrin Regulation of Lymphatic Metastasis

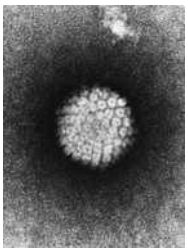


Blood and lymphatic vasculature are essential components of all organs by virtue of their responsibility for maintaining organ fluid dynamics and tissue homeostasis. Whereas both vessel systems are composed of similar lineages of endothelial cells whose crude functions include fluid and cell transport, each system also possesses distinctive physiologic properties enabling its functions in tissues. Lymphatic capillaries, unlike blood capillaries, lack pericytes and continuous basement membrane that in part contribute to increased permeability of lymphatics, as well as the association between tumor lymphangiogenesis and lymph node metastases. Garmy-Susini and colleagues have now revealed that the fibronectin-binding integrin $\alpha4\beta1$ represents a novel functional marker of proliferative lymphatic endothelium whose expression in tumor lymphatics is induced by vascular endothelial growth factor (VEGF)-C and VEGF-A. Loss of $\alpha4\beta1$ expression in mice blocked growth factor, tumor-induced lymphangiogenesis, and lymphatic metastases. These novel findings link $\alpha4\beta1$ expression in lymphatic endothelial cells with metastasis and reveal $\alpha4\beta1$ as a useful target for suppression of metastatic disease in multiple tumor types. (*Image courtesy of L. Coussens, University of California, San Francisco.*)

Garmy-Susini B, Avraamides C, Schmid M, et al. Integrin a4b1 signaling is required for lymphangiogenesis and tumor metastasis. Cancer Res 2010;70:3042–51.

Oncogenic Role for HPV16 E5

Human papillomaviruses (HPVs) have been implicated in the genesis of several human epithelial malignancies, particularly squamous cell carcinomas of the anogenital region. HPV types 16 and 18 are found in a large percentage of invasive carcinomas of the cervix. HPV16 encodes three oncogenes, E5, E6, and E7. Whereas the oncogenic actions of E6 and E7 have been well described, the mechanisms leading to



malignancy directed by E5 are not as well understood. Maufort and colleagues now report development of a transgenic mouse expressing HPV16 E5 that develops severe neoplastic cervical disease, which, when combined with either E6 or E7, leads to greater severity in the disease. This new model of HPV16-induced cervical carcinogenesis should prove useful for understanding signaling pathways regulated by E5, notably phospho-ERK and EGF receptor activity.

Maufort JP, Shai A, Pitot H, Lambert PF. A role for HPV 16 E5 in cervical carcinogenesis. Cancer Res 2010;70:2924–31.

Endothelial *Ras* and Vascular Morphogenesis

Cancer development is associated with chronic activation of blood vasculature, known as angiogenesis, in premalignant

and malignant tissues. Activation of angiogenic vasculature in premalignant tissue is characterized by increased proliferation of vascular endothelial cells and sprouting of new, immature leaky blood vessels from pre-existing vascular beds. These changes are highly coordinated and require signaling input from a diverse array of cell-extrinsic and cell-intrinsic pathways. Bajaj and colleagues have assessed how chronic activation of *H-Ras* signaling in endothelial cells avoids cell cycle arrest and senescence phenotypes common to melanocytes, fibroblasts, lymphocytes, and mammary epithelial cells when *H-Ras* is active. Instead, endothelial cells bypass *Ras*-induced senescence and demonstrate autonomous growth, enhanced survival, and compromised ability to organize into vascular structures.

Bajaj A, Zheng Q, Adam A, et al. Activation of endothelial Ras signaling bypasses senescence and causes abnormal vascular morphogenesis. Cancer Res 2010;70(9), in press.

Note: *Breaking Advances* are written by *Cancer Research* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

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Cancer Res 2010;70:3855-3856.