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MODERN PATHOLOGY

Wnt signaling in fibrosis, inflammation, and cancer

Laboratory Investigation's themed issue this month focuses on recent advances related to Wnt signaling in fibrosis, inflammation, and cancer. A primary aim of many of the articles is to increase our understanding of the translational aspect of targeting elements of the Wnt pathways for therapy. After 30 years of research on Wnt signaling and its role in development, in different cancers and in normal and cancer stem cells together with normal adult homeostasis, it is clear there remains much we do not understand. The use of novel small-molecule inhibitors of various parts of the canonical Wnt/β-catenin pathway, coupled with targeted deletions in experimental models of various Wnt ligands or deletions of the Wnt cargo protein Wntless/Evi/Gpr 177 itself, is generating surprising findings with considerable translational potential.

The first review, by Yang et al is a comprehensive examination of canonical or Wnt/β-catenin signaling in normal stem cells, cancer stem cells, and tumorigenesis. It highlights the extensive and incompletely understood crosstalk between Wnt and TGF-β/BMP signaling as well as Wnt and Hedgehog, Notch, and Hippo/YAP signaling. The review also contrasts Wnt/β-catenin inhibitors, which work either extracellularly or intracellularly. Unanswered questions regarding Wnt/β-catenin and noncanonical Wnt signaling are discussed.

The second review, by Lee *et al*, focuses solely on glioblastoma (GBM) and presents experimental evidence of an oncogenic role for aberrant Wnt/β-catenin signaling in this disease. GBM is distinctive for being the first cancer in which the Wnt cargo protein, Wntless, has been shown to increase. They discuss crosstalk of Wnt with other pathways and evidence suggesting that GBM stem cells require Wnts for maintenance and metastasis. The current use of Wnt-specific drugs in clinical trials is described.

The review by Bergmann and Distler examines Wnt/β-catenin signaling in systemic sclerosis. This group was the first to report in an animal model of systemic sclerosis that transforming growth factor-β (TGF-β) stimulated Wnt/β-catenin signaling using a p38-dependent pathway that decreased the Wnt antagonist Dkk-1. These findings demonstrate that Wnt/β-catenin signaling is required for TGF-β-mediated fibrosis. The authors discuss both the translational implications and potential limitations of sustained Wnt inhibition.

The dual roles of Wnt/β-catenin signaling in the kidney—promoting repair or facilitating progression to chronic kidney disease (CKD)—are reviewed by Zhou *et al*. They document the repertoire of Wnt ligands and their regulation in a variety of kidney diseases and present the novel hypothesis that sustained activation of Wnt/β-catenin after acute kidney injury can result in CKD. They suggest that further insight into Wnt/β-catenin signaling might lead to therapies that would either promote kidney repair or contribute to preventing progression to CKD.

Uitterdijk *et al* measured remodeling in a swine model of reperfused myocardial infarction in the presence of UM206, an antagonist of Fzd1 and Fzd2. Inhibiting Wnt/β-catenin activity reduced infarct mass and attenuated remodeling in this model, suggesting that blocking Wnt/Frizzeled interaction may improve infarct healing.

The review by Reuter *et al* focuses on Wnt-mediated regulation of allergic airway diseases such as asthma and chronic pulmonary disease (COPD). The authors highlight the roles of canonical Wnt (Wnt/β-catenin) signaling and noncanonical Wnt signaling effectors in airway inflammation and various structural changes in asthma and COPD and argue that targeting certain Wnt pathways may be options in these diseases.

The final review, by Usami *et al*., comprehensively describes Wnt signaling in cartilage development and osteoarthritis. Again, several therapeutic options for osteoarthritis have arisen from targeting either noncanonical Wnt signaling or Wnt antagonist secretion.

Tang *et al*. investigated the relationship of Klotho, an inhibitor of Wnt/β-catenin signaling, to hepatocellular carcinoma (HCC). They found that HCC patients with Klotho-expressing tumors had longer survival periods than Klotho-negative patients, and that serum levels of Klotho were higher in HCC patients. *In vitro*, increased Klotho inhibits Wnt/β-catenin, while activation is seen by knockdown of Klotho. Their work elegantly demonstrates that Klotho inhibits Wnt/β-catenin in HCC.

Using a bleomycin-induced model of pulmonary fibrosis, Andersson-Sjöland *et al* found that reactive oxygen species from endothelia contributed to the production of both Wnt3a and Wnt5a, while pericyte differentiation was altered. Further work is needed on the endothelial niche in the development of pulmonary fibrosis.

Guo *et al*. demonstrated that cigarette smoke reduces Wnt/β-catenin activity in human bronchial epithelial cells and in mouse models. They show that inflammatory

cytokines stimulated by cigarette smoke are downregulated by a β-catenin activator and enhanced by small interfering RNA knockdown of β-catenin. Their findings suggest that inhibition of Wnt/β-catenin by cigarette smoke is a key determinant of inflammatory cytokine production in the airway epithelia.

Matsushita *et al* examined the effect of deletion of nuclear hormone receptor LXRα from mesenchymal stem cells (mSCs) on Wnt/β-catenin activity. mSCs may be induced to differentiate to adipocytes. It is known that Wnt/β-catenin can regulate mSC fate and that activating Wnt/β-catenin blocks adipogenesis in these cells. The authors report that deletion of LXRα from mSCs decreases Wnt1, Wnt5a, and Wnt10b and reduces β-catenin levels, consistent with the inhibitory effect of LXRα on mSC adipogenesis being associated with Wnt/β-catenin activity.

Not all Dickkopf proteins are Wnt antagonists. Lu *et al* elegantly examined the effect of Dkk3 on adriamycin-induced dilated cardiomyopathy using both Dkk3 knockout and transgenic mouse models with overexpression of Dkk3 in the heart. They found that Dkk3 prevents development of familial dilated cardiomyopathy in mice during the compensatory stage and suggest that Dkk3 may be a therapeutic target for cardiomyopathy and heart failure.

Wnt ligands must be processed before they are secreted as active ligands. Porcupine (PORCN) is an acyl transferase that begins this processing in the Golgi. When PORCN is inhibited, Wnt ligand secretion is reduced. WNT974 is an orally bioavailable PORCN inhibitor. As reported in the final paper in this issue, Boone and colleagues investigated the effect of WNT974 on the viability of ascites cells from patients with primary ovarian cancer. They found that WNT974 enhanced the sensitivity of the ascites cells to carboplatin and that increased PORCN expression in the ascites cells led to increased sensitivity of WNT974.
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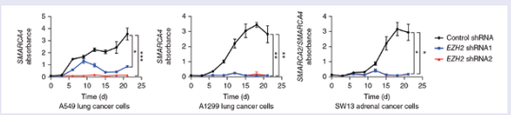
SWI/SNF mutant cancers and EZH2



As reported in *Nature Medicine*, Kim *et al* investigated mutations within the SWI/SNF chromatin remodeling subunits in order to demonstrate whether there were shared dependencies between them and the polycomb group genes. They demonstrated that a catalytic subunit (EZH2) of the polycomb repressive complex 2 (PRC2) reduced H3K27 di- and trimethylation, cell proliferation, and colony formation while not affecting control cell lines. Disparate responses were seen in cell lines containing *EZH2* gain-of-function mutations where three scored as dependent on each PRC2 subunit and many did not. Ras-pathway mutations can reduce dependence on EZH2, suggesting that that EZH2 inhibition might enhance proliferation in the setting of Ras mutation. The authors investigated a small-molecule inhibitor of EZH2 (GSK126) on SWI/SNF mutant cancer cell proliferation. All the SWI/SNF mutant lines were sensitive to EZH2 knockdown but showed different responses to the GSK126. They concluded that the nonenzymatic contribution of EZH2 should be explored in next-generation EZH2 inhibitors.

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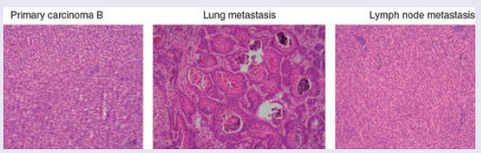
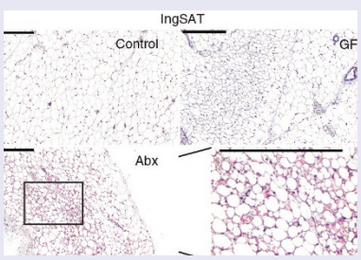
Mutational landscape and metastasis in skin cancer



In a study reported in *Nature Medicine*, McCreery *et al* investigated the processes that influence tumor heterogeneity, including the timing and route of metastases. Using genetically heterogeneous mice and whole-exome sequencing of matched benign, malignant, and metastatic skin tumors, they found that metastases disseminated synchronously from primary tumors. This suggests parallel evolution of metastases rather than via a lymph node because only one of their mouse models showed this type of linear progression. The fact that the same animal could exhibit tumors that both did and did not metastasize suggested tumor-intrinsic factors that influenced metastatic evolution. No obvious candidate metastasis driver mutations were identified in early comparative analysis, although several genes were identified as being highly expressed in metastasizing tumors. The authors went on to investigate mesenchymal-to-epithelial transition as well as mutations in *Hras* and *Kras*. They propose that their model provides a useful tool for identifying drug candidates that might be activated by *Hras* or *Kras* mutation.

Nature Medicine 2015;21:1514–1520; doi:10.1038/nm.3979

Regulation of obesity by microbiota



Suárez-Zamorano *et al*, in a study reported in *Nature Medicine*, demonstrated that development of functional white adipose tissue was promoted by depletion of microbiota. This led to improved glucose tolerance and insulin sensitivity. There was a morphological difference as well as an increase in the number of small adipocytes in white fat deposits with multilocular phenotypes. The authors showed that metabolic improvements were mediated by eosinophil infiltration, enhanced type 2 cytokine signaling, and M2 macrophage polarization in subcutaneous white fat deposits in microbiota-depleted mice. Inhibition of type-2 cytokine signaling led to a reduction in the browning effect of the subcutaneous fat and could even reverse it by recolonizing either antibiotic-treated or germ-free mice with microbes. The study provides insight into the microbiota–fat signaling axis, white adipose tissue development, and insulin sensitivity, providing scope for novel therapeutic approaches for treatment of obesity and other metabolic disorders.

Nature Medicine 2015;21:1497–1501; doi:10.1038/nm.3994

Emma Judson contributed these summaries.