Laboratory Investigation (2013) 93, 2-3

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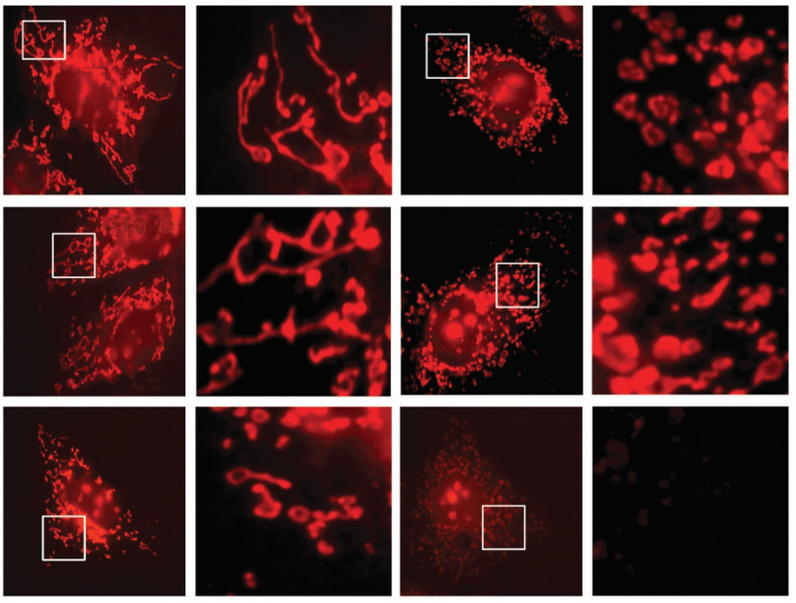
doi:10.1038/labinvest.2013.169



Mechanism of sorafenib action in hepatocellular carcinoma

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Sorafenib is a small-molecule tyrosine kinase inhibitor that targets Raf, Fms-like tyrosine kinase 3, c-Kit (CD117), p38 (mitogen-activated protein kinase), stem cell growth factor receptor 1, vascular endothelial growth factor receptors, and platelet-derived growth factor receptor-β. It has been approved by the US Food and Drug Administration for the treatment of unresectable hepatocellular carcinoma (HCC) and has been shown to improve overall survival from a median of 7.9 to 10.7 months. However, the response to sorafenib is uneven, and its mode of action in HCC is unclear. Because mitochondria are dynamic organelles and the structure of mitochondria has been associated with response to therapy, Zhao *et al* examined mitochondrial dynamics in HCC cells treated with sorafenib.

The authors discovered that treatment with sorafenib resulted in mitochondrial fragmentation, release of cytochrome c, and apoptosis. Mechanistic evaluation identified optic atrophy 1 (OPA1) as a target of sorafenib. OPA1 facilitates mitochondrial fusion, which increases cell survival during cell stress by limiting the release of cytochrome c and other pro-apoptotic factors. Interestingly, inhibition of OPA1 appeared to be independent of Raf and phosphoinositide 3–kinase–Akt signaling, which were, surprisingly, activated by sorafenib in HCC cells. Furthermore, depletion of OPA1 sensitized HCC cells to sorafenib, suggesting that cellular resistance to sorafenib may be determined by endogenous OPA1 levels in different HCC isolates. Although these experiments demonstrate that OPA1 is decreased by sorafenib, it is not clear whether OPA1 is a direct or indirect target. Additional studies are required to determine the precise mechanism by which OPA1 and mitochondrial fusion are targeted by sorafenib.

Role for connective-tissue growth factor in wound healing

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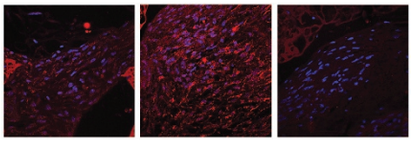
Mesenchymal stem cells (MSCs) hold great promise for treating a wide array of conditions. In previous work, Alfaro and colleagues demonstrated that MSCs expressing secreted frizzled-related protein 2 (sFRP2-MSCs) promoted granulation-tissue formation in a mouse wound healing model and in a postinfarction myocardial repair model. Because there has been speculation that MSCs are able to stimulate wound healing by release of soluble factors, Alfaro *et al*, as described in this issue, performed proteomic analysis of conditioned media from sFRP2-MSCs.

The authors found that connective-tissue growth factor (CTGF) had the highest relative abundance in comparison with conditioned media from vector control MSCs, suggesting that CTGF might play a role in sFRP2-MSC-stimulated wound healing. This hypothesis is plausible because CTGF is a secreted matricellular protein belonging to the CCN family of proteins known to bind directly to integrin receptors and heparan sulfate proteoglycans to stimulate cell signaling, resulting in regulation of many cellular processes. Interestingly, they found that



CTGF was produced early in various wound healing responses, with RNA levels reaching maximal levels at 7 days after wounding and decreasing thereafter. Blocking CTGF with antibodies resulted in less granulation tissue than in controls, confirming that CTGF plays a role in early wound healing. Because CTGF expression has generally been associated with pathological fibrosis, there has been great interest in inhibiting its action therapeutically. The authors hypothesized that prolonged exposure to CTGF results in fibrosis. Their results suggest that it may be important to stimulate CTGF early in wound healing, followed by inhibition at later time points.

Sonic Hedgehog is critical for gastric mucosal healing

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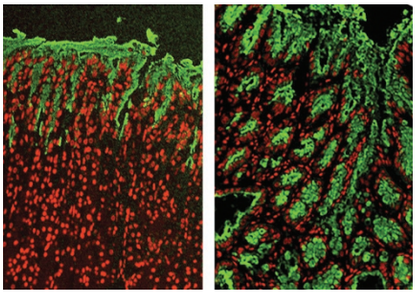
Sonic Hedgehog (Shh) is strongly expressed in gastric tissue and functions as a morphogen to drive epithelial cell differentiation. Loss of Shh is associated



with gastric inflammation. Expression of Shh at the edge of *Helicobacter pylori*–induced gastric ulcers promotes restoration of gastric architecture, implicating Shh in gastric epithelial regeneration. The gradual increase in Hedgehog signaling at the edges of gastric ulcers is accompanied by gland-cell proliferation and differentiation, which is blocked by cyclopamine, a Hedgehog signaling inhibitor. This implies a potential role of Shh as a regulator of gastric epithelial differentiation.

To dissect the complex roles of Shh in gastric ulcer repair, Xiao and colleagues developed an elegant mouse model that deletes Shh from gastric parietal cells when desired, through lineage-specific tamoxifen-inducible Cre-recombinase mediated recombination. They found that loss of Shh from parietal cells did not affect the developmental patterning of gastric epithelium, but it did impair epithelial cell differentiation in the adult stomach. Compared with controls, mice with loss of parietal cell Shh exhibited delayed gastric repair in an acetic acid–induced gastric injury model. The authors' experimental results suggest that, in addition to its role in epithelial cell differentiation, induction of Shh expression from the epithelium adjacent to the area of injury and from infiltrating Shh-expressing cells recruits macrophages and impairs neovascularization. Shh thus appears to contribute to several facets of gastric wound healing. Further studies will be required to determine the precise mechanisms responsible for the different aspects of wound healing mediated by Shh. However, these studies highlight the important roles of Shh in gastric mucosal healing.

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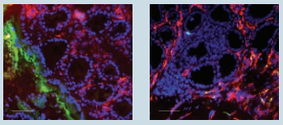
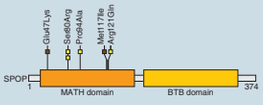
Inflammation contributes to tumor progression in colorectal adenocarcinoma



To understand the mechanisms of how myeloid cells and T-helper interleukin (IL)-17 cells promote tumorigenesis in colorectal carcinoma (CRC), Grivennikov *et al*, as described in a recent letter in *Nature,* used a genetically engineered mouse CRC model. Although early lesions (dysplasias) are driven by underlying genetic lesions such as loss of the adenomatous polyposis coli (*APC)* tumor suppressor gene, the authors also found that epithelial barrier function was compromised in early dysplastic lesions that preceded frank carcinoma. Because the epithelial barriers were compromised, gut bacteria or bacterial products were free to penetrate these lesions, eliciting a macrophage response. Tumor-associated macrophages produced IL-23, which resulted in a tumor response that produced IL-17 mediated signaling, which in turn drove tumor growth. These studies have implications for the pathogenesis and treatment of CRC.

Nature 2012;491:254–258; doi:10.1038/nature11465

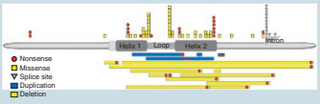
New somatic mutations in serous endometrial carcinoma



Serous endometrial carcinoma is a clinically aggressive subtype of endometrial carcinoma that has been poorly characterized at the genomic level. To learn more about the genomic landscape of serous endometrial carcinoma, Le Gallo and colleagues performed targeted exon capture and next-generation sequencing on 13 primary serous endometrial carcinomas. To prioritize their findings, they focused on genes that had validated nonsynonymous somatic mutations in more than one tumor and had not been previously reported to be mutated in serous endometrial carcinoma. *CHD4*, *SPOP*, and *FBXW7* were mutated in a high frequency of tumors. CHD4 is involved in chromatin remodeling, and SPOP and FBXW7 are involved in ubiquitin-mediated proteasomal degradation, suggesting that these two processes are involved in the pathogenesis of serous endometrial carcinoma.

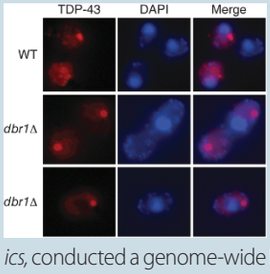
Nature Genet 2012;44:1310–1315; doi:10.1038/ng.2455

ID3 mutations in Burkitt lymphoma



A t(8;14)(q24;q32) translocation, which fuses one of three immunoglobulin loci to *MYC*, resulting in massive *MYC* expression, is the hallmark of Burkitt lymphoma, but it is insufficient to induce Burkitt lymphoma on its own. To identify genetic changes that collaborate with MYC in the pathogenesis of Burkitt lymphoma, Richter *et al*, as reported in a recent letter in *Nature Genetics,* performed integrative whole-genome, whole-exome, and transcriptome sequencing of Burkitt lymphomas. They identified inactivating mutations of *ID3* in more than 50% of molecularly defined Burkitt lymphomas, suggesting that loss of ID3 collaborates with MYC in the pathogenesis of the disorder. Functional analyses from others has shown that loss of ID3 can lead to activation of phosphoinositide 3-kinase (PI3K) signaling, which is known to collaborate with MYC activation.

Nature Genet 2012;44:1316–1320; doi:10.1038/ng.2469



Inhibition of TDP-43 toxicity in ALS

The RNA-binding protein TDP-43 has been found in cytoplasmic inclusions in spinal cord neurons of amyotrophic lateral sclerosis (ALS) patients, and mutations in *TARDBP,* which encodes TDP-43, have been identified in familial and sporadic ALS cases, suggesting that TDP-43 plays an important role in the pathogenesis of ALS. To investigate the roles of TDP-43 in the pathogenesis of ALS, Armakola *et al*, as described in a recent article in *Nature Genetics,* conducted a genome-wide loss-of-function screen to identify yeast genes that modify TDP-43 toxicity. They found that loss of *DBR1*, which encodes an RNA lariat debranching enzyme (DBR1), strongly reduces TDP-43 toxicity by acting as a decoy for TDP-43, presumably by reducing the binding of essential cellular RNAs . The authors suggest that targeting DBR1 with small-molecule inhibitors would be useful as an ALS therapy.

Nature Genet 2012;44:1302–1309; doi:10.1038/ng.2434