DRUG RESISTANCE

The stroma's contribution

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Nature, published online 4 July 2012, doi:10.1038/nature11249

Targeted therapy has profoundly improved outcomes for some cancer patients, yet the emergence of drug resistance remains a major challenge. Two studies now explore the role of tumor microenvironment in resistance to kinase inhibitors. Straussman *et al.* investigated the role of microenvironment in innate drug resistance using a coculture system in which 45 GFP-labeled human cancer cell lines were cultured alone or with 1 of 23 human stromal cell lines in the presence of 35 oncology drugs. The authors noted a particular connection between stroma-mediated resistance and targeted agents and focused their mechanistic investigations on resistance to a RAF inhibitor (PLX4720). The authors discovered that a secreted factor was responsible for resistance and used an antibody array–based analysis of secreted factors to identify HGF, a ligand for the receptor tyrosine kinase (RTK) MET. Validation experiments with recombinant HGF or with HGF-neutralizing antibodies showed that HGF was both necessary and sufficient to confer drug resistance. Wilson *et al.* performed a related matrix analysis to investigate the effects of various RTK ligands on tumor growth in response to drugs, finding that HGF enabled tumor cells to grow in the presence of various targeted drugs. Similar to Straussman *et al.*, these authors found that HGF attenuated the response of MET-expressing melanoma cells to BRAF inhibitor (PLX4032), and they further demonstrated that inhibition of MET could block HGF-induced resistance *in vitro* and *in vivo*. Together these studies suggest that understanding the impact of microenvironment on drug sensitivity could improve outcomes with targeted therapies. *AD*

IRON-SULFUR CLUSTERS

MMS to the nucleus

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Science **337**, 243–245 (2012)

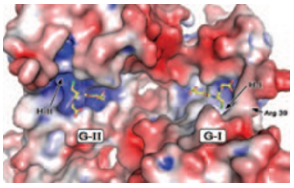
Iron-sulfur (Fe-S) clusters are produced in mitochondria and then exported via a cascade of proteins to the cytosolic iron-sulfur protein assembly (CIA) pathway, but how nascent Fe-S clusters are delivered to their target proteins remains unclear. Two studies identify MMS19 as a component of the CIA machinery that delivers Fe-S clusters to proteins that maintain genomic integrity. In parallel studies involving yeast and human cell lines, Stehling *et al.* and Gari *et al.* used proteomic and ^{55}Fe-labeling experiments to show that MMS19 binds key components of the CIA complex in the cytoplasm and acts late during Fe-S cluster biogenesis. Both groups further showed that MMS19 is required for the maturation of a subset of Fe-S proteins, all of which had roles in DNA metabolism. Stehling *et al.* demonstrated that MMS19-deficient cells were hypersensitive to genotoxic agents and had elevated DNA damage responses. Gari *et al.* showed that MMS19 deficiency lowered the stability of nuclear Fe-S target proteins in cells, and Mms19 knockout mice had an embryonic lethal phenotype. Taken together, these studies explain previously observed effects of *Mms19* mutations, provide a model for how Fe-S clusters may be transferred to subpopulations of the proteome and open the search for other similar adaptor proteins. *TLS*

PRODRUG ACTIVATION

Glutaredoxin family tree

Proc. Natl. Acad. Sci. USA **109**, 11693–11698 (2012)

BILL HUNTER



TDR1 is a thiol-dependent reductase in *Leishmania* and *Trypanosoma* parasites with a known role in redox regulation that is important for the activation of antimonial prodrugs. Fyfe *et al.* now report a crystal structure of TDR1 resolved to 2.3-Å resolution, revealing that TDR1 is a trimer with structural features reminiscent of glutaredoxins. TDR1 subunits consist of two glutathione-*S*-transferase (GST)-like domains fused by a linker with each domain containing a glutaredoxin-like subdomain. Typical GSTs are dimeric with the active site forming the dimer interface, whereas TDR1 is a trimer formed by intersubunit interactions. Each subunit contains two glutathione binding sites in which the cysteine of glutathione forms a disulfide with an active site cysteine as well as other structural features that mirror the situation in cysteine-type glutaredoxins. This observation prompted the authors to test TDR1 for various enzyme activities, including deglutathiolyzation. Biochemical and kinetic assays are consistent with TDR1 having glutaredoxin-like activity and show that it can catalyze the deglutathiolyzation of small-molecule mixed disulfides and protein-glutathione adducts. In these parasites, redox regulation has been thought to depend on trypanothione, but this unexpected activity for TDR1 raises the possibility that glutathione may also contribute to redox regulation in these organisms. *AD*

IMMUNITY

FetA gets fat

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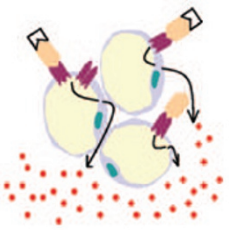
SAMIR BHATTACHARYA



Insulin sensitivity is compromised by an overproduction of proinflammatory cytokines from adipose tissue that has been stimulated by free fatty acids (FFAs). This insulin resistance is mediated through TLR4, a receptor that signals through NF-κB and is involved in innate immunity. However, FFAs do not directly interact with TLR4, so how they activate signaling downstream of the receptor is unclear. Fetuin-A (FetA), a glycoprotein secreted from the liver, is known to be upregulated by FFAs and stimulate production of inflammatory cytokines from adipocytes. Also, FetA knockout mice are protected from insulin resistance triggered by a high-fat diet. Given these clues, Pal *et al.* predicted that FetA could be an endogenous ligand for TLR4. In a first test of this theory, the authors found that serum FetA, TLR4 expression and NF-κB activation were each increased in adipocytes of obese diabetic subjects and insulin-resistant and dislipidemic mice. Similarities between *fetA* and *tlr4* knockdowns indicated that association among FFAs, FetA and TLR4 are most likely linked to lipid-mediated insulin resistance. Indeed, they found that FetA is required for FFA-induced TLR4 signaling. FFAs bound FetA in a lipid-protein overlay assay, by coimmunoprecipitation and in a yeast two-hybrid system. The FetA-TLR4 interaction is of very high affinity as shown by surface plasmon resonance. Finally, mutations that diminish the FetA-TLR4 interaction failed to produce FFA-induced insulin resistance. A ternary FFA–FetA–TLR4 complex therefore mediates lipid-mediated insulin resistance. *MB*

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