■ CANCER METABOLISM

Lipid addiction

A recent study utilizing human and mouse breast, colon and lung tumor models has shown that in response to withdrawal of therapy with sunitinib or sorafenib—which are receptor tyrosine kinase inhibitors considered to be antiangiogenic—tumors shift to lipogenesis, rapid regrowth and metastasis. Inhibiting lipogenesis with orlistat could reduce tumor regrowth, suggesting a new avenue to sensitize tumors. (*Cell Metab.* doi:10.1016/j.cmet.2014.05.022, 2014).

Agnes Noel and her colleagues performed global transcriptomic and proteomic analyses to examine the changes underlying the accelerated growth and metastasis observed after withdrawal of sunitinib or sorafenib therapy in mice bearing human MDA-MB-231 breast carcinoma xenografts. Similar changes in tumor growth have been observed in response to anti–VEGFR-2 and anti-VEGF therapies. Analysis of tumors during sunitinib or sorafenib treatment showed increased glycolysis. However, upon treatment withdrawal, lipid metabolism and regulation were altered, resulting in a boost in fatty acid, pyruvate and amino acid metabolism. Fatty acid synthase (FASN) expression increased, suggesting a shift toward *de novo* lipogenesis.

The authors then treated MDA-MB-231 or HT-29 xenografts and syngeneic mouse models with orlistat, a fatty acid synthase inhibitor, after sunitinib therapy withdrawal, and they noted reduced tumor growth and inhibited metastasis formation without effects on whole-body metabolic profiles.

Treatment with antiangiogenic therapies can lead to more aggressive tumors after therapy withdrawal. Future studies may opt to employ FASN inhibition after therapy cessation to avert such deleterious effects in patients. —*KS*

■ DIABETES

Sensitizing insulin action

Injection of recombinant fibroblast growth factor 1 (rFGF1) potently sensitizes insulin action, according to a new study by Ron Evans and his colleagues (*Nature* doi:10.1038/nature13540, 2014).

Deletion of the gene encoding FGF1 in mice is associated with insulin resistance, and agonist antibodies of FGF receptor modulate glucose homeostasis. Evans and his colleagues therefore hypothesized that treatment with rFGF1 might improve glucose metabolism. They found that acute or chronic injection of rFGF1 in genetic and dietary mouse models of type 2 diabetes normalizes blood glucose levels without affecting body weight or food intake. These effects are dependent on FGFR1 expression in adipocytes, suggesting this tissue is a key cellular target. They also show that unlike treatment with other potent insulin sensitizers, such as thiazolidinediones and FGF21, rFGF1 treatment does not result in detrimental changes in hepatic lipid profiles or bone architecture. Further, the effects of rFGF1 on metabolism were found to be independent of its mitogenic activity, suggesting the chronic benefits of rFGF1 treatment can be disassociated from any negative effects on cell proliferation, such as tumor promotion.

Although the study did not delve into mechanistic insights, the effects on glycemia were quite remarkable, and the dependence on FGFR1 suggests that development of a small-molecule activator of this receptor may be a further avenue to explore as a pharmacological agent to treat diabetes. —*RL*

■ SCHIZOPHRENIA

Risky neurodevelopment

The 15q11.2 microdeletion is among the most frequent copy number variations associated with increased risk for schizophrenia. A recent study using human induced pluripotent stem cells (iPSCs) has identified *CYFIP1*, one of four genes in this locus, to be a modulator of cell polarity and a regulator of maintenance of adherens junctions (*Cell Stem Cell* **15**, 79–91, 2014).

Yoon *et al.* established iPSC lines from three individuals with the 15q11.2 microdeletion and subsequently derived neurons from the iPSCs. The neurons displayed abnormal apical polarity and adherens junctions due to the haploinsufficiency of the *CYFIP1* gene. CYFIP1 forms a part of the actin-modulating WAVE complex, which the authors found is destabilized in the mutant cells.

Knockdown of *Cyfip1* in the neocortex of mice at embryonic day 13.5 indicated that CYFIP1 regulates apical polarity and adherens junction in radial glial stem cells. Biochemical and immunohistochemistry studies indicated that CYFIP1 is involved in cortical development through WAVE signaling.

A human genetic association study including four single nucleotide polymorphisms (SNPs) that altered expression of WAVE pathway–related genes indicated that these SNPs are not themselves risk factors. However, there is increased risk for schizophrenia depending on the genotypes at two of the SNPs, indicating an epistatic interaction.

This study suggests a biological mechanism for a common schizophrenia risk factor. However, it remains to be seen whether WAVE signaling directly regulates cortical development in humans. —*FC*

■ IMMUNOLOGY

Spreading inflammation

The NLRP3 inflammasome is an intracellular complex that activates caspase-1, resulting in the maturation and secretion of interleukin-1 (IL-1) and IL-18. Two reports by Franklin *et al.* and Baroja-Mazo *et al.* find that components of the NLRP3 inflammasome can be released from cells and can activate caspase-1 both extracellularly and in macrophages that phagocytose the secreted inflammasome proteins (*Nat. Immunol.* **15**, 727–737 and 738–748, 2014).

Caspase-1 has previously been found extracellularly in cell supernatants. The two groups independently found all of the components of the NLRP3 inflammasome in macrophage supernatants. They further showed that NLRP3 and the adaptor protein ASC could form oligomeric complexes outside of the cell that can activate caspase-1 both extracellularly and when complexes containing ASC are ingested by macrophages. The authors propose that the inflammasome is released from cells upon induction of pyroptosis, or inflammatory cell death. Bystander macrophages that take up extracellular inflammasome components can thus increase the amount of caspase-1 produced, thereby amplifying cell death and tissue damage. The findings suggest a way that inflammation might spread through tissues.

As for the disease implications of the findings, patients with cryopyrin-associated periodic syndrome (CAPS) have dysregulated IL-1 levels due to gain-of-function mutations in *NRLP3*. Baroja-Mazo *et al.* showed that during active disease, patients with CAPS had higher levels of ASC-containing complexes in their blood than healthy controls. Franklin *et al.* reported that some individuals with autoimmune disease have anti-ASC antibodies that may enhance phagocytosis of extracellular ASC complexes. These aggregates in the blood may play a role in propagating the pathology of CAPS, and possibly autoimmune diseases, by activating the intracellular NLRP3 inflammasome in macrophages that ingest the ASC complexes. —*AF*

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