DRUG RESISTANCE

In the niche

Blood **121**, 1824–1838 (2013)

Effective treatments for chronic myeloid leukemia, which is caused by the expression of the *BCR-ABL* oncogene, rely on inhibition of aberrant tyrosine kinase activity. Resistance to tyrosine kinase inhibitors (TKIs) in leukemia stem cells most likely causes relapse in patients. To understand the molecular events contributing to this resistance, Zhang *et al.* evaluate the impact of the bone marrow niche where stem cells reside. The authors found that immortalized human bone marrow–derived mesenchymal stromal cells (MSCs) protected leukemia cells from TKI-induced apoptosis. TKI treatment induced the expression of N-cadherin in leukemia cells cultured together with MSCs, and blocking N-cadherin interactions with an antibody or cyclic peptide abrogated these protective effects. Using microarrays, the authors also found evidence for activation of Wnt signaling and enriched expression of Wnt signaling pathway genes in leukemia cells treated with TKI and cultured together with MSCs. A small-molecule inhibitor of β-catenin—a key factor in the canonical Wnt pathway—increased apoptosis in TKI-treated leukemia cells. In addition, Wnt1-conditioned medium mimicked the antiapoptotic effects of MSCs on TKI-treated leukemia cells, and these protective effects were dependent on interaction between Wnt and its cellular receptor. These data indicate that N-cadherin–mediated interactions between leukemia and niche cells and increased Wnt signaling in leukemia cells promotes the survival of leukemia stem cells during TKI treatment. *AD*

CHEMICAL ECOLOGY

Caffeine buzz

Science **339**, 1202–1204 (2013)

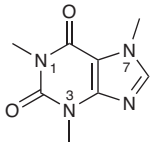
GERALDINE WRIGHT

Most flowering plants require pollinators, which enhance a plant's fecundity by mediating dispersal of pollen. Though plants produce flowers, fragrances and nectars to attract pollinators, it remains unclear whether plants use other molecular mechanisms to reinforce pollinator behavior. Wright *et al.* now show that certain plants produce caffeine, which may induce pollination loyalty in honeybees. LC/MS analysis of the floral nectar for four *Citrus* and three *Coffea* species revealed that these plants all produce caffeine independent of the diversity or concentration of sugars in their nectars. To examine whether caffeine could influence learning and memory in pollinators, the authors trained European honeybees (*Apis mellifera*) to associate floral scent with caffeine-containing sucrose solutions. High caffeine concentrations were repellent, but honeybees exposed to mock nectar dosed with submillimolar caffeine concentrations showed a conditioned response to the floral scent that persisted over days after initial exposure. Patch-clamp recordings revealed that caffeine activates adenosine receptors to influence the kinetic properties of Kenyon cells in honeybee brains, an effect similar to its mode of action in mammals. On the basis of these results, the authors propose that caffeine reinforces pollination loyalty by strengthening honeybee neuronal connections between a genera-specific floral scent and reward pathways associated with nectar sweetness. *TLS*

SYNTHETIC BIOLOGY

Make mine decaf

ACS Synth. Biol., published online 8 March 2013; doi:10.1021/sb4000146



Caffeine has a significant role in human culture, but it has become a pollutant where caffeine-containing products are processed. *Pseudomonas putida* CBB5 can degrade caffeine to xanthine, a triply demethylated analog that can be further transformed into guanine. To transfer this pathway to *Escherichia coli*, Quandt *et al.* developed a screen for functional pathways by knocking out IMP dehydrogenase—an enzyme involved in guanine metabolism—without which cells require an alternate source of xanthine for growth. This strain was not successfully rescued by direct transfer of the 'decaffeination operon' into *E. coli*, but an operon optimized for the new host did allow growth on theophylline, or 7-demethyl caffeine, with accumulation of 7-methyl xanthine from caffeine. On the basis of prior work, the authors speculated that NdmC, the nonheme iron monooxygenase thought to demethylate caffeine at the N7 position, required a glutathione S-transferase partner for function. Introduction of an appropriate homolog yielded cells that could degrade caffeine to allow growth, which the authors termed an 'addiction' to caffeine. Indeed, their calculations suggest that the exact number of caffeine molecules required to replicate a single cell closely matched the expected number of guanine molecules incorporated into RNA and DNA in a single cell. The authors further showed that the engineered bacteria can be used as a biosensor for caffeine in various drinks and suggest addition applications in environmental remediation or the recapture of caffeine for other purposes. *CG*

VIRAL INFECTION

Influenza loses to a lipid

Cell, published online 7 March 2013, doi:10.1016/j.cell.2013.02.027

Numerous host genes and signaling networks are known to be hijacked by the human influenza virus, but few metabolites are known that are similarly exploited by the virus to promote infection and proliferation. To search for lipid metabolites regulated by the influenza virus, Morita *et al.* screened a collection of polyunsaturated fatty acids (PUFAs) and PUFA-derived metabolites for their ability to modulate expression of viral genes in infected cultured cells. Several, including the DHA-derived protectin D1 (PD1), reduced viral replication in cells. PD1 was also effective against the avian influenza virus H5N1, which has the potential to cause a human pandemic. In a lipidomics analysis monitoring the amounts of PUFA-derived endogenous lipid mediators and metabolites in mice, the authors found that PD1 was reduced during infection with the more highly pathogenic viruses. This resulted from viral inhibition of the PD1 biosynthetic enzyme 12/15-lipoxygenase. PD1, when injected into infected mice, even 48 hours after infection, improved their survival, and the prolonged survival did not correlate with any anti-inflammatory action of the lipid, further suggesting direct action on viral replication. Indeed, PD1 could interfere specifically with export of viral RNA transcripts from the host nucleus to the cytoplasm by blocking their recruitment to the transporter NXF1. These results reveal how influenza subverts a nonimmune host defense mechanism and provides a rationale for possible treatment. *MB*