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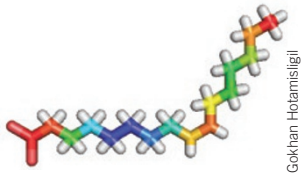
Viral replication in flux

Viruses rely on and perturb the metabolism of host cells for replication. For example, human cytomegalovirus (HMCV) is known to increase glucose uptake in infected cells. However, more detailed mechanistic information on how HCMV perturbs cellular metabolic pathways has been difficult to obtain. Munger *et al.* used liquid chromatography–tandem mass spectrometry to quantify the flux of isotopically labeled glucose and glutamine into host cell metabolites during infection. By combining kinetic information from five unique labeling experiments with measurements of absolute metabolite levels and rates of metabolite influx and efflux, the authors were able to use ordinary differential equations to model global cellular metabolism. Comparing the metabolic flux of infected and uninfected cells revealed that HCMV upregulates a wide range of metabolic pathways, with one of the largest changes being a previously unrecognized increase in fatty acid biosynthesis. Consistent with this model, inhibitors of acetyl-CoA carboxylase and fatty acid synthase, two fatty acid biosynthetic enzymes, reduced levels of HCMV replication. These inhibitors had a similar effect on influenza A replication, which suggests that the viral requirement for host fatty acid synthesis may be general. Although the mechanism by which HCMV upregulates fatty acid biosynthesis and the role of fatty acids in viral replication remain to be determined, these results provide an important first validation for the use of metabolomics to identify new drug targets. (*Nat. Biotechnol.*, published online 28 September 2008, doi:10.1038/nbt.1500) *JK*

Defining a lipokine

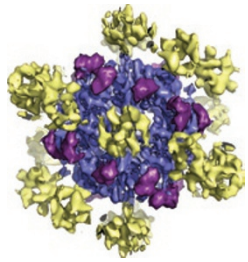


Gokhan Hotamisligil

Metabolic syndrome refers to a cluster of diseases that are defined in part by the dysregulation of lipid metabolism, but the mechanistic link between lipid biochemistry and physiology is not known. Fatty acid–binding proteins (FABPs) are lipid chaperones that regulate lipid partitioning within and between cells and serum; deficiencies in FABPs specific to adipose tissue cause systemic effects in lipid profiles. Cao *et al.* further found that mice lacking adipose FABPs are significantly less responsive to a high-fat diet than wild-type mice, which supports the idea of a privileged role for these FABPs and the lipids that they control in overall metabolism. In a search for functionally important lipids, the authors performed a high-resolution lipidomics analysis and observed a substantial increase in *de novo* lipogenesis in FABP-deficient adipose tissue, which resulted in a rise in blood C16:1n7-palmitoleate levels. Using *in vitro* and *in vivo* systems, the authors showed that palmitoleate suppresses the expression of SCD-1 (a protein involved in lipid biogenesis) in liver and, like insulin, stimulates AKT phosphorylation in muscle cells. Infusion of palmitoleate also resulted in improved insulin action and glycemic control in mice. The ability of adipocyte-derived palmitoleate to act at a distant location defines this compound as the first lipid hormone, or 'lipokine'. Although many questions remain, this result serves as an important step in understanding the molecular basis of metabolic disorders. (*Cell* **134**, 933–944, 2008) *CG*

Written by Amy Donner, Catherine Goodman, Joanne Kotz & Terry L. Sheppard

Stressing signaling



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Single-celled microorganisms, including the Gram-positive bacteria *Bacillus subtilis*, integrate various environmental stress signals at a multiprotein complex called the 'stressosome', which is assembled from RsbR, RsbS and RsbT proteins. Signals processed by the stressosome lead to changes in the expression of stress-responsive genes. Marles-Wright *et al.* now offer insight into this supramolecular complex by reporting a medium-resolution structure of the stressosome from *B. subtilis*. Single-particle cryo-electron microscopy and X-ray crystallography revealed that multiple copies of RsbR and RsbS assemble into a pseudo-icosahedral structure that binds RsbT in proximal sites and presents the N-terminal sensor domains of RsbR on the surface of the particle. Immunofluorescence localization experiments revealed that stressosomes are distributed across *B. subtilis* cells, and the RsbR-RsbS core of these complexes is persistent even after exposure to stressors. Environmental factors known to signal through the stressosome, including ethanol and high-salt conditions, lead to cooperative activation of σ^B-dependent gene expression. Based on these data, the authors suggest that peripheral RsbR domains undergo a conformation change in response to environmental signals, which leads to phosphorylation of RbsR and RbsS by RsbT. Cooperative dissociation of RsbT could then activate σ^B-dependent gene expression. Though higher resolution data will be required to test this model, the current study offers a compelling picture of how microbes may integrate multiple signaling inputs into a well-defined output response. (*Science* 322, 92–96, 2008) *TLS*

Discordant 'omics

Stable isotope labeling by amino acids in cell culture (SILAC) allows for comparison of proteomes between closely related cell populations differentially labeled with heavy or light isotopes of carbon and nitrogen. Bonaldi *et al.* report the first SILAC experiments in cultured *Drosophila melanogaster* cells and compare proteomes between cells depleted of ISWI, the catalytic subunit of several chromatin remodeling complexes, by RNA interference gene knockdown and control cells. Since homozygous mutation of ISWI in flies is lethal and knockdown in cells is tolerated, this approach offered a unique opportunity to evaluate changes in gene expression due to loss of ISWI. Accordingly, the authors report significant expression changes in ~8% of the proteome resulting from ISWI knockdown, which reflects altered abundance of nuclear chromosomal factors and other protein categories, thus indicating broad changes in cell physiology. Surprisingly, protein levels of Acf-1, an ISWI interacting factor, were significantly lowered while transcript levels remained constant. Microarray analysis of the transcriptome revealed that in unperturbed cells, transcript abundance and protein levels were poorly correlated. Microarrays comparing ISWI knockdown and normal cells further revealed that changes in the transcriptome and proteome were likewise only partially concordant. Together, these data indicate that post-transcriptional regulation significantly impacts cellular proteomes, and they also demonstrate that SILAC-based proteomics can provide information about a major fraction of the proteome expressed in a cell line. (*Mol. Cell* **31**, 762–772, 2008) *AD*