Chemical Research in Toxicology

Spotlight

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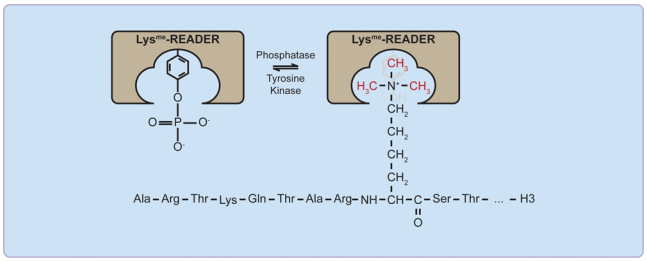
HELMINTH INFECTION IMPACTS HUMAN FERTILITY

Helminths infect over 1 billion people worldwide. These intestinal parastic worms cause systemic immunological changes, altering host susceptibility to other infectious diseases and modulating inflammatory responses. Pregnancy similarly alters the immune system, shifting from a type 1 (TH1) proinflammatory response to a type 2 (TH2) anti-inflammatory response, allowing for maternal fetal tolerance. The immune response to helminth infection therefore resembles the immunological changes that occur during pregnancy. As such, Aaron D. Blackwell and his group looked at the effect of helminth infection on host fecundity ((2015) *Science, 350,* 970−972).

The authors prospectively analyzed nine years of longitudinal data on 986 Tsimane women living in the Bolivian Amazon basin who have a natural fertility rate of nine births per woman and a 70% prevalence of helminth infection. Controlling for other fecundity-related factors, the researchers found that roundworm infection was associated with a younger age of first-time pregnancy and shorter times between subsequent pregnancies. Ultimately, women infected with roundworm were predicted to have two more children than their uninfected peers. Hookworm infection had the opposite effect and was associated with a delayed age of first pregnancy and increased intervals between subsequent pregnancies, such that women chronically infected with hookworm were projected to have three fewer children than their uninfected counterparts. While roundworms and hookworms are both helminths, they have different physiological effects. Roundworms are associated with a TH2 immune response, which resembles the immunological state of pregnancy, while hookworms induce a more pro-inflammatory, mixed TH1/TH2 response. Additionally, hookworm, but not roundworm, infection is associated with anemia and nutrient loss, which may impact fertility. The scientists suggest that roundworm infection does not increase fecundity *de novo* but suppresses responses, such as inflammation, that could impair fertility.

Abigail Druck Shudofsky

TYROSINE PHOSPHORYLATION MODULATES HISTONE−READER INTERACTIONS



Adapted from B. K. Irving-Hooper and O. Binda (2015) *Biochemistry*, DOI: 10.1021/acs.biochem.5b01223. Copyright 2015 American Chemical Society.

Post-translational modifications on histones allow tight regulation of genetic information. They serve as docking sites for histone mark readers, protein effectors that mediate gene transcription. Histone mark readers that associate with methyllysine have a structure composed of aromatic amino acids; several of these readers contain a tyrosine residue within this aromatic cage. Bronwyn Kate Irving-Hooper and Olivier Binda propose that post-translational phosphorylation of this tyrosine serves as an additional regulatory layer of reader−histone interaction ((2015) *Biochemistry*, DOI: 10.1021/acs.biochem.5b01223).

Methyllysine mark readers can distinguish between non-methylated, mono-, di, and trimethylation states based on the size of their aromatic cage. The researchers suggest that phosphorylation of the aromatic cage tyrosine sterically hinders the insertion of a methylated lysine into the cage due to the size of the phosphate moiety. In some cases, the phosphorylation prevents the association of the reader with the upper-methylated histone states due to physical obstruction. In other cases, tyrosine phosphorylation influences specificity and increases reader interactions with unmodified and lower-methylated histones. The authors suggest that tyrosine phosphorylation acts as a molecular switch of reader−histone interactions, controlling access to genetic information. Kinase activities are broadly upregulated in cancer cells. Thus, histone mark readers in those cells may be aberrantly tyrosine phosphorylated, leading to erroneous gene silencing and pathological states.

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BUNYAVIRUSES REQUIRE FUNCTIONAL POTASSIUM CHANNELS FOR PRODUCTIVE INFECTION

Bunyaviruses are negative sense RNA-viruses that are capable of infecting a wide range of humans, animals, and plants. Transmitted by arthopods and rodents, many bunyaviruses cause lethal hemorrhagic fevers in humans and widespread animal and plant disease that are economically devastating. Emerging research shows that host ion channels, which are crucial for maintaining ion homeostasis across cellular membranes, play critical roles during entry, replication, and release of multiple viruses. A team led by John N. Barr and Jamel Mankouri identified the importance of cellular potassium (K^+) channels to bunyavirus growth and infection ((2015) *J. Biol. Chem.*, DOI: 10.1074/jbc.M115.692673).

K^+ channels are instrumental in setting the resting membrane potential of a cell. The authors found that bunyaviruses regulate cellular K^+ flux by activating K^+ channels, resulting in hyperpolarization and a more negative membrane potential. The scientists discovered that bunyavirus infection was repressed by broad spectrum K^+ channel blockers, as well as by the addition of extracellular KCl, which collapsed K^+ gradients and inhibited channel activity. Viral dependence on K^+ channels was seen across invertebrate and vertebrate cell types and throughout the

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bunyavirus family. The researchers found that K^+ channels are required for an early, postentry stage of the viral lifecycle, prior to viral RNA synthesis and replication. Their pharmacological data implicated twin-pore domain K^+ (K2P) channels, specifically, as the K^+ family members required for bunyavirus infection. As K2P channels have distinct structural features, they may represent a drug target for bunyavirus treatment.
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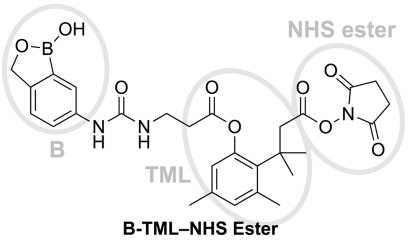
REMOVABLE BORONIC ACID CONJUGATION ALLOWS INCREASED INTRACELLULAR PROTEIN UPTAKE



B-TML–NHS Ester

Reprinted from K. A. Andersen et al. (2015) *ACS Chem. Biol.*, DOI: 10.1021/acschembio.5b00966. Copyright 2015 American Chemical Society.

Intracellular macromolecule delivery is complicated by cellular membranes. Boronic acids covalently react with 1,2- and 1,3-diols to form five- and six-membered cyclic boronic esters, respectively. This spontaneous and reversible bonding aids the delivery of boronic acid-conjugated proteins into diol-rich, glycocalyx-coated mammalian cells. While this conjugation has previously entailed irreversible protein modification, Ronald T. Raines and his team developed a method to successfully deliver native proteins into cells using boronic acid and an immolative linker ((2015) *ACS Chem. Biol.*, DOI: 10.1021/acschembio.5b00966).

The authors synthesized a three-module delivery vehicle comprising 2-hydroxymethylphenylboronic acid (benzoxaborole), a removable linker known as the trimethyl lock (TML), which is an *o*-hydroxydihydrocinnamic acid derivative, and an *N*-hydroxysuccinimide (NHS) ester for chemoselective conjugation to amino groups. This conjugate, known as B-TML-NHS ester (see figure), uses esterase activity to trigger TML lactonization and protein release from benzoxaborole. The researchers found that B-TML-NHS ester labeling was able to dramatically increase the intracellular delivery of green fluorescent protein via endosomal uptake and that the delivery vehicle was stable in the presence of serum. Further experiments confirmed that the boronic acid module was responsible for the increased mammalian cellular uptake. Importantly, B-TML-NHS ester modification is bioreversible, with native protein release activated by cellular esterases, allowing for versatility in use.
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MICRODEVICE ENABLES LONG-TERM COCULTURING OF MICROBES AND CELLS, PROVIDING AN *IN VITRO* MODEL OF HUMAN INTESTINAL DISEASE

Gut microbiota are thought to be involved in many gastrointestinal disorders; they are associated with peristalsis suppression, and their interactions with intestinal mucosa may result in chronic inflammation. Unfortunately, conventional culture systems are not capable of incorporating commensal microbes, and other experimental models are unable to include intestinal attributes such as peristalsis-like motions, villi differentiation, mucosal production, or intestinal cell specialization. As these parameters would be useful for long-term intestinal disease research, Donald E. Ingber, James J. Collins, and their team developed an experimental model which allows the stable, long-term *in vitro* coculture of microbiota and intestinal epithelial cells ((2015) *PNAS, 113,* E7−E15).

The researchers adapted a two microchannel human gut-on-a-chip device which allows the culture of human intestinal epithelial Caco-2 cells in the presence of physiological peristalsis-like motions and luminal flow. These conditions promote the formation of mucus-producing intestinal villi, which allows bacterial populations to reach sustainable steady-state levels. The authors used this intestinal-like microenvironment to stably coculture eight strains of probiotic bacteria with the Caco-2 cells. Microarray analysis indicated that Caco-2 cells cultured on the chip significantly differ in their gene expression profile compared to those cultured in a plate; the gene expression profile of the chip-cultured Caco-2 cells further differs after 72 h of coculture with the commensal microbes, closely resembling the gene expression profile of the normal human ileum. This intestine-mimicking chip device can be used to create disease models of intestinal inflammation and bacterial overgrowth and to investigate the varying factors that contribute to intestinal pathophysiology.
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