EPIGENETICS

The multiple HATs of butyrate

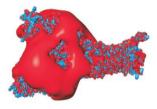
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Butyrate is a short-chain fatty acid and histone deacetylase (HDAC) inhibitor that has opposing effects on growth of normal and cancerous cells in the colon. Donohoe et al. now investigate the mechanisms underlying this paradox. The authors show that inhibition of the Warburg effect—aerobic glycolysis—blocks the inhibitory effects of low concentrations of butvrate on cell proliferation. On the basis of these findings, the authors hypothesized that butyrate is an oxidative energy source for normal cells, whereas it blocks proliferation of cancer cells because it inhibits HDACs. Inhibition of β -oxidation blocked butyrate's effects on proliferation of normal cells but not cancer cells. Inhibition of HDAC activity with trichostatin A (TSA) mimicked the activity of butyrate in cancer cells but had no effect on normal cells. Butyrate increased global histone acetylation in the context of the aerobic glycolysis but was more potent than would be predicted on the basis of its known half-maximum inhibitory concentration for target HDACs, so it might affect acetylation by additional mechanisms. Indeed, the authors showed that butyrate can increase acetylation in the presence of TSA, and metabolic flux experiments indicate butyrate can be a source for acetyl-CoA in cells and thereby stimulate histone acetyltransferase (HAT) activity. These data provide a mechanistic explanation for the butyrate paradox and demonstrate that butyrate can promote histone methylation by two mechanisms.

CHANNELS

Targets for toxins

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The intense pain produced by a bite from the Texas coral snake is due to activation of several acid-sensing ion channels (ASICs) in higher organisms, including humans. To identify potential inhibitors of ASICs, Diochot et al. performed a screen of venom from different animals and found that black mamba venom reversibly inhibited ASIC1a. Activity-guided fractionation led to identification of two 57-membered cysteine-rich peptides that the authors named mambalgin-1 and mambalgin-2. The mambalgins inhibit a number of CNSexpressed as well as sensory neuron-specific ASICs. Structural modeling showed that mambalgins resemble the structure of three-finger neurotoxins, stabilized by four disulfide bonds, consistent with the fact that cysteine-rich disulfide-bonded proteins are prevalent components of various snake venoms. Mambalgins bind the channels and modify their affinities for protons. Unlike many toxins, mambalgins do not produce physiological effects such as motor dysfunction, convulsions or death, but they do induce analgesic effects against acute and inflammatory pain, with a potency similar

to that of morphine. In a mouse model, ASIC1a and ASIC2a were required for the central analgesic effects, whereas ASIC1b was required for the peripheral analgesic effects. These results indicate that the analgesic effects of mambalgins occur via both primary nociceptors and central neurons through blockade of different ASIC subtypes, and because they do not seem to have the liabilities of other analgesics, mambalgins could prove useful clinically.

IMMUNOLOGY

A B-cell time and place

Immunity **37**, 535-548 (2012)

B cells of the immune system follow a defined path through secondary lymphoid organs that culminates in interactions with T cells and movement to inter- and outerfollicular regions of the spleen that are required for an efficient antibody response. EBI2 is a G proteincoupled receptor that guides B cells during this process. To define the molecular basis of these movements. Yi et al. monitored the activities and localizations of the biosynthetic enzymes involved in generation and metabolism of the EBI2 ligand, 7a,25-dihydrocholesterol (7α,25-OHC). Using flow cytometry, real-time PCR on follicular cells and selective ablation of follicular dendritic cells, the authors found that the two enzymes responsible for generation of 7α,25-OHC from cholesterol, CH25H and CYP7B1, along with the enzyme that degrades 7a,25-OHC, HSD3B7, are all required for a humoral immune response. In a first clue that spatial organization is important in this response, the authors find that the sequential action of CH25H and CYP7B1 do not necessarily occur within the same

cells. Also, the biosynthesis of $7\alpha,25$ -OHC is highest in outer follicular regions, including stromal cells, in the T zone and at the B-cell zone-T-cell zone (B-T) boundary, whereas degradation is greatest in the T zone. These actions mirror the sequential movement of B cells from follicles to the B-T boundary, where they are activated through to the interfollicular and outer follicular regions, suggesting that a ligand gradient guides the movements of naive and activated B cells. MB

METABOLISM

Catching cheaters

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CDC/JANICE HANEY CARR



Bacteria use quorum sensing to time the expression of certain genes, such as extracellular proteases, with population density. Within Pseudomonas aeruginosa, which uses the LasR transcriptional activator to sense the acylhomoserine lactone C12-HSL, some cells develop mutations in LasR that exempt them from responding to community signals. These 'cheaters' thus exploit the products of the community without investing effort to generate those 'public goods' and so must be kept at low enough levels such that the community can continue to flourish. Dandekar et al. speculated that the 'private goods', or intracellular pathways activated by LasR, might explain how cheaters are kept under control. For example, LasR positively regulates nucleoside hydrolase, a key degradative enzyme in adenosine catabolism. The authors observed that the proportion of cheaters in groups grown with combinations of casein and adenosine as carbon sources were lower at higher concentrations of adenosine. This effect was not observed when adenosine was replaced with glucose, the catabolism of which is not regulated by LasR. Adenosinedependent cheater suppression was observed across five of six other P. aeruginosa isolates, suggesting that quorum-sensing metabolic cheater restraint is a common mechanism. Though it is unclear whether the coregulation of public and private goods arose specifically as a mechanism to limit cheating, these results have immediate implications for the further development of antimicrobials and quorum sensing-based synthetic circuits. CG

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