PNAS Plus Significance Statements

Hypochlorite-induced structural modifications enhance the chaperone activity of human α_2-macroglobulin

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Hypochlorite is a powerful oxidant that is generated within the body by activated innate immune cells. When hypochlorite is produced, the host organism sustains collateral damage, particularly to proteins, and the accumulation of damaged (misfolded) proteins is a hallmark of inflammatory processes (e.g., in Alzheimer's disease, atherosclerosis, and arthritis). In the present study (pp. E2081–E2090), we show that the chaperone activity of human α_2-macroglobulin, a highly abundant secreted protein, is dramatically increased by hypochlorite-induced structural modifications. The data support the conclusion that α_2-macroglobulin is a unique component of the innate immune system that is posttranslationally regulated by hypochlorite to facilitate the clearance of potentially pathogenic misfolded proteins.

Two glycosylase families diffusively scan DNA using a wedge residue to probe for and identify oxidatively damaged bases

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Base excision repair, an evolutionarily conserved process responsible for the repair of most endogenous damage, is initiated by DNA glycosylases. Observation of the motion of single molecules of three bacterial glycosylases in two structural families, Fpg, Nei, and Nth, together with mutational analysis, has demonstrated that both families use a wedge residue to scan DNA for damage. Glycosylases pause during diffusion to interrogate bases and upon encountering a damage stop to evert and excise it. Moreover, we have derived (pp. E2091–E2099) a simple chemomechanical simulation that fits our data and is in agreement with ensemble studies.

Antibiotics induce redox-related physiological alterations as part of their lethality

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Substantial knowledge exists about how antibiotics interfere with core bacterial processes by binding to specific targets. Recently it has become appreciated that blocking these functions alters cellular redox state, and these perturbations may contribute to the lethality of antibiotics. In this work (pp. E2100–E2109) we explore whether antibiotic treatment of bacteria affects cellular oxidative stress and the role of such stress in antibiotic-mediated killing. We find that antibiotics dynamically alter cellular respiration and induce lethal levels of intracellular hydrogen peroxide. Antioxidants, including oxidative stress defense proteins, significantly reduce the killing by antibiotics, which is highly sensitive to the presence of molecular oxygen. These findings underscore the complex nature of antibiotic action and suggest practical approaches to enhancing our current antibiotic arsenal.

NLRX1 prevents mitochondrial induced apoptosis and enhances macrophage antiviral immunity by interacting with influenza virus PB1-F2 protein

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Apoptosis refers to the ability of a cell to undergo programmed cell death under normal physiological conditions or in response to stress signals. During infection, influenza A viruses have the capacity to induce early apoptosis of immune cells, thereby preventing them from performing their antiviral function. In this study (pp. E2110–E2119), we identified that a host innate immune sensor [NLRX1 (nucleotide-binding oligomerization domain-like receptor X1)] has the capacity to bind a small death-inducing protein from influenza A virus [PB1-F2 (polymerase basic protein 1-frame 2)] and defend immune cells against virus-driven apoptosis. This phenomenon allows the immune cells to survive longer and effectively restrict viral replication, protecting the host against the detrimental consequences of influenza.

Hypoxia-inducible factor-dependent signaling between triple-negative breast cancer cells and mesenchymal stem cells promotes macrophage recruitment

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The recruitment of host stromal cells, such as macrophages and mesenchymal stem cells (MSCs), to the primary tumor is a critical step toward cancer malignancy. We have identified signals (pp. E2120–E2129) that are exchanged between breast cancer cells (BCCs) and MSCs. This signaling increases the recruitment of both MSCs and macrophages to primary tumors and increases metastasis of BCCs to lymph nodes and lungs. Reduced oxygen levels (hypoxia) in breast cancers are associated with increased risk of metastasis and decreased patient survival. We show that hypoxia stimulates signaling between BCCs and MSCs due to the activity of hypoxia-inducible factors (HIFs). Drugs that block HIF activity prevent signaling and macrophage recruitment, which suggests that they may be useful additions to breast cancer therapy.

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Evolution of the primate trypanolytic factor APOL1

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African trypanosomes are parasites that can cause African sleeping sickness in humans. Humans and some primates, but not other mammals, have a gene called *APOL1* that protects against certain trypanosomes. Genetic variants in *APOL1* that arose in Africa are strongly associated with kidney disease in African Americans. These kidney disease-associated variants may have risen to high frequency in Africa because they can defend humans against a particularly pathogenic trypanosome. In this paper (pp. E2130–E2139), we show how APOL1 has evolved by analyzing the distribution of these variants in Africa and then elucidating the molecular mechanisms that enhance their trypanosome killing capacity. We also show that these antitrypanosomal APOL1 variants may have adverse consequences for the host.

The evolution of self-control

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Although scientists have identified surprising cognitive flexibility in animals and potentially unique features of human psychology, we know less about the selective forces that favor cognitive evolution, or the proximate biological mechanisms underlying this process. We tested 36 species in two problem-solving tasks measuring self-control and evaluated the leading hypotheses regarding how and why cognition evolves. Across species, differences in absolute (not relative) brain volume best predicted performance on these tasks. Within primates, dietary breadth also predicted cognitive performance, whereas social group size did not. These results (pp. E2140–E2148) suggest that increases in absolute brain size provided the biological foundation for evolutionary increases in self-control, and implicate species differences in feeding ecology as a potential selective pressure favoring these skills.

Syntrophic exchange in synthetic microbial communities

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Metabolic exchange between microbes is a crucial process driving the development of microbial ecosystems. The exchange of essential amino acids presents an opportunity to investigate the guiding principles underlying microbial trade in nature. In this study, we devised synthetic communities of *Escherichia coli* bacteria of increasing complexity to measure general properties enabling metabolic exchange of amino acids. We identified numerous syntrophic interactions that enable cooperative growth, which exhibited both positive and negative epistasis with increasing community complexity. Our results (pp. E2149–E2156) suggest that amino acid auxotrophy may be an evolutionarily optimizing strategy to reduce biosynthetic burden while promoting cooperative interactions between different bacteria in the microbiome.