PNAS Plus Significance Statements

Joint CO_2 and CH_4 accountability for global warming

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We develop (pp. E2865–E2874) a transparent climate debt index, termed international natural debt, which combines historical emissions of CO_2 from fossil sources and land use/forestry as well as CH_4. It covers 205 countries and is a function of emissions, lifetimes, and radiative forcings. This index can be used to assess the implications of choosing between CO_2 and CH_4 control measures and facilitates more accurate international comparisons of a range of climate-change-related phenomena, as illustrated by imposed versus experienced health impacts. Including the two most important greenhouse gases in one index shifts the basic international narrative about differential accountability for climate change.

Atg29 phosphorylation regulates coordination of the Atg17-Atg31-Atg29 complex with the Atg11 scaffold during autophagy initiation

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In eukaryotes, the Atg1 kinase complex controls both autophagy induction and the recruitment of other autophagy proteins to the phagophore assembly site (PAS); however, it remains unclear how the Atg1 kinase complex itself is targeted to the PAS or regulated. In this study, we showed (pp. E2875–E2884) that the Atg17-Atg31-Atg29 complex displayed an elongated S-shaped structure, and the interaction of this complex with Atg11 was essential for recruiting the intact Atg1 kinase complex. The phosphorylation of Atg29 is the "switch" controlling the interaction, as it is required for both binding to Atg11 and the PAS targeting of the Atg17-Atg31-Atg29 complex.

EVI1 oncoprotein interacts with a large and complex network of proteins and integrates signals through protein phosphorylation

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Although ecotropic viral integration site 1 (EVI1) oncogenic transcription factor was discovered in 1988, its molecular functions and regulations are still underexplored. Through characterization of few EVI1-interacting proteins, EVI1 was identified as dynamic modulator of transcription and chromatin remodeling. We used proteomics approaches to define the EVI1 interactome. We found associations of EVI1 with not only transcriptional regulators, but also components of signaling pathways, DNA repair, DNA recombination, and mitosis complexes. We also identified functional EVI1 phosphorylation sites modified by casein-kinase II and protein phosphatase-1α that impact EVI1 activity. Thus, our study (pp. E2885–E2894) provides critical molecular insights on EVI1 action and regulation.

Homologous recombination rescues ssDNA gaps generated by nucleotide excision repair and reduced translesion DNA synthesis in yeast G2 cells

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DNA damage challenges genome integrity. Bulky DNA lesions, which are subject to nucleotide-excision repair, induce homologous recombination (HR). However, because there is no direct generation of double-strand breaks (DSBs), the underlying mechanism has been obscure. By investigating UV-induced lesions in nonreplicating G2 cells of budding yeast, we found (E2895–E2904) that translesion DNA synthesis (TLS) and HR are redundant in repair. Using a physical assay that detects recombination between circular sister chromatids, we establish that UV-induced recombination is not attributable to DSBs but instead is associated directly with expanded ssDNA gaps and is increased in cells defective in TLS.

Asymmetric thymocyte death underlies the CD4:CD8 T-cell ratio in the adaptive immune system

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Thymocytes express a diverse repertoire of T-cell antigen receptors. Stringent selection processes eliminate autoreactive cells and guide useful thymocytes to develop into CD4 or CD8 lineages. Development always generates more CD4 than CD8 T cells, but it is not understood why. Our study (pp. E2905–E2914) used mathematics to investigate the basis of this asymmetric lineage development. Although similar numbers of CD4 and CD8 precursors start selection, our analysis revealed unexpectedly high death rates in developing thymocytes. In particular, CD8 precursors were more susceptible to death than CD4 lineage cells, and this was a major contributor to the high CD4:CD8 ratio of development.

Extracellular matrix of secondary lymphoid organs impacts on B-cell fate and survival

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We describe (pp. E2915–E2924) a unique extracellular matrix (ECM) niche in the spleen, the marginal zone (MZ), that supports a specialized population of MZ B lymphocytes that respond rapidly to blood-borne antigens and are therefore crucial for the first line of immune defense. We show, for the first time, that both the novel 3D structure and the biochemical composition of the ECM impacts on B-cell fate and survival. Similar pericellular ECM networks occur in thymus, bone marrow, and lymph node; hence, our data are likely to have broader ramifications to the fate and survival of other immune cells.

Modulation of B-cell exosome proteins by gamma herpesvirus infection

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Exosomes are released from tumor cells at high levels, and multiple studies have determined that the secreted exosomes enter recipient cells and can affect their biologic and biochemical properties. In this study (pp. E2925–E2933), the specific effects of the oncogenic herpesviruses, EBV and Kaposi sarcoma-associated virus, on the proteomes of B-cell exosomes were determined using global quantitative proteomics. The data indicate that the viruses greatly impact the protein content of exosomes with common and distinct changes induced by both viruses. It is likely that these alterations in exosome content modulate the tumor environment, potentially to enhance viral infection and promote tumorigenesis.

Pseudophosphatase STYX modulates cell-fate decisions and cell migration by spatiotemporal regulation of ERK1/2

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The role of catalytically inactive phosphatases (pseudophosphatases) remains enigmatic. Using a combination of experiments and modeling, we identified (pp. E2934–E2943) the pseudophosphatase serine/threonine/tyrosine-interacting protein (STYX) as a nuclear anchor and modulator of ERK signaling. Thereby, STYX regulates the morphology of the Golgi apparatus and its polarization in migrating cells. Consequently, STYX influences directional cell motility, a process that determines the invasive and metastatic ability of cancer cells. By controlling spatiotemporal ERK signaling, STYX plays a role in cell-fate decisions, such as PC12 cell differentiation.