[1] Neurons in the brain seldom act alone; they are highly interconnected and often fire together in a rhythmic or repetitive pattern. One such pattern is the sharp-wave ripple, in which a large group of neurons fire with extreme synchrony, then a second large group of neurons does the same and so on, one after the other at a particular tempo. These ripples occur in a brain area called the hippocampus, which is key to memory formation. The patterns are thought to facilitate communication with the neocortex, where long-term memories are later stored. One clue to their function is that some of these ripples are accelerated re-runs of brain-activity patterns that occurred during past events. For example, when an animal visits a particular spot in its cage, a specific group of neurons in the hippocampus fires in unison, creating a neural representation of that location. Later, these same neurons might participate in sharp-wave ripples — as if they were rapidly replaying snippets of that experience.

[2] An essential prerequisite for evolution by natural selection is variation among individuals in traits that affect fitness. The ability of a system to produce selectable variation, known as evolvability, thus greatly affects the rate of evolution. The immune system belongs to the fastest evolving components in mammals, yet the sources of variation in immune traits remain largely unknown. Here, we show that an important determinant of the immune system's evolvability is its organisation into interacting modules represented by different immune cell types. By profiling immune cell variation in bone marrow of 54 genetically diverse mouse strains from the Collaborative Cross, we found that variation in immune cell frequencies is polygenic and that many associated genes are involved in homeostatic balance through cell-intrinsic functions of proliferation, migration and cell death. However, we also found genes associated with the frequency of a particular cell type, which are expressed in a different cell type, exerting their effect in what we term cyto-trans. Vertebrate evolutionary record shows that genes associated in cyto-trans have faced weaker negative selection, thus increasing the robustness and hence evolvability of the immune system. This phenomenon is similarly observable in human blood. Our findings suggest that interactions between different components of the immune system provide a phenotypic space where mutations can produce variation without much detriment, underscoring the role of modularity in the evolution of complex systems.

[3] Alterations of bases in DNA constitute a major source of genomic instability. It is believed that base alterations trigger base excision repair (BER), generating DNA repair intermediates interfering with DNA replication. Here, we show that genomic uracil, a common type of base alteration, induces DNA replication stress (RS) without being processed by BER. In the absence of uracil DNA glycosylase (UNG), genomic uracil accumulates to high levels, DNA replication forks slow down, and PrimPol-mediated repriming is enhanced, generating single-stranded gaps in nascent DNA. ATR inhibition in UNG-deficient cells blocks the repair of uracil-induced gaps, increasing replication fork collapse and cell death. Notably, a subset of cancer cells upregulates UNG2 to suppress genomic uracil and limit RS, and these cancer cells are hypersensitive to co-treatment with ATR inhibitors and drugs increasing genomic uracil. These results reveal unprocessed genomic uracil as an unexpected source of RS and a targetable vulnerability of cancer cells.

[4] Threatened species are by definition species that are in need of assistance. In the absence of suitable conservation interventions, they are likely to disappear soon. There is limited understanding of how and where conservation interventions are applied globally, or how well they work. Here, using information from the International Union for Conservation of Nature Red List and other global databases, we find that for species at risk from three of the biggest drivers of biodiversity loss—habitat loss, overexploitation for international trade and invasive species—many appear to lack the appropriate types of conservation interventions. Indeed, although there has been substantial recent expansion of the protected area network, we still find that 91% of threatened species have insufficient representation of their habitats within protected areas. Conservation interventions are not implemented uniformly across different taxa and regions and, even when present, have infrequently led to substantial improvements in the status of species. For 58% of the world's threatened terrestrial species, we find conservation interventions to be notably insufficient or absent. We cannot determine whether such species are truly neglected, or whether efforts to recover them are not included in major conservation databases. If they are indeed neglected, the outlook for many of the world's threatened species is grim without more and better targeted action.

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