that the language model can extract functional meanings from protein sequences. The clustering patterns also revealed interspecies transmissibility and antigenic similarity. The correspondence of grammaticality to fitness was assessed more directly by using deep mutational scans evaluated for replication fitness (for HA and Env) or binding (for Spike). The combined model was tested against experimentally verified mutations that allow for immue escape. Scoring each amino acid residue with CSCS, the authors uncovered viral protein regions that are significantly enriched with escape potential: the head of HA for influenza, the V1/V2 hypervariable regions for HIV Env, and the receptor-binding domain (RBD) and amino-terminal domain for SARS-CoV-2 Spike.

The language of viral evolution and escape proposed by Hie *et al.* provides a powerful framework for predicting mutations that lead to viral escape. However, interesting questions remain. Further extending the natural language analogy, it is notable that individuals can interpret the same English sentence differently depending on their past experience and the fluency in the language. Similarly, immune response differs between individuals depending on factors such as past pathogenic exposures and overall "strength" of the immune system. It will be interesting to see whether the proposed approach can be adapted to provide a "personalized" view of the language of virus evolution. ■

"...immune escape will be achieved by the mutations that change the semantics of the virus while maintaining its grammaticality so that the virus will remain infectious..."

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METABOLISM

Targeting metabolism to influence aging

Inhibition of glutamine metabolism promotes death of senescent cells and improves healthy life span in mice

By **Christopher Pan** and **Jason W. Locasale**

Glutamine has a host of metabolic functions, including biosynthesis, redox maintenance, and chromatin biology. Drugs are currently available to target glutamine and related metabolism. However, the use of these compounds has been limited by finding appropriate applications because the role of glutamine in health and disease is still poorly understood. Some studies have pointed to a limited role of glutamine metabolism in vivo; others have found specific roles in critical areas of biomedical interest, such as the potentiation of immune responses in cancer. On page 265 of this issue, Johmura *et al.* (*1*) report a role for glutamine in maintaining the viability of senescent cells and the senescence-associated secretory phenotype, which may be a major factor in the aging process. Thus, targeting glutamine and associated metabolic processes could be an attractive, clinically feasible way to modify the aging process.

It was noted in the 1950s that culture of cell lines such as mouse fibroblasts and human HeLa cells requires copious amounts of glutamine, which was counter to its identification as a nonessential amino acid (*2*). Almost 70 years later, glutamine continues to be the most abundant amino acid in many formulations of cell culture media (*3*). Glutamine metabolism has many functions, including the use of the carbon atoms of glutamine to fuel the biosynthetic tricarboxylic acid (TCA) cycle in mitochondria, a process called anaplerosis (*4*). Furthermore, nearly all other functions of glutamine have been found to have some role in supporting cell proliferation. Moreover, many of the major oncogenes and tumor suppressor genes, such as *KRAS*, *MYC*, and *TP53*, can influence the activity of glutamine metabolism (*5*). Other studies have indicated that tumor glutamine metabolism and cancer phenotypes could be affected by dietary glutamine (*6*).

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Drug development efforts to target glutamine metabolism have focused on glutaminase 1 (GLS1), the enzyme that converts glutamine to glutamate and ammonia as the initial step in the breakdown of glutamine (glutaminolysis). For example, CB-839, a small molecule derived from the parent compound bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES), and the compound IACS-6274 have been administered in humans with, for example, renal cell carcinoma (*4*). Additionally, analogs and derivatives of glutamine involving 6-diazo-5-oxo-L-norleucine (DON) have been developed as agents that have pleiotropic effects on glutamine metabolism (*7*).

The role of glutamine metabolism has had its controversies. One study concluded that the use of glutamine, particularly in the TCA cycle, in vivo was less than anticipated in certain mouse cancer models, which suggested that the importance of glutamine may have been overemphasized in part owing to stronger effects in cell culture that result from high concentrations of glutamine in culture media (*8*). Nevertheless, several studies have found an essential role for glutamine in mice, including situations that have clinical application, such as combining GLS1 inhibition with immunotherapies in mice (*7*).

Aging can be defined by a progressive decline in tissue function and is a risk factor for many pathologies, including fibrosis and cancer. There is emerging evidence suggesting that cellular senescence, which has been studied in cancer, is a key biological process that links multiple pathologies of aging. Cellular senescence is characterized by a stable cell cycle arrest that is thought to occur after exposure to stress, including oxidative, mitochondrial, and replicative stress (*9*). Senescent cells secrete a myriad of proinflammatory chemokines and cytokines, called the senescence-associated secretory phenotype (SASP). SASP alters the surrounding microenvironment and may propagate tissue senescence though paracrine signaling. Senescent cells have been proposed to accumulate during aging and underlie chronic inflammation mediated by SASP, eventually leading to tissue dysfunc-

tion and the onset of various age-associated pathologies. Recent observations in mice support the idea that removal of senescent cells can extend healthy life span (*10*, *11*). These findings have led to the exploration of pharmacological approaches to induce selective death in senescent cells (senolysis).

Although it has been found that metabolism can influence cellular senescence, a general understanding of the links between metabolism, senescence, and aging is still in its early stages (*12*). Johmura *et al*. reveal that glutamine metabolism may contribute to the pathogenesis of age-related disorders (see the figure). They found that *GLS1* expression was up-regulated in multiple cell types in response to diverse senescent stimuli, and its depletion induced senolysis and improved various age-associated organ dysfunctions in mice. As a possible mechanism, the authors present evidence that senescent cells utilize glutamine to neutralize the intracellular acidosis that results from senescence-associated lysosomal dysfunction. Indeed, supplementation of ammonia could ablate the senolytic activity of GLS1 inhibition. A number of interpretations are consistent with this finding, including the anabolic functions of ammonia that could then couple to the activity of the TCA cycle. More analysis of metabolic pathway activity in the presence of ammonia and supplementation with other nutrients might address this. These possibilities could be separate or interconnected metabolic mechanisms from those that involve nicotinamide adenine dinucleotide (NAD^+), which along with mitochondrial metabolism are perhaps the most studied molecular features associated with aging (*13*). Given the pleotropic roles of glutamine metabolism, more work is needed to better define the metabolic requirements of senescent cells.

The general molecular traits of senescent cells and their contribution to aging and related diseases remain open questions (*14*). The identification of GLS1 as a senolytic target confirms metabolism as a major regulator of aging, thus providing some rationale for how therapeutics that target metabolism might achieve specificity for senescent cells as anti-aging agents. GLS1 is an attractive target for anti-aging therapies because clinical studies for cancer indications have so far established safety (*4*). Much attention has been focused on the use of dietary supplementation or possibly metformin or rapamycin use to manipulate aging. These efforts have included increasing NAD^+ concentrations and altering mitochondrial metabolism, which, although promising, may not be the entire picture (*13*). The findings of Johmura *et al*. suggest a complementary strategy, although more research is needed. ■

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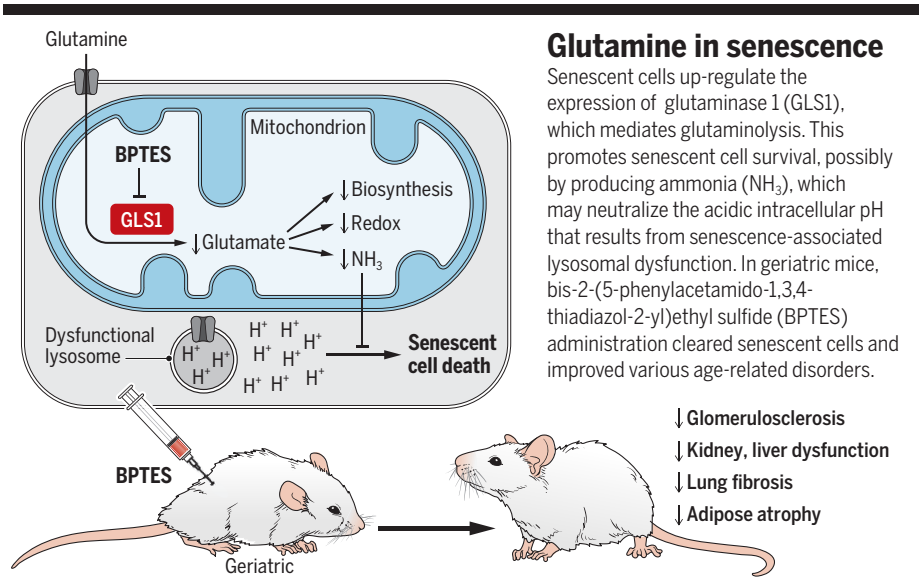

Glutamine in senescence

Senescent cells up-regulate the expression of glutaminase 1 (GLS1), which mediates glutaminolysis. This promotes senescent cell survival, possibly by producing ammonia (NH_3), which may neutralize the acidic intracellular pH that results from senescence-associated lysosomal dysfunction. In geriatric mice, bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES) administration cleared senescent cells and improved various age-related disorders.

GRAPHIC: KELLIE HOLOSKI/*SCIENCE*

CULTURAL EVOLUTION

Behavioral convergence in humans and animals

Local ecology combines with culture to produce behavioral variation in hunter-gatherers

By **Kim Hill** *and* **Robert Boyd**

Over the 20th century, the social sciences developed without taking much notice of humans' nature as products of evolution. In the 1970s this attitude was challenged by behavioral biologists (*1*, *2*) who asserted that general principles concerning the behavior of life forms must also be relevant to understanding human behavior. They argued that because human cognition and emotions had evolved by natural selection, these behavior-generating mechanisms should generally shape behavior so that it maximizes biological fitness. Not all social scientists agreed. Cultural anthropologists, in particular, were mostly aghast at the rigidly scientific and overtly biological nature of this perspective, viewing it as blatantly flawed (*3*). They claimed that differences between and within human societies were mainly due to variant cultural belief systems. On page 292 of this issue, Barsbai *et al*. (*4*) show that adaptation to local ecological conditions is an important determinant of variation in human behavior in traditional societies.

The sample analyzed by Barsbai *et al*. consists of 339 hunter-gatherer societies that are most appropriate for comparison because their members' lives and livelihoods are intimately constrained by the natural world. The authors show that variation in hunter-gatherer patterns for 15 behavioral variables statistically converges on the same characteristics that are most common in birds and mammals in the same local regions of the world. These traits include diet composition, mobility patterns, paternal invest-

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