ARCHAEOCHEMISTRY

Raising a glass

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In 2010, a collection of intact ~170-year-old champagne bottles was recovered from a shipwreck in the Baltic Sea near the southwestern coast of Finland. Jeandet *et al.* now report the application of analytical techniques to probe the chemical composition of these sea-aged champagnes, providing a molecular view into their tasting profiles and potential insights into early-nineteenth-century winemaking. The authors profiled the metal ion, sugar and metabolite contents of three recovered bottles of Veuve Clicquot Ponsardin (VCP) and three modern VCP champagnes. Inductively coupled plasma atomic emission spectrometry (ICP-AES) and sector field mass spectrometry (ICP-sfMS) revealed high concentrations of the transition-metal ions iron and copper, as well as substantially higher sodium, chloride and bromide ion concentrations, in the recovered wines relative to modern champagnes. The authors excluded seawater as the source of these elevated ion concentrations and instead suggest that the ion composition derives from winemaking processes of the time. The Baltic samples had lower alcohol concentrations (9.5% v/v) relative to modern averages (~12%), but were substantially sweeter, featuring sugar contents of ~140 g/L. The sugar composition and the identification of 5-hydroxymethylfurfural, revealed by NMR, were consistent with supplementation of the wine with grape syrup that had been heat concentrated. The recovered champagnes showed no visible bubbles in the glass, because of loss of CO_2 over time, but expert tasters detected effervescence consistent with residual CO_2 in the sub-gram-per-liter range. Finally, metabolomics profiling of the wines by Fourier-transform ion cyclotron resonance mass spectrometry (FTICRMS) and aroma analysis by GC-MS revealed molecular profiles that established that the wines were barreled in oak and that were consistent with tasting notes describing the champagne as having 'animal' and 'cheesy' notes, which mellowed upon air oxidation to more palatable 'smoky' and 'leathery' flavors. Taken together, the results provide molecular and oenological insights into these recovered champagnes and have inspired conversations about optimal storage conditions for these celebratory libations. *TLS*

PROTEIN STRUCTURE/FOLDING

Shape your duty

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Cytochrome *c* (cytc) has a central role in electron transport, but it can also have a proapoptotic role by interacting with membrane cardiolipin (cdl) and acting as a peroxidase. The conformational landscape of cytc is large, varying in both degree of extension and oligomeric state. To determine the function of particular conformers, Paul *et al.* have characterized the interaction of single cytc molecules with cdl. Two types of cytc, mammalian (m-cytc) and yeast (y-cytc), were studied. The authors observed that cdl binding changes the conformation of both m-cytc and y-cytc, although the yeast protein is perturbed to a greater extent. Interaction with cdl stimulates m-cytc peroxidase activity, but it suppresses that of y-cytc. Fluorescence correlation spectroscopy was used to follow conformational fluctuations between three states—N (compact), E (extended) and O (oligomeric)—as a function of cdl concentration. For m-cytc, increased cdl prompted a switch from the N to the E state, whereas for y-cytc, cdl leads to a large population of O. In both cases, the abundance of the E state is correlated with peroxidase activity. Whereas in m-cytc cdl induces formation of E (via partial unfolding) to activate the peroxidase, in y-cytc, cdl decreases conformational stability and drives the protein into an inactive oligomer. Computational analysis of the stability of m-cytc and y-cytc shows that although their cores are superimposable, their surface residues have regional variations, with y-cytc containing one positively and one negatively charged cluster compared to m-cytc's more even surface charge distribution. This is reflected in greater root mean square fluctuations (RMSF) of y-cytc relative to m-cytc. Thus, the nonuniform response of cytc from different species to cdl can be attributed to the effect of surface residues and their impact on folding landscape. *AKE*

PROTEOSTASIS

Found in translation

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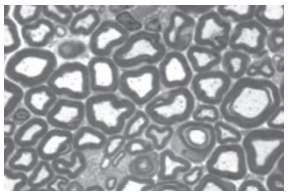

SCIENCE

The accumulation of unfolded proteins triggers the unfolded protein response (UPR), which incorporates a more global stress response, the integrated stress response (ISR). The ISR is triggered by phosphorylation of the α subunit of translation initiation factor 2, inhibiting eIF2B, the guanine nucleotide exchange factor (GEF) for the eIF2 complex. The ISR thereby restores proteostasis by globally attenuating translation, mitigating the risk of proteotoxicity. Guanabenz (GBZ) and ISRIB are two small molecules that have been used to probe the ISR pathway. GBZ increases levels of phosphorylated eIF2α by inhibiting the regulatory subunit, PPP1R15A, of the eIF2α phosphatase, thereby delaying translation recovery and protecting cells from otherwise lethal proteotoxicity. ISRIB potently reverses the effects of eIF2α phosphorylation, but its precise target was not known. Because GBZ also targets the α2-adrenergic receptor, its utility as a therapeutic or as a specific eIF2α phosphatase probe is limited. Das *et al.* therefore synthesized a GBZ derivative, Sephin1, with the same selectivity and activity but without off-target liability. Through this unique targeting of the phosphatase regulatory subunit, these authors found that Sephin1 could prevent the molecular, morphological and motor defects in mouse models of two protein-misfolding diseases, Charcot-Marie-Tooth disease type 1B (CMT-1B) and amyotrophic lateral sclerosis (ALS). To define ISRIB's target, Sekine *et al.* isolated ISRIB-resistant cell lines and looked for mutations within eIF2B and eIF2, as they had biochemical evidence that ISRIB counteracts the effects of eIF2α phosphorylation on translation at the level of GEF activity by eIF2B. The ISRIB-resistant mutations all affected the delta subunit of eIF2B, which fits the biochemical observations of Sidrauski *et al.* These studies highlight the druggability of the ISR and utility of its modifiers as potential therapeutics and as probes. *MB*