An ancient E2/E3 independent Ubl conjugation mechanism protects the proteome under oxidative stress

Ubiquitin related modifier-1 (Urm1) is a Ubiquitin-like (Ubl) protein that is well known for its role as a sulfur carrier in thiolation of tRNAs. Urm1 is also known to conjugate to substates like Ubiquitin but in response to oxidative stress. Ubiquitin-like protein conjugation by Urm1 was discovered and was termed as Urmylation by the Nobel Laureate Yoshinori Ohsumi & his team in 2000. Uba4 (Ubiquitin activating enzyme 4), the E1 enzyme for Urm1, activates and thiocarboxylates the Urm1. However, unlike Ubiquitination, the specific E2 / E3 enzymes and the specific mechanism and function of conjugation by Urm1 (Urmylation) was unknown. There was a long-standing question if Urmylation even existed and if so, what would be the conjugation mechanism and function. Our research answers them. The structural and molecular insights of the Urm1 activation was extensively studied and was previously published in The EMBO Journal in 2020 (Link 1) by the team.

PhD student Keerthiraju E Ravichandran along with the team members have now deciphered the function and mechanism of Urmylation. The ground-breaking results were recently published in The EMBO Journal (Link 2). In brief, the recent findings provide an advancement in Ubiquitin field providing substantial evidence of an E2/E3 independent Ubl conjugation. Urmylation is independent of E2/E3 enzymes and Urm1 can be conjugated to lysine, serine, or threonine on the substrates. The startling discovery is that the Urmylation is now found to be a critical protection mechanism of proteins in response to oxidative stress. In brief, when the cells undergo oxidative stress, and proteins are oxidised, Urm1 finds the proteins and shields the proteins by giving its sulfur on to the cysteine and conjugate to the lysine, serine, or threonine of the substrates. This mechanism of shielding the cysteine by an extra sulfur moiety is termed Persulfidation and it is known to be an evolutionary conserved constitutive protection mechanism against Oxidative stress. Until now, persulfidation was thought to be carried out by hydrogen sulfide, a gaseous molecule. But our current study shows that Urm1 can do that precisely on certain cysteines of a protein that are important than the other ones. Whereas hydrogen sulfide could do that for all cysteines and that could alter the cellular function. Recent research shows that levels of the persulfided protein decreases with age. Maintaining the persulfidation levels could be the next big thing for ageing. We believe that Urm1 based therapeutics could play a significant role in anti-aging.

Last but not least, the newly obtained knowledge was used to re-engineer known model proteins for new biotechnological application – for this reason, the lead authors also filed a European patent application with the excellent support of the University tech-transfer office CITTRU (Link 3)

For official press release of the research findings (Link 4)

Link 1: https://www.embopress.org/doi/full/10.15252/embj.2020105087

Link 2: https://www.embopress.org/doi/full/10.15252/embj.2022111318

Link 3: https://cittru.uj.edu.pl/

Link 4: https://mcb.uj.edu.pl/en_GB/glowna/aktualnosci/-/journal_content/56_INSTANCE_vciMmSW1J8Fa/26904801/151514428

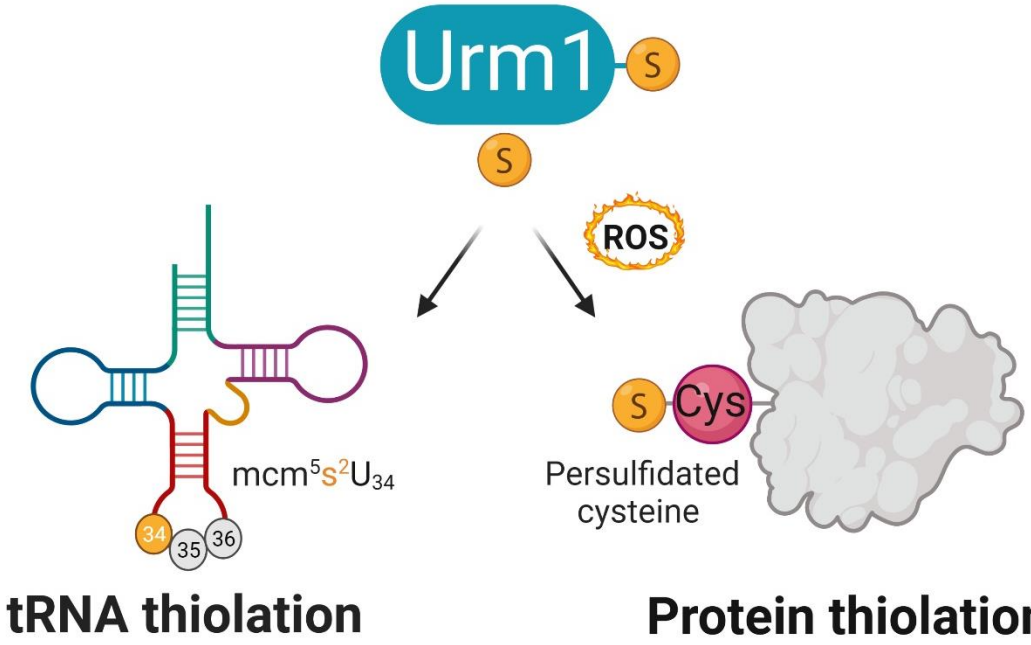

Figure caption: Urm1 can deliver sulfur to certain tRNAs and proteins. The Urm1-mediated tRNA thiolation requires additional downstream enzymes, but the persulfidation of cysteines by Urm1 is directly catalysed by an UBL-like conjugation reaction that is triggered by oxidative stress.