



Identification of the E3 ligase that ubiquitinates frataxin

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Scientific summary

Understanding whether and how frataxin is normally degraded might provide insights on possible strategies aimed at preventing frataxin degradation in FRDA patients, thus allowing frataxin accumulation and increasing frataxin bioavailability. We observed that frataxin is degraded via the ubiquitin-proteasome system and that by preventing the degradation process, frataxin levels in fact rise in FRDA cells. We also identified the lysine responsible for ubiquitination. In fact, a frataxin lacking the critical lysine cannot be ubiquitinated and has a longer half life. We now plan to identify the E3 ligase(s) that interacts with frataxin and mediates frataxin ubiquitination. This information should reveal new potential pharmacological targets for FRDA.

Lay summary

FRDA is caused by the low levels of the protein frataxin in cells of affected individuals, due to scarce production. Since normally all proteins are constantly produced and degraded, one way to possibly increase frataxin levels is to slow down its degradation. We therefore started to understand the mechanisms by which frataxin is degraded in human cells. The aim of this project is to refine our understanding of the modalities of frataxin degradation and to further elucidate the molecular mechanisms. This information could be instrumental in developing new therapeutic approaches focused on preventing frataxin degradation.

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