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Grant Title: Hereditary Glycosylation defect due to failure to protect a sensitive enzyme

Abstract

Life relies on an intricate network of chemical reactions catalyzed by enzymes. Yet, enzymes sometimes make mistakes that might lead to their inactivation and the need for replacement. We discovered an enzyme that produces a metabolite that rescues another enzyme from inactivation by regenerating the enzyme's cofactor in its catalytic pocket. We used a combination of genetic, biochemical and mass-spectrometrical approaches both *in vitro* and *in vivo* to demonstrate that the inability to produce sufficient amounts of this 'enzyme-rescue metabolite' leads to defects in the synthesis of specific glycans crucial for skeletal development, providing a mechanism for the pathogenesis of a rare skeletal dysplasia. The existence of an enzyme-rescue metabolite represents an unexpected mechanism to maintain the activity of an enzyme in a cellular context where other ways to achieve this are lacking. Defects in similar protective layers might contribute to metabolic changes in other diseases that cannot be explained with common concepts in metabolic biochemistry.