P019 Prolyl hydroxylases as regulators of cell metabolism

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Cellular response to oxygen depletion is mediated by *Hypoxia Inducible Factor* (HIF), whose degradation is regulated by prolyl hydroxylation by *EglN* family members. *EglN* activity depends on the availability of molecular oxygen, thus constituting the oxygen sensing system in the cell. However, *EglN* proteins have recently been shown to respond to stimuli other than oxygen, such as α-ketoglutarate, succinate or fumarate, as illustrated by the pseudo-hypoxic response in *SDH*- or *FH*-deficient cells. Moreover, HIF is not the sole *EglN* effector, suggesting that *EglN* proteins have functions that extend beyond oxygen sensing. Currently we are investigating the role of *EglN* proteins in the cellular response to amino acid deprivation, a process regulated by *mammalian target of rapamycin* (mTOR) protein. α-Ketoglutarate is a limiting co-substrate for EglN activity during normoxia. We show that cellular α-ketoglutarate levels decrease upon amino acid depletion, thus compromising not only mTOR, but also *EglN* activities. By artificially increasing α-ketoglutarate levels inside the cell using a cell membrane-permeable α-ketoglutarate derivative, TαKG, we restored both *EglN* and mTOR activities. Increased α-ketoglutarate levels did not cause an increase in cellular ATP, indicating that re-activation of mTOR is not due to a bioenergetic effect of α-ketoglutarate. Interestingly, TαKG-mediated mTOR re-activation was abolished by using EglN inhibitors. *EglN* proteins could thus constitute a sensing mechanism for amino acid availability, through a cellular signalling pathway which could involve α-ketoglutarate, *EglN* and mTOR.