Dissertation

Kim Jasmin Lapacz

Abstract

AK2 has recently been discovered as a non-canonical substrate of the MIA40 disulfide relay system. Its stability is subject to regulation through processing events mediated by the dipeptidyl peptidases DPP8 and DPP9, which target AK2 for proteasomal degradation via its processed N-terminus. Nevertheless, the precise mechanisms governing AK2's degradation and additional factors involved in this process have yet to be elucidated. This study reveals that the cytosolic degradation of AK2 is mediated by Inhibitors of Apoptosis (IAPs), a class of E3 ligases that interacts with specific target proteins through their IAP-binding motif (IBM). We have identified an IBM at the very end of AK2's novel N-terminus, which becomes exposed due to processing by DPP8 and DPP9. N-terminal acetylation mediated by the N-acetyltransferase NatA prevents this interaction with IAPs, stabilizing AK2 in the cytosol and therefore adding another complexity to the regulation of cytosolic levels of AK2. Furthermore, we have explored a potential redundancy of AK2 and its cytosolic isozyme AK1. In yeast as a lower eukaryote, only one adenylate kinase (Adk) is present, dually localizing to the cytosol and the IMS. Our findings indicate that the presence of one of the two adenylate kinases AK1 and AK2 is indeed sufficient to buffer any disturbances in cellular metabolism and beyond. To understand the necessity of both, AK1 and AK2, in human cells, it was focussed on the unique characteristics of each of the adenylate kinases revealing the disulfide bridge of AK2 formed during import to have a stabilizing function in vivo.