

P012 Coordinated deregulations of Fos-related antigen 1 and -2 proteasomal degradations in cancer cells

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Fra-1 and Fra-2 are transcription factors of the Fos family. They are implicated in the progression of breast-, colon- and thyroid cancers where they can accumulate together to particularly high levels in hyperphosphorylated forms. There, they oncogenically collaborate by regulating both redundant and non-redundant cell functions. We have combined genetic, cell biology and signalling studies to understand how they accumulate abnormally. We show that both proteins are intrinsically unstable and degraded by the proteasome without, however, requiring prior ubiquitylation. When unstable, both proteins are degraded owing to a natively unfolded C-terminal destabilizer conserved in all Fos family members. Neither the 11S PA28 α/β - nor the PA28 γ proteasome regulator is instrumental for their destruction. Aberrantly high Erk1/2 MAP kinase activity is responsible for their co-stabilization in invasive cancer cells with. This stabilization is due neither to inhibition of cell proteasomal activity nor to that of a putative system addressing Fra-1 and Fra-2 to the proteasome. Rather, it directly results from phosphorylations at two serines residues conserved between the two proteins within their C-terminal destabilizers, meaning that the C-termini of Fra-1 and Fra-2 contain overlapping destabilizing and anti-destabilizing elements whose respective activities determine the proteins' half-lives. Taken together, our data both reveal novel mechanisms for recognition and degradation of proteins by the proteasome and pose novel questions regarding how substrate degradation by the proteasome can be inhibited.