Cell Death and Differentiation (2005) 12, 1218

www.nature.com/cdd

## News and Commentary

# Caspase inactivation of the proteasome

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*Cell Death and Differentiation* (2005) **12,** 1218.
doi:10.1038/sj.cdd.4401693

It is an honour and privilege to write a short commentary in this special issue of Cell Death and Differentiation, which contains lectures and interviews with Aaron Ciechanover, Avram Hershko and Irwin Rose, the 2004 Nobel Laureates in Chemistry for their pioneering work on the discovery of ubiquitin-mediated protein degradation.[1–3] This is the first time that a Nobel Prize for science has been awarded to Israeli scientists. It is an additional tribute to these scientists that the discovery and characterisation of ubiquitin proteasome system (UPS) was made in a small laboratory in a small country with limited resources. It is also particularly appropriate that the award should go to two Israeli scientists at a time when supposed 'enlightened' academics in the UK are considering boycotts of Israeli universities.

The UPS by virtue of its controlled degradation of many short-lived intracellular proteins is now recognized to be important in the control of many fundamental cellular processes including the cell cycle, cell division, transcription and antigen processing.[4,5] Aberrations in the UPS have been implicated in the pathogenesis of many diseases.[4–6] Recent studies have begun to realise the many ways in which the UPS also impinges on apoptosis. The UPS plays a key role in the regulation of the degradation of many of the key regulatory molecules involved in apoptosis, such as p53, mdm2, IkB$\alpha$, and proapoptotic Bcl-2 family members, including Bax, Bad, Bim and Bid and caspases.[7–9] Many of the critical biochemical and morphological changes occurring during apoptosis are brought about by activation of caspases, and caspase activity is regulated partly by the inhibitor of apoptosis (IAP) family of proteins, such as XIAP, c-IAP-1 and c-IAP-2, and also by Smac/DIABLO (second mitochondrial activator of caspases) and Omi/Htra2.[10] The IAP proteins, particularly XIAP, are very potent inhibitors of some caspases, such as caspase-3, -7 and -9. However XIAP, c-IAP1 and -2 also contain a C-terminal RING domain and act as E3 ubiquitin protein ligases, regulating the degradation of several proteins as well as themselves.[11]

Recently, we unraveled a novel interaction between the UPS and caspases during apoptotic cell death. Almost all previous studies had concentrated on how the UPS system regulated apoptosis by controlling the degradation of key apoptotic regulators. However, our data showed how key events in apoptosis, namely the activation of caspases, can modulate the function of the proteasome. We were greatly aided in these studies by our collaborator Dr. Aaron Ciechanover and we were able to show that the cleavage of certain key regulatory subunits of the 26S proteasome occurred at an early stage of the apoptotic process.[12] Independent confirmation of the cleavage of certain proteasomal subunits has recently been obtained and this appears to be a conserved process during programmed cell death in Drosophila and man.[13] During apoptosis, caspase activation resulted in the cleavage of three specific subunits, S6′, S5a and S1, of the 19S regulatory subunit of the proteasome. Two of these subunits, S6′ and S5a, are involved in the recognition of polyubiquitinated substrates in the proteasome and S1 is involved in holding together the lid and base of the 19S regulatory complex. Caspase-mediated cleavage of these proteasomal subunits resulted in an inhibition of both ubiquitin dependent and -independent substrates and we hypothesised that this could facilitate apoptosis by providing a feed forward amplification loop.[12] However, this would clearly depend on the balance of pro- and antiapoptotic molecules to be degraded by the proteasome and the relative availabilities and affinities of the various E2 and E3 enzymes for these different substrates and whether any of these was affected during apoptosis. In this regard, it is also worth considering the *in vivo* relevance of some of the *in vitro* findings. For example, a number of studies have described the ubiquitination and degradation of Smac by the UPS. Several candidate E3 ligases have been identified including XIAP, c-IAP-1 and -2 and Bruce, all of which are capable of ubiquitination of Smac under optimal conditions *in vitro*. However at the present time, it is difficult to discern the relative contribution of these different ligases to the *in vivo* degradation of Smac. We hypothesised that caspase-mediated cleavage of the proteasome may preserve ATP required for several steps of the apoptotic programme. Inactivation of the proteasome following caspase-mediated cleavage may disable the proteasome, so interfering with its role in the regulation of key cellular processes, facilitating an increase in the induction of apoptosis.

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