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Roles of Lysine-63-Linked Ubiquitination in Cell Decision Fate between Cell Proliferation and Apoptosis

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Abstract : K63-linked ubiquitination — i.e. conjugation of a chain of ubiquitins (Ub) linked through lys63 — has emerged as a key mechanism regulating signalling transduction pathways. Although critical, very little information is currently available about how subversion of K63 ubiquitination might contribute to cancers and inflammatory diseases. The present study provides the first evidence that Cadmium (Cd), a widespread environmental carcinogen and toxicant, is a powerful activator of K63 ubiquitination. Indeed, Cd induces accumulation of K63 polyUb proteins. Importantly, Cd-induced ubiquitination does not stem on oxidative damage or proteasome impairment. Rather, we demonstrate that Cd not only activates K63 ubiquitination but also amplifies their accumulation by overloading the capacity of autophagy pathway. At molecular level, Cd-induced ubiquitination is correlated with stabilization of HIF-1 and the activation of NF-B, two transcription factors. Strikingly, prolonged cell exposure to high Cd concentrations induces an exaggerated K63 ubiquitination that fosters aggresome formation, thus precluding these proteins from interacting with their downstream nuclear targets. We therefore propose that the aberrant activation of K63 ubiquitination by the carcinogen Cadmium could promote cell proliferation and inflammation at low levels while high levels committed cell to death.

Keywords : cadmium, environmental exposure, Lysine-63-ubiquitination, kidney, apoptosis, proliferation, autophagy
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