

# CELL SIGNALING, CELL THERAPY AND CANCER THERAPEUTICS

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## Regulation of proteostasis in hMSCs: Proteasome activation enhances stemness and delays senescence

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Proteostasis is a fundamental process, essential for the majority of cellular functions. Numerous studies have demonstrated that ageing is accompanied by a failure of proteostasis, while chronic exposure to denatured or aggregated proteins contributes to the development of age-related diseases. The proteasome, being the main proteolytic cellular system, plays a pivotal role in maintaining proteostasis. Essentially, we have established a direct link between the proteasome mediated protein degradation and aging. In detail, we have revealed that senescent human mesenchymal stem cells (hMSCs) exhibit a decrease in expression of proteasome subunits, proteasome content and peptidase activities, accompanied by alterations of proteasomal complexes. Additionally, we show that senescence and the concomitant failure of proteostasis negatively affects stemness. Remarkably, the genetic activation of the proteasome through the overexpression of the catalytic  $\beta 5$  subunit, doubled the lifespan, induced the expression of the core pluripotency factors and enhanced the differentiation capability of hMSCs. Based on these observations, we postulated that the molecular factors and mechanisms that regulate the expression of proteasome subunits can be critical determinants of both aging and stem cell function. Shedding light on the limited data regarding the regulation of proteasome subunits' expression and the mechanisms underlying its age-related decrease, we demonstrated that the transcription factors Oct4 and FoxO1 bind at the promoter region of catalytic proteasome subunits and thus possibly regulate their expression. A firm understanding of the mechanisms regulating proteostasis in stem cells will pave the way to innovative stem cell-based interventions to improve healthspan and lifespan.

### Biography

Marianna Kapetanou graduated from University of Crete, Biology Department in 2012, having achieved a first-class honor's degree. She obtained her PhD from University of Athens, with an excellent grade. She is currently carrying out Post-doctoral research at the National Hellenic Research Foundation (NHRF). Her excellence has been proven by the reception of the IKY-Siemens Scholarship of Excellency for PhD Studies and for Post-doctoral Research. In addition, she has published articles in reputed journals, participated in numerous conferences, has given a lecture at Seminars of NHRF and has reviewed scientific manuscripts for IUBMB Life.

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