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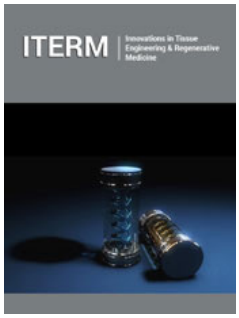
Opinion

Poly (ADP-Ribose) Polymerase: Role in Regenerative Medicine and Stemness

Jyotika Rajawat* and Monisha Banerjee

Institute of Advanced Molecular Genetics & Infectious Diseases, ONGC, Centre for Advanced Studies, University of Lucknow, Lucknow-226 007, UP, India



***Corresponding author:** Jyotika Rajawat, Institute of Advanced Molecular Genetics & Infectious Diseases, ONGC, Centre for Advanced Studies, University of Lucknow, Lucknow-226 007, UP, India

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Opinion

Stem cell therapy is one of the numerous strategies of regenerative medicine which effectively replaces the damaged tissue and ultimately heals the tissue. Controlling the transformation of stem cells is a big question for researchers and hence exploiting their genetic makeup and stemness characteristics is crucial. Maintenance of stemness and lineage commitment are regulated by epigenetic mechanisms. The dynamic mechanism of epigenetic is controlled by several factors and, Poly (ADP-ribose) Polymerase (PARP) being one prominent factor. Amongst different epigenetic modification approaches, histone ADP-ribosylation is one such mode of post-translational modification, which is regulated by PARP1. Hence, PARP1 is considered as a guardian of the genome besides p53. PARPs are multifunctional proteins which play pivotal roles in major signalling pathways and affect diverse cellular and biological processes. PARP1 is a key member which is omnipresent in different cellular signalling [1,2]. PARP1 mediated PARylation regulates RNA metabolism and RNA binding protein [3]. Recent work has shed light on the involvement of PARP1 in stemness, where it is reported to interact and regulate a few stem cell marker genes like Sox2 [4]. PARP1 downregulation was correlated with impairment of pluripotency factors like POU5F1, SOX2, and ZFP42 [5]. NAD^+ is already proposed as a modulator of stem cell pluripotency and in some cell types it also regulates differentiation. NAD^+ alone is not able to induce complete stemness and hence it works in coordination with other factors [6]. Current findings have revealed NAD^+- PARP1 axis in oxidative stress signalling [7]. Interplay in the availability of NAD^+ and catalytic activity of PARP1 is crucial where ADP-ribosylation of RNA binding proteins regulates splicing programs in differentiation of mouse embryonic stem cells [8]. PARP1 and PARP7 are reported to safeguard the pluripotency state of embryonic stem cells and hence positioned at the interface of genetics-epigenetics network [9].

Cancerous cells which have tumor-initiating power are termed Cancer Stem Cells (CSCs). Such CSCs express specific stem cell markers and acquire self-renewal and proliferative capability. CSCs are also considered now as a major reason for therapeutic resistance resulting in treatment failure. Epigenetic mechanisms have emerged in cancer initiation as well as in attaining functional heterogeneity [10]. PARP1 not only promotes induced pluripotent stem cells but it also regulates stemness in tumors via controlling telomerase and its regulatory factors like KLF4 [11] and c-myc. PARP1 also interacts with specific epigenetic factors and regulates the expression of stem cell markers namely Oct4 and Sox2 [12]. PARP inhibitor (PARPi) mediated therapy failed in several cancers due to cancer stem cells. PARPi failed to affect the stem cell population in ovarian cancer and thus possibly contributed to the resistance [13]. Alternatively, PARP inhibition is known to sensitize glioblastoma initiating cells to radiation [14].

Given the role of PARP1 in regulating transcription factors, long non-coding RNAs, microRNAs and RNA binding proteins, targeting PARP1 might be an effective strategy in several diseases and in therapeutic resistance. Induction of key epigenetic or reprogramming factors in stem cells with respect to PARP1 indeed would have major applications in stem cell research and/or regenerative medicine. To summarize, PARP1 is well thought-out as a guardian of the genome and a prominent player in epigenetics and stemness, whereby it regulates the expression of stem cell markers as well as promotes cancer stemness. Hence, PARP inhibitors can be a game-changer in certain cancer therapies. Efforts to delineate PARP1-mediated signalling in stem cells and stem cells derived exosomes will provide a clear understanding of reprogramming in stem cells via PARP1 and PARylation.

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