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DNA damage-induced activation of ATM/ATR is not accompanied by G1/S arrest in mouse embryonic stem cells

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Abstract

Embryonic stem cells (ESCs) are pluripotent, self-renewing cells that represent the point of origin of all cells in a given organism and must protect their genomes from both endogenous and exogenous genotoxic stresses. ESCs are characterized by high proliferation rate and do not undergo G1/S arrest upon DNA-damage. This creates an issue of how ESCs maintain DNA stability and genome integrity. In this study we focused at functional state of ATM/ATR and the p53-p21/Waf1 signaling pathways that in somatic cells provide G1/S checkpoint and DNA repair. ATR-Chk1 pathway plays an important role in cell cycle progression and cell viability of irradiated mESCs. Both sensor kinases ATM and ATR are activated in mESCs followed by activation of p53, the accumulation of gH2AX foci and their co-localization with 53BP1 and Rad51. However, activation of p53 does not lead to an accumulation of p21Waf1 protein as its expression is under negative control at the levels of epigenetic gene transcription and protein degradation. Activation of p53-p21Waf1 pathway by MDM2 antagonist nutlin leads to accumulation of mESCs in G1 phase, decreases expression of pluripotency markers and induces apoptosis. The findings suggest that in spite of ATM/ATR activation in mESCs, DNA damage does not induce functional G1 checkpoint due to a dysfunction p53-p21/Waf1 pathway.

Biography

Irina I. Suvorova completed her Master of Biology in Saint-Petersburg State University, Russia. Now she is doing her PhD (2010-2013) in the Institute of Cytology of the Russian Academy of Sciences. She has a review published in Int. Rev.Cell & Mol.Biol. (2012), pp. 161–198, two papers are submitted. She attended at domestic conferences with oral and poster presentations.