World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:18, No:04, 2024

Melanoma Antigen Proteins Are Involved in DNA Damage Response

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Abstract : The SMC5-SMC6 complex helps replication and repair of DNA double-strand breaks. Nse1, Nse3 and Nse4 are non-SMC components of the complex in which Nse3 stimulates the E3 ubiquitin ligase activity of Nse1 and is required for recruiting the complex on DNA. In most eukaryotes, Nse3 is a single protein, but in eutherians (placental mammals), it belongs to a large family of proteins called MAGE (Melanoma antigen) that share a conserved domain of about 200 aa known as MHD (Mage homology domain). MAGE assembles specific RING and HECT ubiquitin ligases and determines new substrates for ubiquitination. The MHD is required for the interaction with the cognate E3 ligase. Some MAGEs (referred to as Type I) are exclusively expressed in germ cells of the testis but are often expressed ectopically in cancer cells as the result of epigenetic modifications. The 12 MAGE-A genes belong to this category. Serval MAGE-A proteins could promote tumorigenesis by targeting tumor suppressor proteins (including p53) for ubiquitination and degradation. We showed that depletion of MAGE-A proteins in melanoma cells results in impaired DNA damage response and increased double-strand breaks after exposure to camptothecin. Moreover, it was shown that other actors of the DNA Damage Response were impacted when cells were depleted of MAGEA proteins.

Keywords : DNA damage response, melanoma, camptothecin, new role, MAGEA
Conference Title : ICCRDDR 2024 : International Conference on Chromatin Remodeling and DNA Damage Repair
Conference Location : Lisbon, Portugal
Conference Dates : April 11-12, 2024