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Regulation of Cell Cycle and Replication in Cancer Cells

ABSTRACT

Human Papilloma Virus (HPV) is an important pathogen; the high risk strains cause cancers while the low risk strains cause benign growths like papillomas and condylomas. Cdt2 (also known as DTL in Humans) is an important regulator of replication, cell cycle and other cellular events. It is essential for genomic stability as the substrate recognition adaptor of the CUL4-DDB1 E3 ubiquitin ligase complex to promote the timely polyubiquitination and degradation of CDT1 (replication licensing factor), p21 (cell cycle regulator) and Set8 (histone methyl transferase) proteins. Cdt2 itself is polyubiquitinated and degraded during S-phase. In this talk, I will present the mechanism that how Cdt2 is stabilized by a de-ubiquitinase USP46 in high risk HPV infected cancer cells. Silencing of USP46 destabilizes Cdt2 in these cells. This stabilization by USP46 is only seen in the presence of E6 from high risk HPV strains. Recruitment of a cellular de-ubiquitinase to substrate proteins is a novel activity of the viral E6 oncoprotein.

Also, I will talk briefly about regulation of replication and cell cycle in mammalian cells by Fanconi anemia complex. Also, I will try to touch upon replication termination in mammalian cells (as a part of my future proposal).