รูปแบบ Abstract (บทคัดย่อ)

Project Code : RSA5880038

(รหัสโครงการ)

Project Title : Roles of Cyclin D1 Oncogenic Network in Tumorigenesis and Cancer Targeted Therapy

(ชื่อโครงการ)

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Project Period :

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ABSTRACT

Expression of cyclin D1 is required for cancer cell survival and proliferation. This is presumably due to the role of cyclin D1 in RB inactivation. Here we investigated the prosurvival function of cyclin D1 in a number of cancer cell lines. We found that cyclin D1 depletion facilitated cellular senescence in several cancer cell lines tested. Senescence triggered by cyclin D1 depletion was more extensive than that caused by the prolonged CDK4 inhibition. Intriguingly, the senescence caused by cyclin D1 depletion was independent of RB status of the cancer cell. We identified a buildup of intracellular reactive oxygen species, in the cancer cells that underwent senescence upon cyclin D1 depletion, but not in CDK4 inhibition, and that ROS buildup was responsible for the senescence. Lastly, the senescence was found to be instigated by the p38/JNK-FOXO3a-p27 pathway. Therefore, expression of cyclin D1 prevents cancer cells from undergoing senescence, at least partially, by keeping the level of intracellular oxidative stress at a tolerable sub-lethal level. Depletion of cyclin D1 promotes the RB-independent pro-senescence pathway, and cancer cell succumbing to the endogenous oxidative stress.

Introduction

Cyclin D1 is a cell cycle regulatory protein, that is amplified and overexpressed in a large number of human cancer (Sukov et al., 2009, Musgrove et al., 2011, Lee et al., 2016). Expression of cyclin D1 is essential for oncogenic transformation, as well as, for cancer cell survival. Activation of Kras or HER2 pathways targeted in mouse breast tissue resulted in breast cancer, but failed to induce any tumor in cyclin D1-deficient breast(Yu et al., 2001). In addition, shutdown of cyclin D1 expression in breast tumor resulted in tumor cessation associated with cancer cell senescence (Choi et al., 2012).

The cancer supporting role of cyclin D1 in cancer formation and survival represents a curious circumstance, in that although it is required for cancer formation, cyclin D1 does not appear to be a strong cancer driver. Forced expression of cyclin D1 in mouse model did not promote cancer formation until after a very long latency(Wang et al., 1994, Casimiro and Pestell, 2012). Thus, expression of cyclin D1 may be required to support oncogenic transformation, possibly by creating permissive cellular condition for cancer cell transformation.