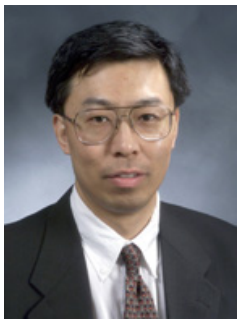
第26回次世代シグナル伝達医学の教育研究国際拠点
グローバルCOE学術講演会

Ubiquitin-proteolytic control of DNA repair and carcinogenesis



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日時：2010年6月29日（火）18:00-19:30
場所：神戸大学医学部臨床研究棟6階　大講義室

Abstract

The cullin 4A (CUL4A) ubiquitin ligase regulates nucleotide excision repair (NER) through proteolytic destruction of the heterodimeric DNA damage sensor: damaged DNA binding proteins 1 and 2 (DDB1 and DDB2). Recent studies revealed a second function of DDBs as integral components of the CUL4A ubiquitin ligase complex: DDB1 is the specific adaptor that bridges CUL4A and the DCAF (DDB1, CUL4A associated factors) substrate receptors, and DDB2 is a DCAF that recruits substrates to the DDB1-CUL4A complex for ubiquitination. However, the physiological role of CUL4A in DNA repair and tumorigenesis remains unknown. We have generated conditional floxed alleles of the *Cul4a* gene in mice, and report that skin-specific *Cul4a* knockout mice displayed markedly increased resistance to UVB-induced skin cancer. Deletion of *Cul4a* resulted in a dramatic increase in global genomic NER activity and an enhanced G1/S DNA damage checkpoint respectively. While germline *Cul4a* null mice are healthy and display no developmental abnormalities, abrogation of both CUL4A and its family member CUL4B resulted in profound growth inhibition, underscoring an essential functionally redundant role for CUL4A and CUL4B ubiquitin ligases in maintaining genomic integrity and cell survival. These studies reveal the critical physiological function of CUL4A in suppressing nucleotide excision repair and antagonizing the DNA damage-responsive cell cycle checkpoint, and highlight the benefit of attenuating CUL4A in protection against UVB-induced skin carcinogenesis.

(References: Zhou et al., Cell 124, 105-117, 2006., Cell 124: 256-257, 2006, Mol. Cell 22: 489-499, 2006., Cell 127: 929-40,2006., Cancer Res 66: 11781-791, 2006., PNAS 104: 2733-37, 2007., Mol. Cell 26: 775-780, 2007., DNA Repair 8: 536-543, 2009., Mol. Cell 34, 451-460, 2009., Cell 140, 477-90, 2009)

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