

## ***Rb* deficiency couples DNA damage signaling with DNA methylation during C cell carcinogenesis**

**Awad Shamma**

*Division of Oncology and Molecular Biology, Cancer Research Institute,  
Kanazawa University,  
Kakuma-machi, Kanazawa 920-1192, Japan*



The retinoblastoma tumor suppressor gene (*RB*) product has been implicated in epigenetic control of gene expression; however, the biological and clinical significance of this function is not yet known. To address this, we performed genetic and epigenetic analyses in *Rb*-deficient mouse thyroid C (Calcitonin-producing) cell tumor model. We demonstrate that the genetic interaction of *Rb* and *ATM* regulates DNMT1 protein stability and hence controls the DNA methylation status in the promoter of at least *Ink4a*, *Shc2*, *FoxO6* and *Noggin* genes. Further, we report that inactivation of pRB promotes the Tip60 (acetyltransferase)-dependent ATM activation, allows activated ATM to physically bind to DNMT1 forming a complex with Tip60 and UHRF1 (E3 ligase), and consequently accelerates DNMT1 ubiquitination driven by Tip60-dependent acetylation. Our results indicate that inactivation of pRB pathway in coordination with aberration in DNA damage response leads to abnormal DNA methylation pattern by affecting the stability of DNMT1. Our study revealed a novel mechanism in regulation of the epigenetic control of cancer progression.

Reference: Shamma A et al., *Mol. Cell Biol.* 33: 3113-3124, 2013.

### **EDUCATIONS AND POSITIONS**

1986	Mansoura University, Egypt, M. B. B. Ch.
1995	Zagazig University, Egypt, M.S.
1999	Osaka University Hospital, Japan, Advanced Clinical Training
2001	Osaka University, Japan, Ph.D., M.D.
1987–1988	Mansoura University Hospital, Egypt, Intern
1988–1990	Ghamra military Hospital, Egypt, Resident of Surgery
1993–1994	Ministry of Health and Welfare, Republic of Maldives Senior House Officer
1990–1993	Nasser Institute Hospital, Egypt, Resident of Surgery
1994–1996	Al-Shefaa Clinic, Egypt Consultant Surgeon
1996–1997	Osaka University, Japan, Visiting Researcher
2000–2001	Osaka University, Japan, Teaching Assistant
2001–2004	Ohio State University, U.S.A., Postdoctoral Fellow
2004–2010	Kyoto University, Century 21 of Excellence formation (COE), Japan, Assistant Professor,
2010–Present	Kanazawa University, Cancer Research Institute, Japan, Assistant Professor