Stress-induced changes in CARF expression determine growth arrest, apoptosis, or malignant transformation in cultured human cells: Molecular evidence and its application

Mallika Khurana[1,2], Rajkumar Singh Kalra[1], Anupama Chaudhary[1], Amr Omar[1], Xiaoshuai Li[1], Sunil C Kaul[1], Renu Wadhwa[1]*

[1]AIST-INDIA DAILAB, DBT-AIST International Center for Translational & Environmental Research (DAICENTER), National Institute of Advanced Industrial Science & Technology (AIST), Tsukuba 305-8565, Japan
[2] Tsukuba Life Science Innovation, School of Global and Integrative Majors, University of Tsukuba, Tsukuba 305-8577, Japan

Background: CARF (Collaborator of ARF)/CDKN2AIP is an essential protein, first cloned as a binding partner of ARF. It was subsequently shown to interact with p53, HDM2 proteins and regulate growth arrest and apoptosis by its multimodal mechanism of action. Overexpression of CARF caused senescence like growth arrest of cells, its knock-down triggered apoptosis. Intriguingly, malignantly transformed cells showed high level of CARF expression. Based on these Sproliferation fates; where an increase in its levels causes growth arrest/senescence, but beyond a threshold it activates carcinogenesis. **Methods:** We utilized *in vitro* cell culture models using retrovirus-driven expression of CARF to achieve overexpression and super-expression of CARF. Analysis of CARF levels was undertaken by biochemical and imaging protocols. Cells exposed to a variety of stresses including physiological, environmental, oxidative, radiation and chemotherapeutics was examined for CARF expression and corresponding cell proliferation fates. **Results:** Induction of Senescence was seen in cells overexpressing CARF. On the other hand, cells compromised for CARF showed apoptosis, and the ones with super-expression of CARF exhibited malignant transformation. CARF expression analysis in these experimental models endorsed the concept of cell-fate determining role of CARF. **Conclusions:** We present molecular evidence of the bridging role of CARF in stress-aging-cancer phenotypes and its application in pharmaceuticals and nutraceuticals as a diagnostic and prognostic marker for stress and cancer treatments.

Keywords: CARF/CDKN2AIP, Stress, Growth arrest, apoptosis, malignant transformation molecular mechanisms