EPA-3 CARF determines proliferative fate of cell by a two-way regulation of DNA damage and growth arrest signaling

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CARF (Collaborator of ARF) is an ARF-interacting protein that also binds and regulates activities of HDM2 and p53 proteins.[1,2] It was earlier shown that CARF upregulates ARF-p53-p21 tumor suppressor axis resulting in growth arrest in cancer cells.[2,3] Consistent to above functionality of CARF, it was found upregulated in cells undergoing a variety of stresses and replicative senescence[4]. It was shown to be an essential cell survival protein; CARF compromised cells underwent apoptosis.[5] Furthermore, level of CARF expression determined the fate of cells to growth arrest or malignant transformation by fine-tuning of DNA damage response involving damage-signaling and -responding proteins. We found that super-high level of expression of CARF resulted in negative regulation of p53, driven by HDM2 feedback circuit and transcriptional upregulation of CHK2. These resulted in abrogation of CARF induced growth arrest and induced malignant transformation.[6] In line with this, p53 deficient cells were found to escape CARF-induced growth arrest, and instead, showed increase in malignant characteristics that was mediated by transcriptional repression of $p21^{WAF1}$, a critical mediator of growth arrest. Taken together, we discovered that CARF determines cell fate by a two-way regulation of DNA damage and growth arrest signaling.

References

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