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医療・福祉・介護

CARF Overexpression-mediated Growth Arrest of Cancer Cells Involve p53 Protein

■ はじめに

Collaborator of ARF (CARF) has been shown to bind to ARF, p53 and HDM2 resulting in activation of p53-p21 pathway. Overexpression of CARF was shown to cause growth arrest of osteosarcoma (U2OS) that harbors wild type p53 function. Its knockdown caused apoptosis suggesting that it is an essential survival protein. In order to investigate the critical involvement of p53 in CARF-induced growth arrest, we used p53-compromised (Saos-2, MCF7) cells.

■ 活動内容

In order to validate the involvement of p53 in CARF-induced growth arrest of cells, we presently used cells that lack functional p53.

1. *In vitro*/*in vivo* assays for CARF-OE Saos-2 cells

We found that CARF overexpression (OE) in these cells lead to increase in proliferation rate and malignant transformation (Fig. 1 b and d).

2. Molecular analysis

We investigated DNA damage response (of ATM/ATR/CHK1/CHK2 pathway) in p53-compromised cells, similar to the one performed for p53-functional cells. We observed that although the early DNA damage response elements were upregulated in p53-compromised cells similar to the one observed in p53-functional cells, pERK1/2 was upregulated and was in sharp contrast to the p53 fucntional cells that showed its downregulation (Fig. 1 a and b). In addition, treatment of CARF-OE Saos-2 cells with ERK1/2 inhibitors caused decrease in their proliferation rate suggesting that the activation of ERK1/2 was involved in increase in proliferation caused by CARF-OE in Saos-2 cells. Furthermore, overexpression of CARF in MCF7 cells also led to an increase in the expression level of CHK1/2 and γH2AX, compared with the controls (Fig. 2).These data suggested the activation of DNA damage response by CARF is normal in p53-compromised cells and lack of growth arrest is due to absence of p53 and its down-stream effector pERK1/2.

■ 関連情報等（特許関係、施設）

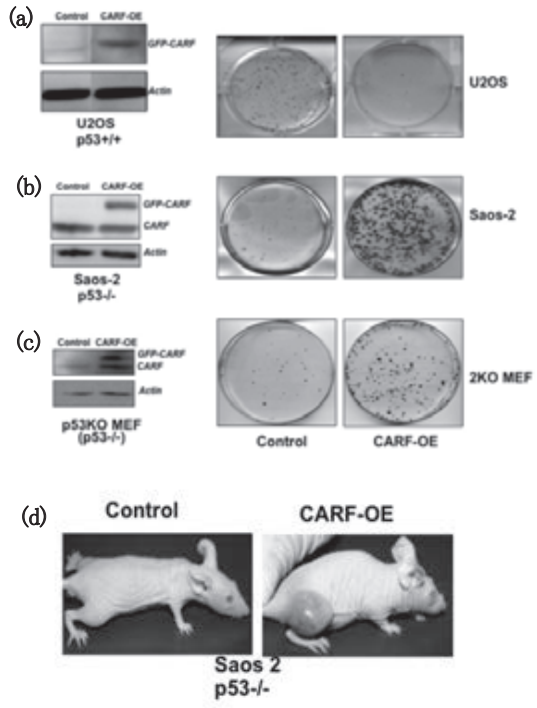

Fig.1. Overexpressing CARF (CARF-OE) caused growth arrest in cancer cells with functional p53 plus cells (a). p53 minus cells showed increase in proliferation *in vitro* b and c, and malignant transformation in *in vivo* assays (d).

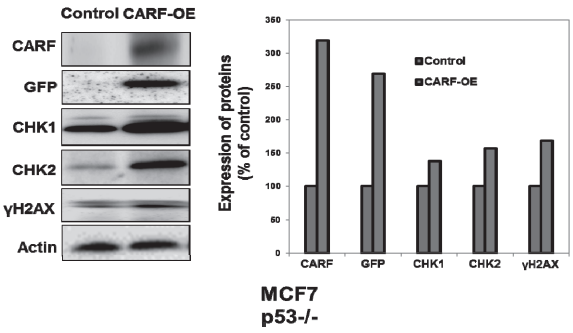

Fig.2. Overexpression CARF caused DNA damage response in Human breast carcinoma (MCF7) with compromised p53 function.

代表発表者 Mijung KIM（キム ミジョン）
所　属 National Institute of Advanced Industrial Science & Technology (AIST)
問合せ先 Central 4, 1-1-1 Tsukuba, Ibaraki 305-8562, Japan
TEL：029-861-2900 FAX：029-861-2900

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(2) p53
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