Targeting epiregulin in treatment-damaged tumor microenvironment restrains therapeutic resistance

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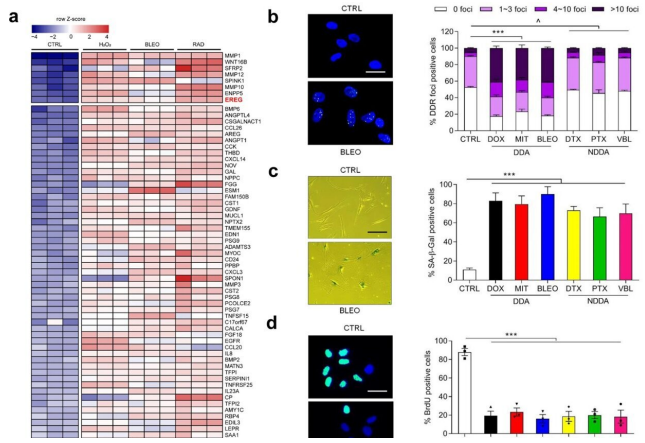

Genotoxicity induces expression of EREG and other secreted factors of the SASP spectrum in human stromal cells. **a** Transcriptome-wide profiling of gene expression changes in primary normal human prostate stromal cell line (PSC27) by microarray. Cell lysates were collected for analysis 7 days after treatment. CTRL control. H_2O_2 hydrogen peroxide. BLEO bleomycin. RAD radiation. Red highlighted, EREG. Agilent microarray data adapted from Sun et al. with permission from *Nature Medicine*, copyright 2012, Springer Nature. **b** Representative immunofluorescence staining images (?H2AX and p-53BP1 co-staining, left) and comparative statistics (right) of DNA damage response (DDR) in PSC27 cells treated by DOX (doxorubicin), MIT (mitoxantrone), BLEO (bleomycin), DTX (docetaxel), PTX (paclitaxel) and VBL (vinblastine). DDA DNA-damaging agents (DDAs). NDDA non-DNA-damaging agents. DDR were classified into four sub-categories including 0 foci, 1–3 foci, 4–10 foci and >10 foci per cell. Scale bars, 15 ?m. **c** SA-?-Gal staining of PSC27 cells treated by various agents used in **b**. Cells were stained 7 days after in vitro treatments. Scale bars, 30 ?m. Right, comparative statistics. **d** BrdU staining of stromal cells treated by different agents as indicated in **b** and **c**. Scale bars, 15 ?m. Right, comparative statistics. **e** Quantitative RT-PCR of EREG expression after treatment of PSC27 cells by various agents. Cell lysates were collected for measurement 7 days after treatment. Signals normalized to CTRL. **f** Immunoblot analysis of EREG expression in stromal cells 7 days after treatments performed as indicated. IC intracellular samples. CM conditioned media. GAPDH, loading control. **g** Time course expression assessment of a subset of EREG and other typical SASP factors (CXCL8, CSF2, WNT16B, IL6 and MMP3) after drug treatment of stromal cells in vitro. Numeric numbers indicate the individual days after treatment. **h** Immunoblot measurement of EREG expression at the protein level in the time course described in **g**. **i** Comparative appraisal of EREG transcript expression in stromal cells (PSC27) versus cancer epithelial cells (PC3, DU145, LNCaP and M12). Signals normalized to untreated sample per cell line. **j** Immunoblot assessment of EREG expression in protein lysates of stromal and epithelial cells after bleomycin treatment as performed in **i**. Data are representative of three independent experiments. ^*p* > 0.05, **p*