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ATF4 gene network and ROS mediate cellular response to the anticancer PAD inhibitor YW3-56

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We previously reported that a pan-PAD inhibitor YW3-56 activates *p53* target genes to inhibit cancer growth. However, the broad anticancer efficacy and drug mechanisms of YW3-56 remained largely elusive. Here, gene expression analyses found that ATF4 target genes involved in ER stress response and oxidative stress response were activated by YW3-56. Depletion of ATF4 greatly attenuated YW3-56 mediated activation of the mTORC1 regulatory genes, SESN2 and DDIT4. Using the ChIP-exo method, high-resolution genomic binding sites of ATF4 and CEBPB were generated prior to and after YW3-56 treatment. Moreover, YW3-56 increases cellular ROS levels to facilitate ATF4 target gene activation and cancer cell killing. YW3-56 mediated cell death features mitochondria depletion and autophagy perturbation. At last, YW3-56 treatment effectively inhibits the growth of triple negative breast cancer xenograft tumors in nude mice. Taken together, we unveiled the anticancer mechanisms and therapeutic potentials of the pan-PAD inhibitor YW3-56.

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