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Therapeutic potency and mechanisms of polyI:C in triple negative breast cancer

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Triple negative breast cancer (TNBC) is one of the most aggressive types of cancers that requires more innovative therapy. Activating retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) including melanoma differentiation-associated gene 5 (MDA5) and RIG-I in cancer cells such as by transfection of dsRNA (e.g. polyI:C) is suggested as new beneficial strategy to combat cancer cells by triggering cancer cell death including TNBC. However, crosstalk between RLR signaling pathway and other tumor promoting signaling pathways is not fully elucidated. Here we showed that cytosolic induction of polyI:C which is now in clinical trials by intratumoral transfection suppressed tumor-promoting transforming growth factor- β (TGF- β) signaling in TNBC by attenuating phosphorylation of Smad3. Abrogation of TGF- β signaling by transfection of polyI:C accelerated cell death, which was inhibited by forced expression of constitutively active Smad3. We further characterized cell death and found polyI:C transfection caused pyroptosis accompanied by GSDME cleavage. Intratumoral polyI:C treatment *in vivo* resulted in suppression of tumor progression with attenuation of pSmad3. These results suggested that transfection of polyI:C is a promising method to combat TNBC through attenuation of TGF- β signaling.