The Hormone Response Element Mimic Sequence of GAS5 LncRNA is Sufficient to Induce Apoptosis in Breast Cancer Cell Lines

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Growth arrest-specific 5 (*GAS5*) encodes snoRNAs and lncRNA. The latter promotes apoptosis, but its expression is down-regulated in breast cancer. The mTOR and nonsense-mediated decay pathways together regulate GAS5 transcript levels but rapalogues fail to enhance GAS5 levels in triple-negative breast cancer cells, so that mTOR inhibitor-independent induction of GAS5 may be more productive in enhancing apoptotic responses to therapies in breast cancer. Notably, GAS5 lncRNA acts by riborepression of glucocorticoid/related receptors; a stem-loop sequence constitutes the GAS5 hormone response element mimic (HREM). The aim of this study was to determine if the GAS5 HREM sequence alone is sufficient to promote the apoptosis of breast cancer cells.

Cells were nucleofected with a DNA oligonucleotide corresponding to the GAS5 lncRNA HREM; controls received oligonucleotides either with scrambled GAS5 sequence or with stem complementarity present but lacking the GAS5 HRE consensus. Cells were irradiated with ultraviolet-C (UV-C) light at 20 h *post*-transfection to induce apoptosis.

The basal apoptotic rate almost doubled in MCF7 and MDA-MB-231 cells transfected with the HREM oligonucleotide compared with controls. This effect was apparent at 20 h *post*-transfection, and a corresponding decrease was observed in culture viability; clonogenic activity was also impaired. The HREM sequence also enhanced UV-C-induced apoptosis in an additive manner in both cell lines. Endogenous GAS5 lncRNA expression was unaffected by transfection of the HREM sequence. Thus the GAS5 lncRNA HREM is sufficient to induce apoptosis in breast cancer cells, including TNBC cells and this may serve as the basis for the development of novel oligonucleotide cancer therapies.