GAS5 oligonucleotides as therapeutic agents in breast cancer

Merdan Fayda¹, Ugur Gezer²

¹Department of Radiation Oncology, Istinye University Faculty of Medicine, Cevizlibag, Istanbul, Turkey; ²Department of Basic Oncology, Institute of Oncology, Istanbul University, Capa, Istanbul, Turkey

Correspondence to: Merdan Fayda, MD. Associated Professor, Department of Radiation Oncology, Istinye University Faculty of Medicine, Cevizlibag, Istanbul, Turkey. Email: merdanfayda@yahoo.com.

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Although relatively less is known about the long non-coding RNA (lncRNA) than the essential protein coding genes, several of them have organismal functions such as lethal knockouts, apoptosis etc. (1,2). Growth arrest specific genes 5 (GAS5) has proven to be pro-apoptotic in breast cancer (BC) cell lines (3). In their paper entitled “The hormone response element mimic sequence of GAS5 lncRNA is sufficient to induce apoptosis in breast cancer cells” published in March issue of Oncotarget by Pickard and Williams (4) report that an oligonucleotide representing the hormone response element mimic (HREM) sequence within GAS5 alone is able to promote the apoptosis of BC cells similar to full-length GAS5.

As BC is a heterogeneous disease with many molecular subtypes harboring different biological characteristics and clinical outcomes (5), there is a need for novel therapies, especially for hormone-insensitive breast tumors such as triple-negative BC (TNBC) that are characterized by highly malignant behavior and resistance to cytotoxic therapy (6).

Increasing evidence reveals that lncRNAs, a major component of the human transcriptome with thousands of functional transcripts are key regulatory molecules in fundamental cellular processes, and their deregulation contributes to carcinogenesis (7). Consequently, the lncRNAs are considered as emerging candidates for the development of novel diagnostics and therapeutics. Hereof, GAS5 could be an appropriate mean of anticancer therapeutics as an apoptosis-inducer in multiple cell types, including hormone-sensitive and -insensitive BC cells (3). It is downregulated in multiple cancers including BC and therefore presumed to be a tumor suppressor (8).

Recently, Hudson et al. (9) have shown that HREM sequence within GAS5 is crucial for the GAS5-induced apoptosis of BC cells. Now the same group demonstrates that the GAS5 HREM oligonucleotide alone is able to promote apoptosis and strengthen the effect of an external apoptotic stimulus (e.g., UV-C irradiation). The authors suggest that in combination with conventional onco therapies this oligonucleotide can be used to treat therapy-resistant cancer cells. The gain could be more meaningful in tumors that lack GAS5 expression (9,10).

This article reveals the ability of a partial sequence to replace parental lncRNA in terms of its function and describes it as the oligonucleotide mimic-based onco therapeutic approach (4). It is certain this article’s findings will stimulate further research in this field to identify and develop novel oligonucleotide-based therapeutics. Employing such oligonucleotides are feasible as they are short, less complex and can be easily modified. Furthermore, the ability of such small molecules to mimic the activity of tumor suppressor genes may be benefited to restore the expression of many cancer-critic genes that are silenced in human tumors. However, the overcoming of common challenges such as in vivo stability or targeted tumor delivery will affect clinical translation of mimic-based oncotherapeutic approaches. In addition, further research is needed to identify the steroid hormone receptor GAS HREM interacts with.

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Footnote

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