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EDITORIAL

Long Non-coding RNAs in Gastric Cancer: A True Relationship or miR Chance?

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Long non-coding RNAs (lncRNAs) are gradually drawing the attention of the cancer research community due to their pivotal involvement in tumorigenesis and tumor progression [1]. These non-protein coding, >200 nucleotides long transcripts are aberrantly expressed in the majority of human malignancies, including gastric cancer (GC) [1, 2].

The discovery that lncRNAs are severely deregulated across different human malignancies [1] has prompted the pursuit of revealing a possible central involvement of lncRNAs in carcinogenesis. Indeed, it seems that lncRNAs influence, through epigenetic and transcriptional regulation, key events during malignant transformation and tumor progression that include apoptosis, epithelial-to-mesenchymal transition, and metastatic spread. As a result, many lncRNAs are now categorized as oncogenes (e.g., HOTAIR, ANRIL, MALAT1) or tumor suppressor genes (e.g., GAS5, MEG3, TUG1) [1, 2].

But how can lncRNAs affect so many biological processes of such importance? The answer is apparently simple: by interacting with most types of biomolecules (DNA, RNA, and proteins). In GC, in particular, lncRNAs, such as ANRIL, H19, HOTAIR, and MALAT1, recruit molecular complexes that modify histones and at the same time inhibit the transcription of target genes via the formation of DNA–RNA complexes. Furthermore, lncRNAs directly interact and modify the activity (e.g., GAS5, H19, and MEG3) of well-known tumor suppressor (p53) or tumor promoting (c-Myc) proteins. Another central mechanism of action of lncRNAs is the interaction with other RNA types and the resulting modulation of their bioavailability. MALAT1, for example, can form complexes by complementary base pairing with mRNAs, or, interestingly, with microRNAs (miRNAs), another RNA species that also exert a broad range of regulatory functions in human malignancies. By "sponging" miRNA molecules, lncRNAs not only modify the target miRNA levels but also affect the transcriptional profile of the mRNA target of the miRNA [1–3]. One such case has been recently reported for GC, where HOTAIR sponges miR-331, alleviating the inhibitory effect of the latter on the oncogene HER2, thus increasing the oncogenic potential of GC cells [3]. All of these interactions give shape to complex competing-endogenous RNA networks.

An analogous network of interactions is described in this issue of *Digestive Diseases and Sciences* by Li et al. [4] for PVT1, a known oncogenic lncRNA for GC [5]. More precisely, they reported that PVT1 sponges miR-152 in vitro, as perhaps expected by the in silico analysis that revealed three binding sites for miR-152 in the PVT1 sequence. As a consequence of the above-mentioned interaction, CD151 and FGF2 mRNA levels are decreased. A significant inverse correlation between miR-152 and PVT1, as well as a positive correlation between PVT1 and both CD151 and FGF2 (targets of miR-152), was detected in GC tissues [4]. The regulatory effect of PVT1 needs to be validated using in vivo models, and, most importantly, the consequences of miR-152 sponging should also be investigated in vivo in terms of GC cell proliferation, migration, and metastatic potential. Nonetheless, the approach described in this work serves as a definite impetus for further research. Starting from a simple targeted analysis of a specific lncRNA, previously

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unidentified GC-related RNA networks can take shape (Fig. 1). All the involved molecules of the PVT1 network, including PVT1 itself [5], are associated with GC prognosis. MiR-152 suppresses GC cell proliferation and is inversely related to tumor stage and size [6, 7]. HOTAIR, another lncRNA implicated in GC, also targets the PVT1-regulated miR-152 [8]. CD151 and FGF2 [9], as well as HLA-G [10] another target of miR-152, have all been associated with poor GC prognosis.

The unmet clinical need for accurate GC prognostic biomarkers enhances the value of such networks that bear high translational potential. GC is considered one of deadliest diseases worldwide, mainly due to its late diagnosis and to the lack of precise prognostic markers. The tumor-node-metastasis (TNM) classification is currently the most important prognostic factor. Nonetheless, in many cases that require accurate staging, complete pathological staging is still unavailable. The identification of improved, straightforwardly determined and evidence-based prognostic markers for GC should be prioritized. It is envisaged here that the individual assessments of lncRNAs and their associated molecules (Fig. 1) can be effectively combined into novel, multifactorial molecular tools used for GC prognosis. Studies like the one performed by Li et al. promote the idea of investigating for such prognostic biomarker panels. The individual clinical value of PVT1, miR-152, HOTAIR, CD151, FGF2, HLA-G, miR-186, and possibly other components of this network could be combined into an enhanced predictive model that will also include established conventional indicators with the ultimate goal of improving prognostic power. Such panels could be easily assessed via methods already in wide use in clinical practice (polymerase chain reaction [PCR] or immunohistochemistry).

Successful examples of biomarker panels for human malignancies include Oncotype DX® for breast cancer and the four-kallikrein panel for prostate cancer. Oncotype DX® is a cancer-related tissue-assessed multigene assay that provides important prognostic information for estrogen-receptor-positive, lymph-node-negative breast cancer patients by identifying those that could benefit from chemotherapy. The four-kallikrein serum panel has shown very promising results toward reducing the number of unnecessary prostate biopsies with enhanced sensitivity and specificity in prostate cancer detection [11].

The most prominent example of a lncRNA-based application in routine clinical practice so far is PCA3, a food and drug administration (FDA)-approved biomarker for prostate cancer. The biomarker and therapeutic potential for lncRNAs in GC is only now starting to be realized. The oncogene HOTAIR, one of the most widely studied lncRNAs at the pre-clinical level, has already been identified as a potent prognostic marker for major malignancies of the gastrointestinal tract. Other lncRNAs with

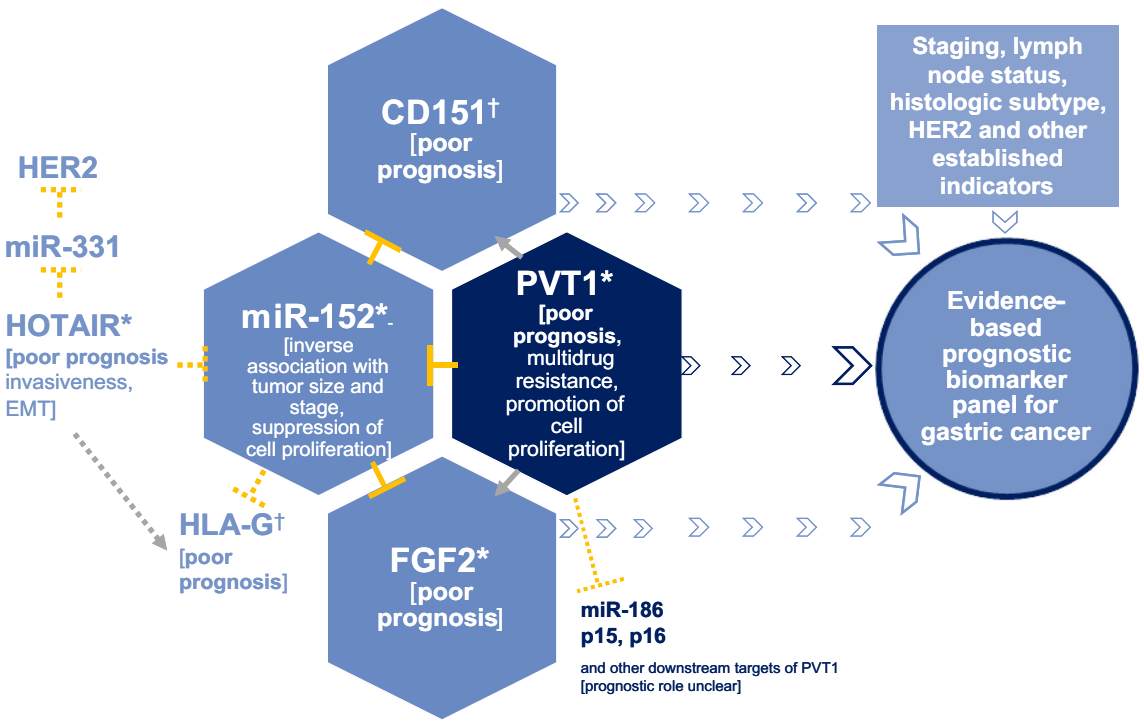

Fig. 1 PVT1 network of interactions in gastric cancer and its potential for clinical translation. Biomolecules that can be routinely measured by PCR* or immunohistochemistry†

implications in GC prognosis include HOTAIR, H19, ANRIL, GHET1, HULC, CCAT2, CCAT1, LSINCT5 (associated with unfavorable prognosis) and GAS5, LET, GACAT1, BM742401, MEG3 (associated with favorable prognosis) [2, 3]. The potential of lncRNAs as novel cancer therapeutics has also been on the spotlight recently. DTA-H19, a plasmid construct that carries the gene for diphtheria toxin-A controlled by the H19 transcriptional regulatory sequences, is used to target and kill H19-overexpressing cells. Therapeutic benefit has been reported in clinical trials primarily for bladder cancer patients, with promising results obtained also for pancreatic cancer. Another therapeutic approach that has been proposed is the suppression of oncogenic lncRNAs by antisense oligonucleotides or small molecule inhibitors [1, 2].

The targeted investigation and the deciphering of novel lncRNA networks in GC offers new opportunities for targeted therapeutics and evidence-based biomarkers. The combinatory prognostic performance of the molecules comprising these networks is worthy of investigation using well-characterized, multiple, and independent patient cohorts.

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