Significance of long non-coding RNA AGPG for the metabolism of esophageal cancer

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Over the years, thousands of long non-coding RNAs (lncRNAs) have been identified to be exclusively expressed in specific cancer types and for their unique functions in tumorigenesis. This has led to an increasing interest in elucidating the vital roles [1] and underlying mechanism [2, 3] of such non-coding genome in driving cancerous phenotypes. A number of studies have pinpointed the key functions of lncRNAs in diverse biological events including chromatin interactions, transcriptional regulation, RNA processing, mRNA stabilization, signal transduction, and metabolic regulation; highlighting their essential roles in both physiology and diseases such as cancer [4].

A classic hallmark of cancer is the reprogramming of glucose metabolism that occurs to redirect glycolytic intermediates toward the biosynthetic production of macromolecules needed for cancer progression [5-7]. The metabolic role of lncRNAs has been also discovered [8, 9], while the mechanistic details on how lncRNAs regulate metabolic processes remain to be investigated. Notably, a recent study conducted by Liu and colleagues [10] revealed a novel lncRNA, named as actin gamma 1 pseudogene (AGPG), as a key regulator of 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3), in driving glycolysis and cell cycle progression, and a biomarker in esophageal squamous cell carcinoma (ESCC; Figure 1).

Abbreviations: AGPG, actin gamma 1 pseudogene; APC/C, anaphase-promoting complex; ESCC, esophageal squamous cell carcinoma; lncRNA, long non-coding RNA; PFKFB3, 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3; siRNA, small interfering RNA.

1 | AGPG IS A NOVEL STIMULATOR OF GLYCOLYSIS AND CANCER DEVELOPMENT

In that study [10], the authors aimed to identify oncogenic lncRNAs in ESCC with a focus on their involvement in glucose metabolism. To achieve this, they conducted a small interfering RNA (siRNA) screening by taking cell viability and lactate production as readouts, where AGPG stood out as one of the top candidates. The authors further validated their findings by measuring the glycolytic flux and found that glycolysis was significantly diminished when AGPG was depleted. Additionally, the downregulation of AGPG inhibited cancer cell proliferation and cell cycle progression. Discovery of such a novel lncRNA adds to the developing body of literature, showing the importance of lncRNAs in metabolic regulation. However, a lack of understanding in the field is how specific can lncRNAs mechanistically modulate cancer metabolism. To address this, the authors further performed mass spectrometry analysis and successfully discovered PFKFB3 as a putative binding partner for AGPG.

2 | AGPG ACTS THROUGH PFKFB3 INTERACTION

Through a variety of in vitro and in vivo experiments, the authors successfully elucidated the functional significance of AGPG and PFKFB3 binding in reprogramming glucose metabolism. So far, this is the first study to report the lncRNA binding partner of PFKFB3, making it possible to study PFKFB3 from a new perspective. Mechanistically,
AGPG sterically blocks the association between anaphase-promoting complex (APC/C) and PFKFB3, ultimately halting the ubiquitination and degradation of PFKFB3. As previously reported, PFKFB3 is an important target for cancer therapeutics because of its role in driving glycolysis and cell proliferation in cancer cells [11]. Therefore, such AGPG-mediated PFKFB3 stabilization nicely explained how AGPG is involved in these two oncogenic processes. Notably, a previous study reported a lncRNA-PFKFB2 complex in promoting metastasis through the alteration of glycolysis [12]. Together with current findings for the AGPG-PFKFB3 complex, it would be interesting to see if a general lncRNA-based regulation of the PFKFB family of enzymes could exist. Taken together, these data provide the first step for understanding the intricate mechanism of the fundamental concepts missing regarding the stabilization of PFKFB3 and its novel regulator, AGPG, in metabolic remodeling.

3 | AGPG SERVES AS A NON-CODING LINKER BETWEEN P53 AND GLUCOSE METABOLISM

To explore the upstream regulation of AGPG, the authors further discovered p53 as a putative transcription factor that negatively regulates AGPG expression. This intriguing finding not only connected AGPG with various cellular stresses signaling via p53, but also explained the oncogenic upregulation of AGPG in ESCC with p53 deficiency. Given the critical role of p53 in controlling glucose metabolism [13], the discovery of AGPG as a non-coding transcript of p53 provides a novel insight into this process.

4 | AGPG IS A BIOMARKER AND A THERAPEUTIC TARGET FOR ESCC

While metabolic reprogramming in cancer is vital for cancer initiation and progression, efficacious therapeutics are limited. Despite the numerous available therapies, ESCC is currently the foremost cause of cancer associated deaths, thus calling for a need to identify novel biomarkers [14]. Pathologically, the authors showed that the overexpression of AGPG was correlated with poor survival rates in ESCC patients. Notably, upon depletion of AGPG using an optimized lncRNA inhibitor, a dramatic decrease in ESCC patient-derived xenograft tumor growth was observed. Therefore, identification of novel cancer-associated lncRNAs, such as, AGPG, makes it an attractive biomarker and a therapeutic target in ESCC. With this important information, it would be also interesting to see AGPG exploited pharmaceutically into inhibitors for personalized cancer therapy.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE
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CONSENT FOR PUBLICATION
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AVAILABILITY OF DATA AND MATERIALS
Not applicable.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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AUTHORS’ CONTRIBUTIONS
REV and WW wrote the manuscript. All authors read and approved the final manuscript.

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