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RESEARCH HIGHLIGHT

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,

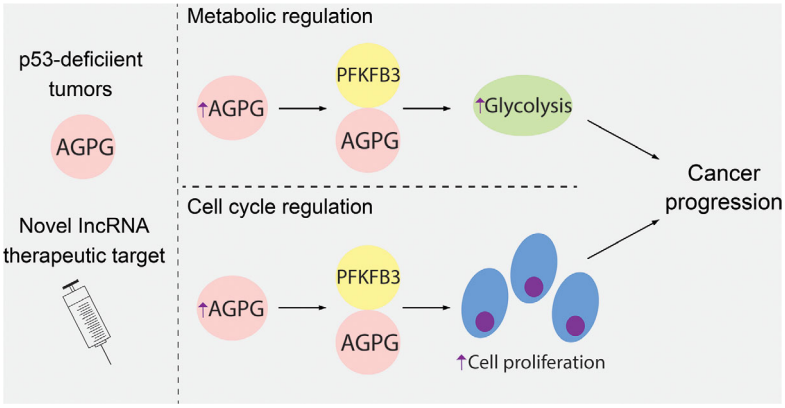

FIGURE 1 Illustration of the oncogenic role of lncRNA *AGPG* in driving p53-deficient ESCC development. Loss of p53 promotes *AGPG* expression, which in turn forms a complex with PFKFB3 to induce glycolysis and cell cycle progression. This *AGPG*-dependent oncogenic alteration contributes to the ESCC development and could be used as a therapeutic target for ESCC treatment

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.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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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