Canadian Journal of Cardiology 35 (2019) 1433–1434

Editorial

Early Evidence for the Role of lncRNA TUG1 in Vascular Remodelling in Pulmonary Hypertension

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See article by Wang et al., pages 1534–1545 of this issue.

Pulmonary arterial hypertension (PAH) is a multifactorial and life-threatening condition driven by progressive vasoconstriction and remodelling of distal pulmonary arteries (PAs) with resulting elevation of PA pressure that inexorably progresses toward right ventricular (RV) dysfunction. Despite recent advances in the available therapies, PAH remains a serious disease with significant morbidity and mortality.[1] It is now established that aberrant proliferation and resistance to apoptosis of PA resident cells, especially PA smooth muscle cells (PASMCs), sustained by epigenetic alterations, are key components of vascular remodelling for which current available therapies are largely ineffective.[2] Although substantial advances have been made in deciphering the pathogenesis of PAH, our understanding of the epigenetic landscape responsible of the cancer-like phenotype of PAH cells remains limited, hence precluding the development of new and effective therapeutic modalities.[3]

With the advent of next-generation sequencing and bioinformatics tools, a class of nontranslated transcripts longer than 200 nucleotides, called long noncoding RNAs (lncRNAs), have surfaced. By serving as scaffolds (by binding multiples proteins and facilitating the assembly of chromatin regulatory complexes), decoys (by binding and sequestering proteins/miRNA, thereby inhibiting their normal functions), or guides (by recruiting epigenetic regulators onto specific chromosomal loci), lncRNAs have emerged as new and versatile regulators of gene expression, thus arousing a great interest in various areas of research.[4] In recent years, the repertoire of lncRNA aberrantly expressed in pathological conditions has rapidly expanded.[5] Nevertheless, their functional significance and therapeutic potential remain poorly defined, especially in pulmonary hypertension (PH).

In a paper published in this issue of the *Canadian Journal of Cardiology*,[6] Wang et al. reports that the evolutionarily conserved lncRNA taurine-upregulated 1 (TUG1) is upregulated in lung tissues from patients with PAH and mice exposed to chronic hypoxia. Consistently, *in vitro* exposure of PASMCs to hypoxia or interleukin 6—2 triggers of vascular remodelling in PH—stimulated TUG1 expression. To determine whether the hypoxia-induced hyperproliferative and apoptosis-resistant phenotype of PASMCs is influenced by TUG1, a bidirectional approach, using small interfering RNA and CRISPR/Cas9-based synergistic activation mediator system, was used. The authors demonstrated that knockdown of TUG1 reduces PASMC proliferation and survival, whereas its overexpression exerted opposite effects. To mechanistically explain its function, the authors hypothesized that TUG1 acts as an endogenous competing RNA that sponges miR-328-3p previously linked to PH pathogenesis.[7,8] As predicted, interaction between miR-328 and TUG1 was experimentally validated, and subsequent analyses demonstrated that the effects of TUG1 on PASMC proliferation are largely mediated by miR-328-3p. Accordingly, expression of key factors of PAH progression and direct targets of miR-328, such as provirus integration site for Moloney murine leukemia virus (PIM-1) and insulin growth factor 1 receptor (IGF-1R),[7-9] were diminished by TUG1 inhibition under hypoxic conditions. It must be noted that, in addition to miR-328, TUG1 was reported to serve as a molecular sponge for other microRNAs, including miR-223,[10] miR-29,[11] and miR-204,[12] for which the downregulation in PASMCs promotes a proliferative/synthetic state.[13-16] Although the relationship between TUG1 and these miRNAs remains to be investigated in the context of PAH, the observation that TUG1 targets multiple miRNA suggests that its inhibition may exert combinatorial effects on multiple factors and signalling pathways that contribute to vascular obliteration of small PAs. The nonspecific location of TUG1 in PASMCs, distributed both in the nucleus and cytoplasm, also suggests that TUG1 regulates nuclear events in addition to gene expression at the post-transcriptional step.

Received for publication June 21, 2019. Accepted June 25, 2019.

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See page 1434 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.06.023

From a clinical perspective, Wang et al. tested the preventive effect of lung-targeted TUG1 knockdown in mice challenged with chronic hypoxia. Although the relevance of this animal model to human PAH is uncertain, as mice subjected to long-term hypoxia do not develop severe pulmonary vascular remodelling and RV failure, *in vivo* silencing of TUG1 markedly attenuated chronic hypoxia-induced elevation of the RV systolic pressure and PA wall thickening. Given that most of patients with PAH are diagnosed at an advanced stage of the disease, further experiments are necessary to determine whether TUG1 suppression improves established PAH in more clinically relevant animal models (namely, the monocrotaline and Sugen/hypoxia rat models).[17] Interestingly, recent works have also provided evidence that downregulation of TUG1 inhibits cardiomyocyte apoptosis[18] and prevents cardiac fibroblast activation.[19] Because cardiomyocyte cell death and fibrosis constitute key features of pathological RV remodelling, it can be speculated that inhibition of TUG1 may exert direct cardioprotective effects in the setting of PAH. Thus, assessing the therapeutic value of TUG1 inhibition in the PA banding model in which RV remodelling and dysfunction occur independently of changes in the pulmonary vasculature could be informative.

Additional work thus needs to be done to understand the role played by TUG1, or lncRNAs in general, in PAH. However, the identification of TUG1 as new lncRNA implicated in PH is an important step toward dissection of the molecular mechanisms underlying vascular remodelling and offers an interesting option for therapeutic development.

Disclosures

The authors have no conflicts of interest to disclose.

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