The miRNA-Kallikrein interactions: Adding a new dimension

Maria D Pasic^{1,2}, Georgia Sotiropoulou³, and George M Yousef^{1,4,*}

¹Department of Laboratory Medicine and Pathobiology; University of Toronto; Toronto, Canada; ²Department of Laboratory Medicine; St. Joseph's Health Centre, Toronto, Ontario, Canada; ³Department of Pharmacy; School of Health Sciences; University of Patras; Rion-Patras, Greece; ⁴Department of Laboratory Medicine and the Keenan Research Centre for Biomedical Science at the Li Ka Shing Knowledge Institute of St. Michael's Hospital; Toronto, Canada

Kallikrein-related peptidases (KLKs) represent the largest cluster of serine proteases in the human genome, comprising 15 genes located on chromosome 19q13.¹ Members of the human kallikrein family were found to be involved in carcinogenesis and represent potentially useful clinical biomarkers and therapeutic targets, especially for endocrine-related malignancies.² Apart from a well-characterized promoter of the prostate specific antigen gene (PSA; KLK3), little is known about the factors that control kallikrein expression at the transcriptional and post-transcriptional levels. Recently, the miRNA-kallikrein axis of interactions was reported by different research groups.³ Target prediction analysis and experimental validation have shown that multiple kallikrein genes are miRNA targets and that miRNAs contribute to the regulation of kallikreins at the post-transcriptional level. A recent study published in *Oncoscience*⁴ added a new dimension to the story by showing, for the first time, that the kallikrein-miRNA interaction is bi-directional as miRNAs can act as downstream effectors of kallikreins. When human kallikrein-related peptidase 5 (KLK5) was stably transfected to KLK5 non-expressing breast cancer cell lines, this led to significant global downregulation of numerous miRNAs, while only few miRNAs were upregulated. Bioinformatic analysis showed that many of the targets of these miRNAs are related to extracellular matrix degradation. Taken together, these results show that kallikreins can

affect the extracellular matrix either directly through their proteolytic activity or indirectly through miRNA-mediated pathways.

In a search for potential mechanisms by which KLK5 could alter the expression of miRNAs, key molecules that are involved in miRNA biogenesis, (including Dicer, Drosha, and a number of argonautes) were compared between KLK5 stably transfected cells and their parental counterparts. There was a significant decrease in the expression of these critical enzymes, which could explain, at least in part, the effect of KLK5 on miRNAs. Increasing/Scaling up complexity, the study showed that KLK5-upregulated miRNAs target Dicer, Drosha and other key enzymes in miRNA biogenesis. Adding the pieces of the puzzle together, these findings and other recent studies⁵ show the presence of kallikrein-miRNA networks of interactions with both divergent (when the same miRNA can control multiple kallikrein and non kallikrein targets) and convergent (when multiple miRNAs can target the same kallikrein or non-kallikrein gene) properties. The results hint to the presence of feedback mechanisms that control this network. Another innovative message conveyed by the study is the use of a “multiparametric” predictive score for assessment of recurrence-free survival in breast cancer.

The study also highlights the great advantage of “integrated genomics.” It shows clearly that different levels of molecular alterations interact to produce the disease phenotype and that

understanding the crosstalk between distinct classes of molecules can provide a clearer/more representative picture by eliminating the limitations resulting from looking at one type of change at a time.

Furthermore, this study raises new/additional questions that need to be addressed. For instance, what is the exact mechanism by which kallikreins affect miRNA expression? Is it possible that at least some kallikreins function as nuclear transcription factors that can control miRNA promoters? Moreover, as recently postulated in the competing endogenous RNA hypothesis, could miRNAs be the letters of a new language through which kallikrein genes crosstalk with each other through competing over a limited pool of miRNAs?⁶

Recent Genome Wide Association Studies (GWAS) revealed important single nucleotide polymorphisms (SNPs) in the kallikrein locus.⁷ Could these SNPs affect KLK-miRNA interactions by altering miRNA response elements of the kallikrein genes and contribute to cancer pathogenesis or progression? The study also opens the door for further investigation of the molecular attributes of the different breast cancer subtypes to understand the biology behind the aggressive or indolent tumor behaviors. This represents a key step toward developing new more-effective targeted therapies directed to specific patient subsets, heralding the era of personalized medicine.

Finally, it is now clear that molecular profiling approaches can enable the use of a combination of multiple biomarkers

*Correspondence to: George M Yousef; Email: yousefg@smh.ca

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(genes, proteins, miRNAs, etc.) to significantly enhance our ability to assess prognosis. This study and similar ones also

highlight the important utility of publicly available databases, for example The Cancer Genome Atlas (TCGA). These

high quality databases are a great asset for researchers in the rapidly expanding era of genomic medicine.

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