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Educational Article

The orchestration of gene expression and the editing role of microRNA

M. Fossum [a,b,*], M. Kaefer [c], K.W. Herbst [d], L. Harper [e], G.M.A. Beckers [f], C.P. Nelson [g], M. Garriboli [h], A. Nieuwhof-Leppink [i], D. Bagli [j], N. Kalfa [k,l], On behalf of ESPU Research Committee

[a]Department of Pediatric Surgery, Rigshospitalet, Dept of Medical Sciences, Copenhagen University, Copenhagen, Denmark

[b]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[c]Riley Hospital for Children, Indiana University, Indianapolis, IN, United States

[d]Division of Urology, Department of Research, Connecticut Children's Medical Center, Hartford, CT, United States

[e]Service de Chirurgie Pédiatrique, Hôpital Pellegrin-Enfants, CHU de Bordeaux, France

[f]TZ Turnhout, Turnhout, Belgium

[g]Department of Urology, Boston Children's Hospital and Department of Surgery, Harvard Medical School, Harvard University, Boston, MA, USA

[h]Department of Paediatric Urology, Evelina Children's Hospital, Guy's and St. Thomas NHS Foundation Trust, London, United Kingdom

[i]University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, Netherlands

[j]Division of Urology, Departments of Surgery and Physiology, University of Toronto, Developmental and Stem Cell Biology, The Hospital for Sick Children and Research Institute, Toronto, Ontario, Canada

[k]Service de Chirurgie Urologique Pédiatrique, Hôpital Lapeyronie, CHU de Montpellier, Université de Montpellier, France

[l]Institut Debrest de Santé Publique IDESP, UMR INSERM — Université Montpellier, Montpellier, France

* Correspondence to: Prof. Magdalena Fossum, Department of Pediatric Surgery, Rigshospitalet University Hospital, 2100 Copenhagen, Denmark.
maria.magdalena.fossum@regionh.dk (M. Fossum)

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Abstract
In this short educational communication the ESPU Research Committee presents the role of non-coding RNA and how these can affect gene expression. In particular we discuss the role of microRNA on post transcriptional changes and how these may cause pathological conditions within Pediatric Urology and how microRNA could be useful in future clinical practice.

The central dogma of molecular biology, as described in 1953, is that DNA is transcribed into messenger RNA (mRNA) that is thereafter transported to the cytoplasm and translated into chains of amino acid which make up proteins [1]. Before the entire human genome was deciphered, the belief was that the complexity of different cells, tissues, organs and finally the organism it constituted, could all be found in the well-protected DNA in the nucleus of each cell.

The subsequent understanding that the human genome consisted of merely ~20,500 genes, the same range as other mammals (and only 7% of these are vertebrate specific) was perceived by many as a disappointment [2], as it would not explain the enormous cellular diversity we know exists. Today, we know that only approximately 2% of our genome encodes proteins and the rest, 97–98% of all DNA information, results in non-coding RNAs (ncRNAs; i.e., they do not translate into proteins). According to the logic of nature, it would be surprising if the cell would go through the trouble of producing such a vast array of RNAs unless they served a purpose. Although most of the ncRNA is made up of ribosomal RNA, recent work has shown that the remaining non-coding RNA sequences are essential for cell hemostasis and regulation of biological functions.

Transcriptomics is the study of all RNA molecules in the cell, not only the translated ones. However, this exciting field is yet quite unexplored. There are two key contemporary techniques in the field: microarrays, which quantify a set of *predetermined* sequences, and RNA sequencing (RNA-Seq), which uses high-throughput sequencing to capture *all* sequences.

Non-coding RNA can be divided into different categories, often related to size and form. For instance, long non-coding RNAs (lncRNAs) are more than 200 nucleotides long. These are believed to be important for regulation of transcription [3]. Circular RNAs (circRNA) have an unclear function but several publications have found these cell structures in excess in pathological conditions [4].

One particularly interesting group are called microRNAs (miR), and as suggested by the name, are small; only about 22 nucleotides long. A quantitative increase in miR usually leads to degradation of mRNA (known as 'post-transcriptional negative regulation') thereby acting as down-stream regulators of gene expression itself. Changes in a specific miR concentration can rapidly change cell dynamics, allowing gene expression or mRNA degradation to quickly adjust to cell environmental changes. These changes are much more rapid than pre-translational changes of the DNA structure (i.e., epigenetic histone acetylation and cytosine methylation) [6,7]. MiR molecules can not only cross the nuclear membrane to the cytoplasm but can also pass through the cell membrane itself (a feature which traditional mRNA is incapable of). In so doing, miR are able to act as signaling molecules between cells and their surrounding environment. MiRs have been identified as being important for regulating developmental stages in embryogenesis, circadian rhythm, metabolism, and adaption to environmental changes [8–11].

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The role of miR is analogous to the role of the editorial board of a journal, where the language (mRNA) of a manuscript is reviewed and edited (miR) before finally being sent to the printer (rRNA) to produce the final published article (proteins). To date, over 2300 miRs have been described and these regulate nearly 60% of protein coding genes [5]. MiRs act as master regulators of a myriad of cellular processes, and many miRs are promising therapeutic targets or disease biomarkers.

In pediatric urology, miR may be relevant in different perspectives as: 1) they may explain urological disease despite normal genes, 2) they may be used as therapeutic targets in the future, and 3) they may serve as biomarkers to diagnose or follow some conditions. Despite these observations, there remains a lack of knowledge related to miR in normal urogenital tissues and normal biological processes such as development, growth, wound healing, or pathological conditions [12]. For instance, in the common case of isolated hypospadias, only a few percent of patients present with an identifiable molecular (genetic) reason for their phenotypic appearance. If high levels of miR are associated with hypospadias development, they may help elucidate why hypospadias develops even with the presence of completely normal penile genes [13]. Other studies have proposed tumor-suppressing miR for future treatment of Wilm's tumors or as biomarkers for monitoring urological cancers such as testicular cancer [14,15]. In the future, miR analyses could prove valuable for understanding the etiology of pediatric urological diseases, and act as biomarkers in conditions ranging from chronic cystitis to rejection after renal transplantation. It is also realistic to expect that miR-based pharmaceuticals or molecules interferering with miR, will be developed for local treatment of different bladder conditions.

Within pediatric urology, we need to ally ourselves with basic scientists, high-throughput micro-molecular methodologies, and bioinformaticians to increase our understanding of post-transcriptional gene editing with respect to congenital urinary malformations and their secondary effects on health. Intracellular and extracellular miRs, will likely provide for early detection of diseases and better cure in many of pediatric urological conditions. The future perspectives are exciting, and we may be opening a treasure chest containing a health-related fortune for better diagnostics and new treatment modalities.

References

[1] Watson JD, Crick FH. Genetical implications of the structure of deoxyribonucleic acid. Nature 1953;171(4361):964—7.
[2] Pertea M, Salzberg SL. Between a chicken and a grape: estimating the number of human genes. Genome Biol 2010;11(5):206.
[3] Ma L, Cao J, Liu L, Du Q, Li Z, Zou D, et al. LncBook: a curated knowledgebase of human long non-coding RNAs. Nucleic Acids Res 2019 Jan 8;47(D1):D128—34.
[4] Vromman M, Vandesompele J, Volders PJ. Closing the circle: current state and perspectives of circular RNA databases. Briefings Bioinf 2021 Jan 18;22(1):288—97.
[5] Alles J, Fehlmann T, Fischer U, Backes C, Galata V, Minet M, et al. An estimate of the total number of true human miRNAs. Nucleic Acids Res 2019;47(7):3353—64.
[6] Kaefer M, Bagli D, Kalfa N, Beckers G, Harper L, Herbst K, et al., ESPU Research Committee. Genetics: the diagnostic frontier in pediatric urology. J Pediatr Urol 2021;17(6):803—4.
[7] Bagli D, Fossum M, Harper L, Herbst K, Nieuwhof-Leppink A, Beckers G, et al., ESPU Research Committee. Epigenetics: through the pediatric urology looking glass. J Pediatr Urol 2022. S1477-5131(22)218-2 [Advance online publication].
[8] Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993 Dec 3;75(5):843—54.
[9] Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 1993 Dec 3;75(5):855—62.
[10] Kinoshita C, Okamoto Y, Aoyama K, Nakaki T. MicroRNA: a key player for the interplay of circadian rhythm abnormalities, sleep disorders and neurodegenerative diseases. Clocks Sleep 2020 Jul 23;2(3):282—307.
[11] Vienberg S, Geiger J, Madsen S, Dalgaard LT. MicroRNAs in metabolism. Acta Physiol 2017 Feb;219(2):346—61.
[12] Chamorro CI, Eisfeldt J, Willacy O, Juul N, Fossum M. A database on differentially expressed microRNAs during rodent bladder healing. Sci Rep 2021 Nov 8;11(1):21881.
[13] Elias FM, Nishi MY, Sircili MHP, Bastista RL, Gomes NL, Ferrari MTM, et al. Elevated plasma miR-210 expression is associated with atypical genitalia in patients with 46,XY differences in sex development. Mol Genet Genomic Med 2022 Dec;10(12):e2084.
[14] Luo X, Dong J, He X, Shen L, Long C, Liu F, et al. MiR-155-5p exerts tumor-suppressing functions in Wilms tumor by targeting IGF2 via the PI3K signaling pathway. Biomed Pharmacother 2020 May;125:109880.
[15] Lobo J, Leão R, Gillis AJM, van den Berg A, Anson-Cartwright L, Atenafu EG, et al. Utility of serum miR-371a-3p in predicting relapse on surveillance in patients with clinical stage I testicular germ cell cancer. Eur Urol Oncol 2021 Jun;4(3):483—91.

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