Journal of Pediatric Urology (2022) 18, 464–465

Educational Article

Epigenetics: Through the pediatric urology looking glass

Darius Bagli [a], Magdalena Fossum [b,c,*], Luke Harper [d], Katherine Herbst [e], Anka Nieuwhof-Leppink [f], Goedele M.A. Beckers [g], Nicolas Kalfa [h,i], Martin Kaefer [j], On behalf of the ESPU Research Committee

[a]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

[b]Department of Pediatric Surgery, Rigshospitalet, Copenhagen University, Copenhagen, Denmark

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

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

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

[f]Department Psychology, Urotherapy and Urology Section, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, the Netherlands

[g]TZ Turnhout, Turnhout, Belgium

[h]Service de Chirurgie et Urologie Pédiatrique, Hôpital Lapeyronie, CHU de Montpellier, and Institut Debrest de Santé Publique IDESP, UMR INSERM — Université Montpellier, France

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

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

* Correspondence to: maria.magdalena.fossum@regionh.dk (M. Fossum)

Keywords
DNA; Epigenetics; Methylation; Histones; Genetics

Received 15 March 2022
Revised 20 May 2022
Accepted 23 May 2022
Available online 29 May 2022

A rudimentary understanding of genetics, especially appreciating normal sequence in DNA vs. DNA sequence errors or mutations, is fundamental to the appreciation of clinical care. However, genetics now shares the biological podium equally with the often mentioned but less familiar field of epigenetics. To begin to appreciate the power and relevance of epigenetics to pediatric urology, one must first hold a manageable concept of what epigenetics is in one's mind.

We learn early in our training that all cells in an organism share the same DNA sequence. What then explains the curious mystery of how the same DNA sequence can give rise to both a neuron and a smooth muscle cell? The answer lies within epigenetics which can be defined as cell-selective regulation of expression of different genes from the same normal DNA sequence [1], i.e., in the absence of mutations. If DNA were all 88 keys on a piano, epigenetics governs whether the piano is accessible, and if so, which keys are played and when. This happens though a set of processes no less elegant than DNA replication itself.

Quite simply, for DNA to be 'played' (i.e., transcribed into RNA and then into gene products) one must have physical access first to the piano (the DNA) and then to the keys (the sequence). This transcription access is either granted or restricted in two fundamental ways. DNA spends most of its time locked away and inaccessible, tightly wrapped around proteins in the nucleus known as histones. In this state the piano itself cannot be reached. However, simple chemical modifications to histone proteins (through removal of small molecules such as methyl or acetyl groups, or amino acids such as lysine) will cause DNA to be unwound from the histones. The piano can then be reached. The opposite, chemical addition to histones, will cause the DNA to re-wrap tightly and become inaccessible once again. Furthermore, the DNA keyboard itself can also be modified through simple secondary addition of methyl groups to specific keys (so called, DNA methylation). This makes individual piano keys unplayable. Thus, only specific tunes can be played, and only specific genes can be transcribed, while others remain inaccessible for transcription.

Through a known and recurring set of enzymes that catalyze the above chemical modifications to DNA and histones, we can now appreciate the existence of a sophisticated level of cell-specific regulation of DNA transcription. These enzymes are often named for their roles. For example the DNA methyltransferases (e.g., DNMTs), or histone acetyl transferases (e.g., HATs) transfer methyl groups to DNA or acetyl groups to histones, respectively, while de-methylases and de-acetylases (e.g., HDACs) remove them. There are many such DNA and histone modifying enzymes comprising the epigenetic machinery of the cell.

Indeed, one of the principal ways a cell alters its transcriptional response to environmental stimuli is through a change in its epigenetic status. As such, the epigenetic enzymatic machinery allows for a highly responsive and dynamic sensing system, permitting cells to respond transcriptionally in both appropriate and inappropriate (pathological) ways. Moreover, enzymatic chemical alterations themselves in DNA (commonly known as DNA methylation marks) can be *inherited and replicated through both cell division in an organism as well as generationally passed to offspring*. Such DNA methylation marks may also be detected as biomarkers of disease [2]. This raises some profound implications for perpetuation of pediatric urological disease states. Many of the conditions we manage, such as renal damage

https://doi.org/10.1016/j.jpurol.2022.05.018

after infection or hydronephrosis/UPJ obstruction, bladder damage after obstruction, or genital maldevelopment due to aberrant gestational environments, are so common that they likely do not have a genetic (mutational) basis. From a cell perspective, infection, obstruction, and hormonal milieu may all be considered epigenetically responsive environmental stimuli.

Consider hypospadias. Over the last decades several candidate mutations or sequence variations have been detected and associated with hypospadias. But sequence aberrations alone cannot account for the high incidence of hypospadias (1:150—300 live births). Moreover, the rising tide of environmental hormonal disrupters provides ample opportunity to consider how epigenetic machinery may be altering expression of even the normal sequence of genes in the hypospadias patient. For example, estrogen can stimulate DNMT activity in genital fibroblasts, and reduce expression of principle genital tubercle development genes Wnt5a and HoxA13. Inhibiting DNMT activity can rescue this estrogen-induced Wnt5a and HoxA13 gene dysregulation [3].

Following de-obstruction or de-pressurizing of the obstructed bladder (i.e., by resection of urethral valves or BPH, or for neurogenic bladder), persistent disease in smooth muscle cells (SMC) such as contractile derangement, ongoing fibrosis, and SMC overgrowth is common. Recently, bladder SMCs have been shown to respond epigenetically to the stimulus of their own disorganized extracellular environment, altering both their DNA methylation and the activity of their methylation enzymes. Returning human SMC from obstructed bladders (vs. from normal bladders) to a normal environment, cultured outside the bladder does not rescue their dysfunction [4,5]. Drugs which inhibit the methylation enzymes, though not specific enough for widespread clinical use in non-cancer disease, can rescue and restore more normal phenotype to obstructed bladder muscle in animal models [6], strongly suggesting a role for epigenetic processes in these myopathic conditions [7].

Urothelial cells exposed to uropathogenic E.coli respond with increased DNA methylation activity, and hypermethylation and reduced transcription of p16, a gene that normally suppresses urothelial cell overgrowth [8]. This may underly the urothelial proliferation so common in UTI and may leave permanent methylation marks on DNA that could represent a future way to track subsequent UTI proclivity or better select patients for prophylactic surgery or antibiotics [2,9].

An exciting multitude of biological and extracellular factors regulate the epigenetic machinery. A fuller discussion is beyond the scope of this brief overview. However, appreciating the potential of epigenetic changes and responses on top of specific alterations in DNA sequence (genetics) adds a new level of complexity, and new opportunity to carry us through the looking glass in the discovery of underlying causes of disease in pediatric urology.

References

[1] Rodenhiser D, Mann M. Epigenetics and human disease: translating basic biology into clinical applications. Can Med Assoc J 2006;174:341—8. https://doi.org/10.1503/cmaj.050774.

[2] Levenson VV. DNA methylation as a universal biomarker. Expert Rev Mol Diagn 2014;10:481—8. https://doi.org/10.1586/erm.10.17.

[3] Jiang J-X, Aitken KJ, Kirwan TP, Hopyan S, Bägli DJ. Estrogen induced downregulation of gene expression and cell biological processes critical for genital tubercle formation via DNA methylation. Epigenet Chromatin 2013;6:P33. https://doi.org/10.1186/1756-8935-6-s1-p33.

[4] Herz Db, Aitken K, Bagli DJ. Collagen directly stimulates bladder smooth muscle cell growth in vitro: regulation by extracellular regulated mitogen activated protein kinase. J Urol 2003;170:2072—6. https://doi.org/10.1097/01.ju.0000091810.33953.13.

[5] Lin H-K, Cowan R, Moore P, Zhang Y, Yang Q, Peterson JA, et al. Characterization of neuropathic bladder smooth muscle cells in culture. J Urol 2004;171:1348—52. https://doi.org/10.1097/01.ju.0000108800.47594.8b.

[6] Sidler M, Aitken KJ, Jiang J-X, Yadav P, Lloyd E, Ibrahim M, et al. Inhibition of DNA methylation during chronic obstructive bladder disease (COBD) improves function, pathology and expression. Sci Rep-Uk 2021;11:17307. https://doi.org/10.1038/s41598-021-96155-4.

[7] Liu R, Leslie KL, Martin KA. Epigenetic regulation of smooth muscle cell plasticity. Biochimica Et Biophysica Acta Bba - Gene Regul Mech 2015;1849:448—53. https://doi.org/10.1016/j.bbagrm.2014.06.004.

[8] Tolg C, Sabha N, Cortese R, Panchal T, Ahsan A, Soliman A, et al. Uropathogenic E. coli infection provokes epigenetic downregulation of CDKN2A (p16INK4A) in uroepithelial cells. Lab Invest 2011;91:825—36. https://doi.org/10.1038/labinvest.2010.197.

[9] Tolg C, Bgli DJ. Uropathogenic Escherichia coli infection: potential importance of epigenetics. Epigenomics-Uk 2012;4:229—35. https://doi.org/10.2217/epi.12.5.