A Historical Perspective From One of the First Applications of Omics/Microarray Technology to Sexual Medicine

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NO DISCLOSURES
OMICS TERMINOLOGY

OMICS: technologies and data defining roles, relationships, and actions of various types of molecules in cells

- **TRANSCRIPTOMICS**: multiple DNA transcription into RNA, mainly as global transcriptional signatures (GTS) either mRNA (gene- or mRNA-GTS) or miRs (miR-GTS)

- **GENOMICS**: set of genetic instructions provided by DNA and its mutations

- **PROTEOMICS**: global translational signatures into proteins

- **METABOLOMICS**: global interaction of metabolites
COVERED IN THIS TALK

▪ Only transcriptomics for PD and ED in the penis, not including FSD

▪ Potential implications for stem cells and the genomic clock modulation related to sexual medicine (SM)

▪ Conceptual key stages and promise
# Relative Impact of Transcriptomics in Sexual Medicine Research

<table>
<thead>
<tr>
<th>TRANSCRIPTOMICS</th>
<th>Peyronie's disease</th>
<th>Erectile dysfunction</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td></td>
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<tr>
<td>mRNA-GTS (gene-)</td>
<td>DNA microarray</td>
<td>Year, first one</td>
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<tr>
<td>miR-GTS (miR)</td>
<td>microRNA</td>
<td>Year, first one</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>Number of exp. papers (reviews)</td>
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<td><strong>Our group</strong></td>
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<td>Number of exp. papers (reviews)</td>
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PIONEERING OMICS PAPERS IN SEXUAL MEDICINE FROM 2002-2004

DNA microarrays/mRNA-GTS in Peyronie’s disease (PD)


KEY POINTS FROM THESE 2002-4 PAPERS

- Human PD plaques vs control tunica albuginea (TA). Microarrays/RT/PCR/westerns. **Up**: pleiotrophin (osteoblast recruit), MCP 1 (inflammation), elastase (elastic fiber breakdown), ASMA, desmin (myo-fibroblasts); **Down**: ubiquitin & Id-2 (tissue remodeling), First comprehensive PD plaque transcriptional pathophysiology

- Human PD/TA & Dupuytren nodules (DN)/normal palmar fascia, **Up** common in PD and DN: collagen degradation: MMP2 and MMP9, thymosins (MMP activators); (b) ossification: OSF-1, etc

  Some gene families vary similarly in PD and DD suggesting common pathophysiology and therapy
HOW DID mRNA-GTS STUDIES IN PD CONTINUE OVER THE NEXT 15 YEARS?

JUST THESE PAPERS:


KEY POINTS FROM THESE PAPERS

- mRNA-GTS of human PD cells identified fibro-proliferative, myogenic (myofibroblasts), inflammatory, and collagen turnover genes, differentiating them from TA or CC-SM cells, and responding to TGFβ1, by upregulation of IGF-1, ACTG2, MYF5, ACTC1, PSTN, COL III, MMP3.

- Suggested novel PD combination therapy by targeting genes improving collagenase action and counteracting fibromatosis by inhibiting myofibroblast generation, proliferation, or apoptosis.

- Review paper discussed PD genetics, and PD Omics.
HOW THIS MEAGER OMICS FOCUS ON PD RESEARCH MAY BE INTERPRETED?

Since inception in 2002 just 3 experimental papers and 4 reviews/comments in 17 years (no miR-GTS)!!!

- Virtually non-existent NIH and pharmaceutical funding for PD translational research, particularly for OMICS in sexual medicine
- Difficulties to get MD clinicians interested in OMICS
- Despite predominant focus on miR research in China/Korea, PD may not be significant there?
TRANSCRIPTOMICS IN ED RESEARCH STARTED IN 2005

- Pioneer papers:

- Their key points:
  - Discussion of the most promising methods (such as gene chip) and RNA and protein analysis
  - Type 1 diabetic rats (streptozotocin) by DNA microarrays & qRT-PCR, with some unexpected genes (ceruloplasmin)
SOME RECENT EXAMPLES: 2007-2019


INADEQUATE PROGRESS ON mRNA-GTS FOR ED (15 exp. papers/14 years)

- Publications from various SM basic research intensive groups, mainly in the US, but little or no follow-up or human translation

- Studies on corporal tissue, endothelial cells, pelvic ganglion, in animal models

- ED in diabetes and cavernosal nerve damage

- In vivo effects of PDE5i, BPA, maxiK, stem cells
Small RNAs (22 b) regulating gene expression into mRNAs/proteins

Early indicators of phenotypic changes in plasma, serum, saliva, tissues, and tissue sections; diagnostic and therapy biomarkers for pathophysiology mechanisms, and to devise new therapies
PIONEER 2014 PAPERS ON miR-GTS IN ED

- Pioneer papers (2014):

- Key Points: together with mRNA-GTS, defined corporal pathophysiologial targets of bisphenol A exposure, and aging, and possible mechanisms
THE STUDY OF miR-GTS IN ED RESEARCH IS ADVANCING FASTER

- 7 other exp. papers in 2015-2019, excluding those on individual miRs, mostly from China
- None in men; some led to papers testing selected individual miRs
- Recent examples:


A NOVEL IMPACT OF mRNA-GTS AND miR-GTS IN ED AND OTHER UROLOGY RESEARCH: STEM CELL DAMAGE AND IDENTITY BIO MARKERS

Pioneering (and only ones, so far) papers:


KEY POINTS OF miR-GTS PAPERS FOR STEM CELL DAMAGE AND IDENTITY

- Stem cells are damaged by the noxious systemic disease milieu in diabetes/obesity, impairing their use as autografts for ED and other urological conditions.

- miR-GTS are biomarkers of this process.

- Human stem cell therapy is so far suboptimal, in contrast to animal models, possibly because of the absence of quality control.
FUTURE OF miR-GTS FOR THE THERAPY AND FOLLOW-UP OF ED AND PD IN PERSONALIZED SEXUAL MEDICINE

- If confirmed in men, miR-GTS may improve stem cell therapy and also select individual miR-s or exosomes for ED and PD therapy.

- miR-GTS may follow up the response of any therapy in ED/PD.

- These are key research areas in China and elsewhere, but not really in USA.
miR-GTS MAY ALSO DETECT KEY miRs TO REVERSE THE EPIGENETIC CLOCK IN PERSONALIZED SEXUAL MEDICINE


- miRs are involved in circadian rhythm, stem cell senescence, and aging

- Challenge: may their expression be modulated to “rejuvenate” sexual function?
WILL SEXUAL MEDICINE RESEARCH MATURE INTO PERSONALIZED CLINICAL OMICS DIAGNOSTICS AND THERAPY?
WHAT ELSE OCCURRED IN PD OMICS?

- Nothing in further gene-GTS, or miR-GTS/Inc-RNAs


Key points:
Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and database searching: 9 up and 16 down: transgelin, creatine kinase B, annexin-1, galactin-7.

Then, only 4 other papers (2009-2014)