

The RW Genome, Epigenetics, Evolution and Pregnancy

Extended abstract of the 3rd Annual Robert G. Edwards lecture to The 20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI) – Paris, France – Dec. 4-7, 2014

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ABSTRACT

ABSTRACT: 60 years of molecular biology have changed our view of the genome. Instead of a ROM (read-only memory), we now realize that the genome is a RW (read-write) data storage system. The relevant discoveries included:

- (1) The elucidation of "natural genetic engineering," biochemical systems responsible for genome changes, at all levels of DNA structure;
- (2) The recognition of cells' ability to control genome function and expression by transcription factor complexes and epigenetic chromatin modifications.

These discoveries allow us to see evolutionary processes as active cell-mediated changes to genome structure. Among the main agents of natural genetic engineering and inscription of epigenetic signals are viruses and mobile genetic elements, including retroviruses. Endogenous mammalian retrovirus has played a major role in placental evolution, and epigenetic regulation is key to understanding the development of the placenta and the embryo. The lecture will outline connections between molecular evolution science and real-world influences on fetal health.

Introduction

Why is a bacterial geneticist who has studied mobile DNA and documented its role in evolution (Shapiro 2011) presenting the third annual Robert G. Edward lecture to a conference on human reproductive biology? Although I do not know the precise answer to this question, I will attempt to stay relevant to the goals of the Congress by recounting some aspects of how reproductive functions are expressed from the eutherian mammal genome and how pregnancy evolved with the involvement of mobile DNA. As I intend to show, these topics are central to understanding the biological roots of many reproductive disorders.

Hoping to Follow Robert Edward's Example

It is a distinct honor to present a lecture named after a courageous and innovative scientific pioneer like Robert Edwards. There are three ways I would like to believe that my work follows his example.

1. **Working in a scientific field with social, political and religious connotations.** Both assisted reproductive biology and the mechanistic bases of evolution fall into the tense intellectual region where science intersects with

people's religious and moral beliefs. In evolution science, this tension manifests itself as a heated battle between militant religious fundamentalism and militant atheism, as represented by evolutionary biologists such as Richard Dawkins. Just as Edward's work affected public policy and the treatment of widespread infertility problems, the attempt to provide a more solid scientific basis for understanding evolution has potential for impact on science and education policy in the USA, South Korea, and other countries. In particular, evolution denial is increasingly linked in American politics to climate change denial.

2. Challenging long-held, comfortable certainties in the academic world.

Edwards worked against negativism about *in vitro* fertilization from the reproductive biology establishment of mid-20th Century Britain. Today, it is a challenge to the long-asserted belief that natural selection and random changes are sufficient to explain evolutionary novelties to point out that molecular biology and genome sequencing reveal regulated cellular processes of genome rewriting that play key roles in evolution. This challenge has aroused hostile responses from the evolutionist establishment (*e.g.*, <http://whyevolutionistrue.wordpress.com/2012/02/18/a-colleague-wrongfully-disses-modern-evolutionary-theory/>).

3. Letting rigorous science and empirical demonstrations settle ideological debates. Edwards wisely chose to validate his belief in our ability to achieve human *in vitro* fertilization by demonstrating that it works. This has to be the model for resolving debates about the nature of the evolutionary process. It requires demonstrations that cell actions can rapidly produce novel organisms. Fortunately, some demonstrations have been with us since the late 19th Century in the form of hybrid speciation (Wilson 1876; Meister 1921; Stebbins 1951; Hulse and Spurgeon 1974; Ma and Gustafson 2008). Moreover, a recent *Nature* paper reminds us that interspecific hybrids leading to new species can form by asexual cell mergers (Fuentes, Stegemann et al. 2014).

The following sections of this extended abstract summarize and annotate the series of Powerpoint slides used in my presentation. They provide a broad selection of references to the literature, so that interested readers can delve further into each point for themselves. The slides plus a linked online version of this extended abstract can be viewed at <http://shapiro.bsd.uchicago.edu/Presentations&Videos.shtml>.

What does “RW Genome” Mean?

The genome is a read-write (RW) system for storing, utilizing and modifying data on cell RNAs and proteins, not a read-only memory (ROM) using the genome as a fixed blueprint.

- Cells actively write information *onto* or *into* their DNA genomes as necessary for survival and reproduction (Shapiro 2013).
- Genome writing can be transient (*e.g.*, nucleoprotein complexes with transcription factors) (Edelman and Fraser 2012; de Mendoza, Sebe-Pedros et al. 2013; Payne and Wagner 2014; Villar, Flicek et al. 2014).

- Genome writing can be heritable over multiple cell divisions (*e.g.*, epigenetic chromatin modifications) (Jablonka 2013; Cheedipudi, Genolet et al. 2014; Zhang and Pradhan 2014).
- Genome writing can alter the sequence and structure of the DNA itself by the many processes that comprise “natural genetic engineering” (NGE) (Shapiro 2010; Shapiro 2011).

Cells operate and actively change genome inscriptions on at least 3 time scales:

1. **Within the cell cycle** (chiefly by transcription/translation controls and signal transduction networks) (Elledge 1996; Morgan 2006; Lindas and Bernander 2013);
2. **Over multiple cell cycles**, as in embryonic development (RW chiefly by epigenetic formatting and reformatting) (Christophersen and Helin 2010; Fedoriw, Mugford et al. 2012; Cheedipudi, Genolet et al. 2014);
3. **Over evolutionary time scales**, as in protein evolution by domain shuffling and rewiring of genomic networks by NGE functions (Kaessmann, Zollner et al. 2002; Evlampiev and Isambert 2007; Kawashima, Kawashima et al. 2009; Shou, Bhardwaj et al. 2011; Sun, Sikora et al. 2012).

Why is a theoretical conceptualization of how the genome operates relevant to reproductive biology?

- Gametogenesis, fertilization and embryonic development generate constantly changing conditions (Barroso, Valdespin et al. 2009; Migicovsky and Kovalchuk 2012; Clift and Schuh 2013; Dean 2014).
- Successful establishment and completion of pregnancy involves writing and rewriting by epigenetic reformatting operations (Bazer, Wu et al. 2010; Lim and Ferguson-Smith 2010).
- Pregnancy evolved thanks to NGE operators creating essential coding sequences and rewiring regulatory signals (Noorali, Rotar et al. 2009; Lynch, Leclerc et al. 2011).
- Understanding the evolution and operation of genome writing in pregnancy is key to developing successful new reproductive diagnostics and therapies for multiple reproductive disorders (van Dijk and Oudejans 2013).

New molecular information is bringing revolutionary changes to our understanding of genome expression (reading) and change (writing).

- A wealth of detailed information about the biochemical nature of genome change (*i.e.*, NGE) (Shapiro 2011); see also (Kazazian 2011; Koonin 2011; Haber 2013);
- Epigenetic inheritance, imprinting and regulation of NGE functions (Suzuki, Ono et al. 2007; Eickbush, Ye et al. 2008; Lisch 2009; Kaneko-Ishino and Ishino 2010; Huda, Bowen et al. 2011; Levin and Moran 2011; Lee, Conley et al. 2012);

- Rewritable epigenetic chromatin modifications mark functionally distinct regions of the genome (Cuddapah, Jothi et al. 2009; Dixon, Selvaraj et al. 2012; Natarajan, Yardimci et al. 2012). This means that multiple factors influence establishment, erasure and maintenance of a correct epigenetic status (Lee, Hore et al. 2014; Roy, Walsh et al. 2014).
- Chromatin remodeling complexes regulate cell differentiation and development (Clapier and Cairns 2009; Euskirchen, Auerbach et al. 2011; He, Liu et al. 2012; Wutz 2013; Chen and Dent 2014).

How molecular biology has transformed evolution science.

- Molecular taxonomy (Woese and Fox 1977; Woese 2004).
- Symbiogenesis (Margulis and Sagan 2002; Embley and Martin 2006; Kutschera 2009).
- Horizontal DNA transfer (Whitaker, McConkey et al. 2009; Danchin, Rosso et al. 2010; Pagan, Smith et al. 2010; Grassi, Grilli et al. 2012; Syvanen 2012; Ivancevic, Walsh et al. 2013).
- Hybridization and whole genome duplications (Stebbins 1951; Anderson 1954; Mallet 2007; Fuentes, Stegemann et al. 2014).
- The evolutionary importance of repetitive mobile genetic elements (Lander, Linton et al. 2001; Kazazian 2004; Feschotte and Pritham 2007; Levin and Moran 2011; Lindblad-Toh, Garber et al. 2011; Feschotte and Gilbert 2012; Chuong and Feschotte 2013; Kapusta, Kronenberg et al. 2013).

Genomic Impact of Mobile Elements

- Interrupt, alter or generate coding regions (alternative splicing to create novel exons = “exonization”) (Nekrutenko and Li 2001; Krull, Brosius et al. 2005; Piriyaopongsa, Polavarapu et al. 2007; Schmitz and Brosius 2011; Huda and Bushel 2013);
- Promote protein evolution by “domain shuffling” (Kaessmann, Zollner et al. 2002; Jiang, Bao et al. 2004; Morgante, Brunner et al. 2005; Evlampiev and Isambert 2007; Kawashima, Kawashima et al. 2009);
- Introduce new transcriptional controls (*e.g.*, promoters, enhancers, transcription factor binding sites, terminators) (Thornburg, Gotea et al. 2006; Huda, Tyagi et al. 2011; Lowe and Haussler 2012; Batut, Dobin et al. 2013; Jacques, Jeyakani et al. 2013; Young, Whiddon et al. 2013; Jjingo, Conley et al. 2014);
- Provide sequences and targets for control by “non-coding” RNA molecules (Piriyaopongsa and Jordan 2008; Kelley and Rinn 2012; Hadjiargyrou and Delihis 2013; Kapusta, Kronenberg et al. 2013; Creasey, Zhai et al. 2014; Harding, Horswell et al. 2014; Lu, Sachs et al. 2014; Matylla-Kulinska, Tafer et al. 2014);

- Provide sites for epigenetic modification and imprinting (Slotkin and Martienssen 2007; Suzuki, Ono et al. 2007; Sekita, Wagatsuma et al. 2008; Weil and Martienssen 2008; Huda and Jordan 2009; Pask, Papenfuss et al. 2009; Zeh, Zeh et al. 2009; de Andrade, Wang et al. 2011; Lisch and Bennetzen 2011; Cruickshanks, Vafadar-Isfahani et al. 2013; Schoorlemmer, Perez-Palacios et al. 2014);
- Distribute similar control cassettes to rewire multi-locus networks throughout the genome (Feschotte 2008; Wang, Bowen et al. 2009; Xie, Chen et al. 2010; Freschi, Courcelles et al. 2011; Shou, Bhardwaj et al. 2011; Barbaglia, Klusman et al. 2012; Kim, Kim et al. 2012; Micale, Loviglio et al. 2012; Sun, Sikora et al. 2012; Cowley and Oakey 2013; Ellison and Bachtrog 2013; Xie, Hong et al. 2013).

Multiple syncytin coding sequence captures and diversity of placental structures in eutherian mammals.

The cell fusion “syncytin” proteins needed for placental development evolved from retroviral envelope (Env) proteins, often from different endogenous retroviruses in different mammalian taxa (Rote, Chakrabarti et al. 2004; Esnault, Priet et al. 2008; Noorali, Rotar et al. 2009; Stoye 2009; Black, Arnaud et al. 2010; Dupressoir, Lavalie et al. 2012; Lavalie, Cornelis et al. 2013).

Mobile Genetic Elements Rewire Genome Networks for Pregnancy

- Endogenous retroviruses provide promoters for placental-specific transcripts and sites for their epigenetic regulation (Mallet, Bouton et al. 2004; Prudhomme, Bonnaud et al. 2005; Macaulay, Weeks et al. 2011; Chuong, Rumi et al. 2013; Macaulay, Roberts et al. 2014).
- The MER20 transposon helped establish a pregnancy-related, progesterone induced regulatory network active in endometrial stromal cells (Bazer, Wu et al. 2010; Lynch, Leclerc et al. 2011).
- The MER39 transposon established pregnancy-specific prolactin expression in primates, while other transposons and retrotransposons achieved the same result in other mammalian orders (Gerlo, Davis et al. 2006; Emera and Wagner 2012).

Epigenetic “Imprinting”

- Parental-specific expression of an extended genome locus (i.e. the same DNA sequences behave differently when inherited through the male or female gamete) (Shire 1989; Sapienza 1990; Lalande 1996; Ferguson-Smith 2011).
- Erasure and imprinting occur in the parental germlines or during gametogenesis (Yamaguchi, Shen et al. 2013; Weaver and Bartolomei 2014).
- Differential DNA methylation and histone modifications are found in paternal and maternal alleles of imprinted loci (Weaver, Susiarjo et al. 2009; Abramowitz and Bartolomei 2012; Weaver and Bartolomei 2014).
- DNA methylation is dependent on specific sequences, often derived from mobile elements (Suzuki, Ono et al. 2007; Gehring, Bubb et al. 2009; Hiura,

Okae et al. 2012; Wohrmann, Gagliardini et al. 2012; Dimitriadou, Noutsopoulos et al. 2013; Lewis, Brant et al. 2014).

- Tissue-specific expression of imprinted loci occurs at specific stages in placental and embryonic development (Fowden, Sibley et al. 2006; Wagschal and Feil 2006; Renfree, Ager et al. 2008; Renfree, Papenfuss et al. 2009; Weaver, Susiarjo et al. 2009; Frost and Moore 2010; Hudson, Kulinski et al. 2010; Kaneko-Ishino and Ishino 2010; Fowden, Coan et al. 2011; Fedoriw, Mugford et al. 2012).

Human Disorders Linked to Epigenetic Remodeling and Imprinting in Pregnancy

- Pre-eclampsia and HELLP Syndrome (Smets, Visser et al. 2006; Blair, Yuen et al. 2013; Ruebner, Strissel et al. 2013).
- Prader Willi and Angelman Syndromes (Lalande 1996; Girardot, Feil et al. 2013; Lewis, Brant et al. 2014).
- Beckwith-Wiedemann and Russell-Silver Syndromes (higher incidence following assisted reproduction technologies?) (Lalande 1996; Le Bouc, Rossignol et al. 2010; Hiura, Okae et al. 2012; Girardot, Feil et al. 2013; Azzi, Abi Habib et al. 2014; Uyar and Seli 2014).
- Low fetal birth weight (Koukoura, Sifakis et al. 2012; St-Pierre, Hivert et al. 2012; Himes, Koppes et al. 2013).
- Neurodegenerative disease (autism?) (Choi and Friso 2010; Babenko, Kovalchuk et al. 2012).
- Predisposition to cardiovascular disease, obesity and type II diabetes (Kaati, Bygren et al. 2002; Kaati, Bygren et al. 2007; Pembrey 2010; Li, Young et al. 2013).

Trans-Generational Epigenetic Inheritance of Pregnancy Stress, Nutrition and Other External Influences

(Anway, Cupp et al. 2005; Weaver 2007; Carone, Fauquier et al. 2010; Parle-McDermott and Ozaki 2011; Walker and Gore 2011; Matzkin, Johnson et al. 2013; Sharma 2013; Susiarjo, Sasson et al. 2013; Burris and Baccarelli 2014; Gapp, Jawaid et al. 2014; Gapp, von Ziegler et al. 2014; Ge, Liang et al. 2014; Li, Saldanha et al. 2014; Yao, Robinson et al. 2014).

Two Take-Home Messages

1. Pregnancy in general, and the placenta in particular, provide the best examples we have of evolutionary innovation by cell agents of genome rewriting (endogenous retroviruses and transposons).
2. Epigenetic control of the newly evolved placental reproduction system is deeply involved in the outcome of every pregnancy.

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