The Evolution of Gene Expression in the Term Placenta of Viviparous Mammals

Don L. Armstrong, Michael R. McGowen, Amy Weckle, Jason Caravas, Dalen Agnew, Sue Savage-Rumbaugh, Eviatar Nevo, Chong J. Kim, Günter P. Wagner, Roberto Romero, and Derek Wildman

Institute for Genomic Biology, Computing Genomes for Reproductive Health, University of Illinois, Urbana-Champaign

CARL R. WOESE
INSTITUTE FOR GENOMIC BIOLOGY
Where Science Meets Society

Introduction

- Function and Evolution of Placenta
  - Major function is the transfer of nutrients, oxygen, and waste between mother and offspring.
  - Highly variable structure and form in mammals, even though major function is conserved.
  - Likely arose before the origin of therian mammals.
  - Form relatively well characterized, but diversity of molecular environment understudied.
  - Role in the evolutionary interplay between maternal and fetal strategies.
- Impacts on Human Health
  - Humans possess a deeply invasive trophoblast layer that can penetrate the myometrium of the uterus [1].
  - Defects in placental growth can lead to pre-eclampsia, which can cause hypertension, proteinuria, and mortality of mother and/or infant [2].
  - Pre-eclampsia has been seen in *Pan troglodytes* [3], and *Gorilla gorilla* [4].
  - Far higher incidence in *Homo sapiens*, with as many as 4% of pregnancies United States affected [2].
- Hypotheses
  - Mechanisms of maintaining maternal-fetal tolerance will be conserved.
  - Altered expression of genes correlates with invasiveness, and therefore pre-eclampsia
  - Maternal/Fetal evolutionary strategies will be reflected in gene expression patterns

Methods

- Fetal placenta tissue from 9 mammalian species collected; total RNA isolated and sequenced using Illumina GA II with an average read size of 150nt
- Additional mammalian placenta sequences obtained from SRA
- QCed using FASTQC, aligned using STAR, and quantified using Cufflinks. Species missing suitable reference (Spider monkey, *S. galili*, *S. carmeli*) were assembled using Trinity and annotated using Diamond against the Human or Mouse transcriptome.
- Ensembl build 80 was the source of annotation.
- Enrichment in human and mouse were calculated using a type-III anova, all other enrichments used Student's t test.

Phylogeny of Species

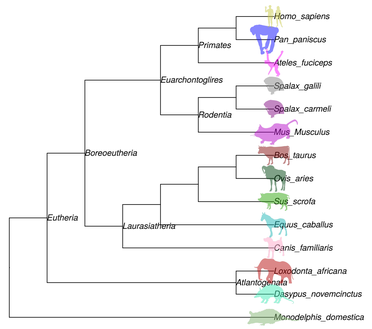

Figure 1: Species tree for organisms studied showing the relationship between species. Silhouettes of species were obtained from `http://phylopic.org`.

Human-specific Genes

Human Symbol	Human Name	FDR	$\log_2$ FC
KISS1	KiSS-1 metastasis-suppressor	0.00032	10.81
MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	0.00019	10.10
CRH	corticotropin releasing hormone	2.1×10^{-5}	9.59
CGA	glycoprotein hormones, alpha polypeptide	1.9×10^{-6}	9.45
ALPP	alkaline phosphatase, placental	2.1×10^{-5}	8.93
7SK		0.00053	8.62
HSD17B1	hydroxysteroid (17-beta) dehydrogenase 1	2.3×10^{-8}	8.60
PAPPA	pregnancy-associated plasma protein A, pappalysin 1	4.7×10^{-9}	8.49
ADAM12	ADAM metallopeptidase domain 12	8.4×10^{-10}	8.45
OLAH	oleoyl-ACP hydrolase	9.7×10^{-7}	8.01

Table 1: 1:1 Human orthologous genes whose expression changed on the human lineage as opposed to all other analyzed species.

Primate-specific Genes

Human Symbol	Human Name	FDR	$\log_2$ FC
FSTL1	follistatin like 1	0.0013	3.41
GNB2L1	guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1	0.64	2.05
CORO1B	coronin, actin binding protein, 1B	0.64	0.25
ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	0.64	0.21
ACTR3	ARP3 actin-related protein 3 homolog (yeast)	0.64	0.42

Core Placenta Transcriptome

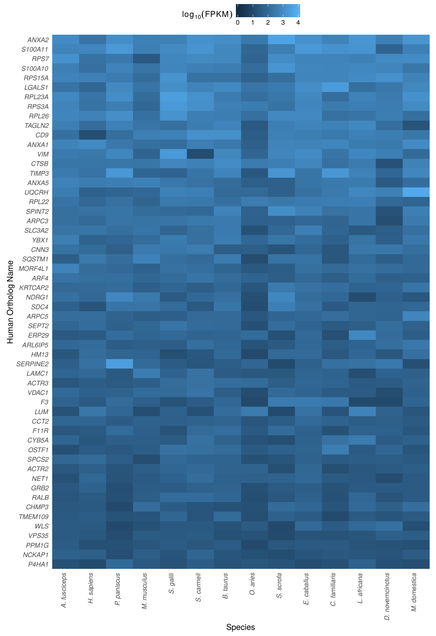

Figure 2: 56 1:1 human ortholog genes expressed (FPKM$\geq$ 10) in placentas of all 14 species studied ordered by median expression without housekeeping genes [5].

PRSS16 Expression

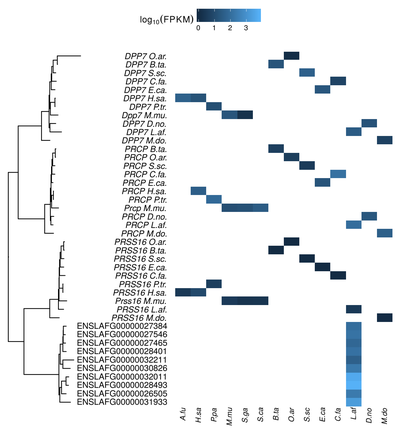

Figure 3: *PRSS16* is highly expressed and massively expanded in *L. africana*, but not in *D. novemcinctus*. It is currently unknown whether this high expression and expansion is a shared feature afrotherians.

KISS1 Expression

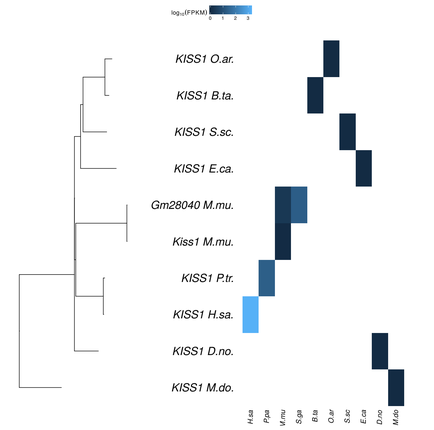

Figure 4: *KISS1*, which is implicated in pre-eclampsia, is significantly more expressed on the human lineage in comparison to all other lineages eamined.

Hormones, Galectins, *IGF* and Pre-eclampsia

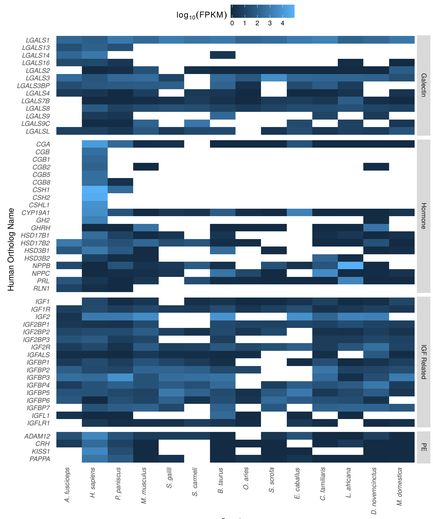

Figure 5: Expression in $\log_{10}$(FPKM) of 1:1 *H. sapiens* orthologs of Hormone Genes, Galectins, genes implicated in pre-eclampsia (PE), and *IGF*-related genes. Empty locations indicate no detectable expression and/or no 1:1 *H. sapiens* ortholog in that species.

Conclusions

- Expression resource of 14 species representing the breadth of mammalia for future research.
- Lineage-specific expansions of gene families and differential gene expression
- Components of annexin complexes, including *ANXA2*, *ANXA1*, *S100A11*, and *S100A10* are expressed in all placentas examined, and argue for the evolution importance of annexins in placenta function, where they likely establish maternal-fetal tolerance[6].
- We identified of multiple genes (*CRH*, *ADAM12*, *KISS1*, *PAPPA*, *IL1RL1*, and *PLAC1*) which are associated with pre-eclampsia which have increased expression on the *H. sapiens* lineage and may explain larger proportion of pre-eclampsia observed in humans.
- Placenta samples from additional species and time points are needed to more completely understand the complex molecular milieu of the developing placenta.

References

1. Carter, A. M. *et al.* Evolution of invasive placentation with special reference to non-human primates. *Best Pract Res Clin Obstet Gynaecol* **25,** 249–257 (June 2011).
2. Chaiworapongsa, T. *et al.* Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* **10,** 466–480 (Aug. 2014).
3. Stout, C. *et al.* Glomerular capillary endothelial swelling in a pregnant chimpanzee. *Am. J. Obstet. Gynecol.* **105,** 212–215 (Sept. 1969).
4. Thornton, J. G. *et al.* Convulsions in pregnancy in related gorillas. *Am. J. Obstet. Gynecol.* **167,** 240–241 (July 1992).
5. Eisenberg, E. *et al.* Human housekeeping genes, revisited. *Trends Genet.* **29,** 569–574 (Oct. 2013).
6. Liu, Y. *et al.* Annexin A2 complexes with S100 proteins: structure, function and pharmacological manipulation. *Br. J. Pharmacol.* **172,** 1664–1676 (Apr. 2015).

The code and underlying data for this poster can be found at

`http://dla2.us/p/pv2016`

ILLINOIS
1867
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

LaTeX TikZposter