Exposure to HIV/combination antiretroviral therapy and smoking during pregnancy systemically modulates mitochondrial DNA content and telomere length across various tissues among HIV-exposed but uninfected infants

Mahtab S. Gill[1*], Nicolas M. T. Gauthier[1*], Abhinav Ajaykumar[1,2], Zeshuo Li[1,2], Izabella Gadawski[1], Beheroze Sattha[1], Hélène C. F. Côté[1,2,3], Anthony Y. Y. Hsieh[1,2]

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada.
[2]Centre for Blood Research, University of British Columbia, Vancouver, Canada.
[3]Women's Health Research Institute, Vancouver, Canada.
*Equal contribution

Contact: zesli@student.ubc.ca

Introduction

- ~18 million women live with HIV, most of whom are of child-bearing age
- Combination antiretroviral therapy (cART) during pregnancy effectively prevents vertical HIV transmission (<1%)
- However, higher risk of growth delay, developmental impairment, and infant mortality from infectious diseases have been shown in children who are HIV-exposed but uninfected (CHEU), compared to HIV-unexposed and uninfected (CHUU) controls
- Mitochondrial DNA (mtDNA) content and telomere length (TL) are associated with age-related diseases, and are considered immune aging biomarkers
- Our lab previously found that smoking during pregnancy affects leukocyte telomere length (LTL) (Figure 1) and blood mtDNA content (Figure 2) among CHEU and CHUU

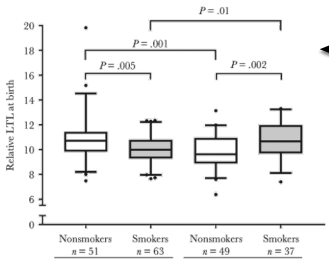

Figure 1 Comparisons of LTL between CHEU and CHUU with or without mothers who smoked during pregnancy.

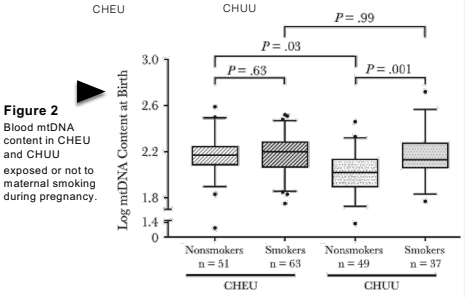

Figure 2 Blood mtDNA content in CHEU and CHUU exposed or not to maternal smoking during pregnancy.

- It is unclear whether HIV/cART and smoking exposure during pregnancy affects TL and mtDNA content occurs consistently across other tissues

Hypothesis and Objectives

- We hypothesized that mtDNA content and telomere length (TL) are affected by maternal exposure to HIV/cART and tobacco smoking during pregnancy in a systemic manner among various infant tissues
- To determine whether these markers are systematically affected across tissues, we investigated several infant tissues from CHEU and CHUU controls

Methodology

- Whole blood, cord blood, cord tissue, and mouth swabs of 229 CHEU and 91 CHUU (Figure 3) were collected at birth as part of three cohort studies
- MtDNA content and TL were measured using a monochrome multiplex quantitative polymerase chain reaction (MMqPCR) optimized in our lab (Figure 4)

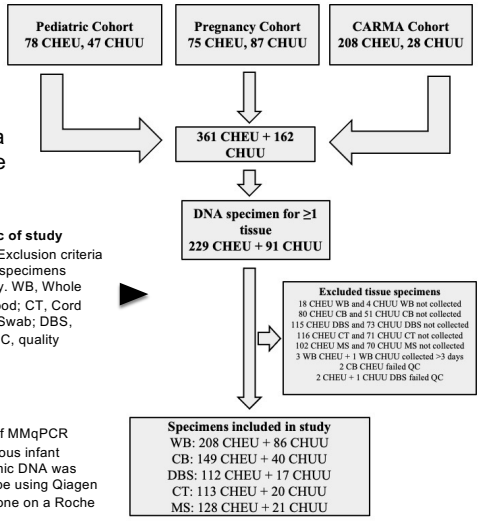

Figure 3 Schematic of study sample selection. Exclusion criteria for participants and specimens included in the study. WB, Whole Blood; CB, Cord Blood; CT, Cord Tissue; MS, Mouth Swab; DBS, Dried Blood Spot; QC, quality control.

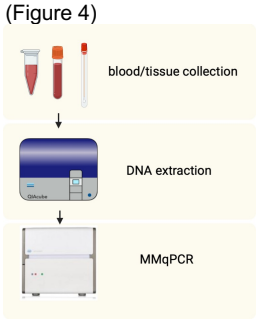

Figure 4 A diagram of MMqPCR measurement for various infant tissues. Whole genomic DNA was extracted on a Qiacube using Qiagen kits. MMqPCR was done on a Roche Lightcycler 480

Results

In whole blood and cord blood

- Maternal smoking was associated with shorter TL among CHEU but longer TL in CHUU
- Maternal smoking was linked to increased mtDNA content in both groups, whereas HIV/cART exposure had the same effect in whole blood only

In cord tissue

- HIV/cART exposure was associated with higher mtDNA content and shorter TL, but smoking had no effect

In mouth swab

- Among all participants, maternal smoking and HIV/cART exposure were associated with longer and shorter TL, respectively, but mtDNA content remained unaffected

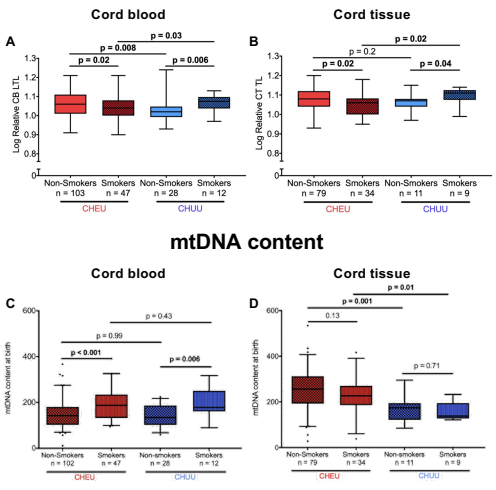

Figure 5 Univariate comparisons of TL (top) and mtDNA (bottom) among cord blood (left) and cord tissue (right). Mann-Whitney U p-values shown. Boxplot whiskers represent 5-95 percentiles.

Table 1. Multivariable adjusted associations of mtDNA content and TL with HIV/cART and maternal smoking exposure across infant tissues. Arrows indicate independent associations with increasing or decreasing TL and mtDNA content after adjusting for other factors*

Telomere length

Exposures	Whole blood		Cord blood		Cord tissue		Mouth swab	
HIV/cART	—		—		↓		↓	
Interaction	+		+		—		+	
Smoking	CHEU ↓	CHUU ↑	CHEU ↓	CHUU ↑	CHEU —	CHUU	CHEU ↑	CHUU ↑↑

mtDNA content

Exposures	Whole blood		Cord blood		Cord tissue		Mouth swab	
HIV/cART	↑		—		↑		—	
Interaction	+		—		—		—	
Smoking	CHEU ↑	CHUU ↑↑	CHEU ↑		CHEU —	CHUU	CHEU —	CHUU

*Potential explanatory variables include maternal history of hepatitis C virus, maternal ethnicity, maternal age at delivery, infant sex, preterm birth, small for gestational age, gestational age at birth, and birth weight.

Conclusions

Both biomarkers were affected by HIV/cART and maternal smoking across multiple tissues. However, the direction of the smoking effect on TL was dependent on HIV/cART exposure in blood tissues only, hence the effects observed were not systemic.

Acknowledgements

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