Pregnancy associated vaginal proteome alterations linked to HIV acquisition risk

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Background

• HIV acquisition risk increases two-fold during pregnancy
• In non-pregnant women, HIV-acquisition is associated with:
  - mucosal inflammation of the genital tract
  - concurrent sexually transmitted infections
  - certain hormonal contraceptives
  - non-Lactobacillus dominant microbiome
  - vaginal dysbiosis
• However, pregnancy is generally associated with a more stable and lactobacillus-predominant microbiome, yet the risk of HIV-acquisition is increased
• We performed proteomic analysis on samples from 23 pregnant and 25 non-pregnant women to try to understand the etiology of the increased risk of HIV-acquisition in pregnancy

Methods

Centrifugal vaginal (CV) samples were collected from 23 pregnant and 25 non-pregnant women from an Obstetrics and Gynecology Clinic in Los Angeles, California and were analyzed by mass spectrometry. Bacterial proteins were identified from a curated TrEMBL database as published in Kotyrba et al., 2015. Science: most proteomic data have been published in the current manuscript. The proteome analysis was performed using the KEGG ontology database. Enrichment analysis of pregnancy signatures to other HIV risk cohorts (Global Karim et al., Science, 2010) were performed using DAVID.

Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Pregnant vs. Not Pregnant</th>
<th>All Pregnant vs. Not Pregnant</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Positive HIV risk signature expansion</td>
<td>0.700</td>
<td>0.02*</td>
<td></td>
</tr>
<tr>
<td>Negative HIV risk signature fold expression</td>
<td></td>
<td></td>
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<td>Positive HIV risk signature fold expression</td>
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<tr>
<td>Negative HIV risk signature fold expression</td>
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</tbody>
</table>

 functional Microbiome

Results - Host Proteome

Figure 1: Pregnancy proteome alterations in CVL were immunosuppressive

HIV acquisition risk increases two-fold during pregnancy. We performed proteomic analysis on samples from pregnant and non-pregnant women, identified human proteins, of which 12% were differentially abundant (P<0.05). [A] Different expressed proteins were evaluated by unsupervised hierarchical clustering. A protein enrichment pregnancy signature (green box) was defined on 17-over expressed and 49-under expressed proteins in pregnant women. (B) Functional enrichment analysis comparing pregnant and non-pregnant women. Cgs and KEGG ontologies were significantly enriched in pregnant women. [C] Enrichment of pregnancy signatures to other HIV risk cohorts (Global Karim et al., Science, 2010). [D] Positive association with pregnancy and negative association with pregnancy, adjusted for proband titer.

Figure 3: Proteome alterations associated with ectopy corresponded to a non-Lactobacillus dominated microbiome

HIV risk in pregnancy is associated with changes to mucosal proteome pathways. Subsequently decreased mucosal barrier function. Immune system depression increases blood vessel formation. Some of the changes during pregnancy are similar to those observed in women who subsequently acquired HIV infection. Microbial metabolic pathways for carbohydrate metabolism and neutrophil function are increased during pregnancy.

Figure 4: Pregnancy status was associated with alterations to bacterial metabolic functions

(A) Bacterial gene expression for pregnant and non-pregnant women was derived from KEGG annotations. (B) Statistically different functions between pregnant and non-pregnant women, as defined by DESeq2. (C) Bacterial gene expression for pregnant and non-pregnant women, as defined by DESeq2. (D) Complementary metabolism and Metabolism of Carbohydrates and Amines are increased in pregnant women. (E) Bacterial gene expression for pregnant and non-pregnant women, as defined by DESeq2. (F) Complementary metabolism and Metabolism of Carbohydrates and Amines are increased in pregnant women. (G) Bacterial gene expression for pregnant and non-pregnant women, as defined by DESeq2. (H) Complementary metabolism and Metabolism of Carbohydrates and Amines are increased in pregnant women.

Conclusions

• Pregnancy is associated with changes to mucosal proteome pathways
  - immune system depression
  - increased blood vessel formation
  - decreased mucosal barrier function
• Some of the changes during pregnancy are similar to those observed in women who subsequently acquired HIV infection
• Microbial metabolic pathways for carbohydrate metabolism and neutrophil function are increased during pregnancy

References

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Acknowledgements

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