Diabetes mellitus in pregnancy activates the innate immune response on neonatal monocyte

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Introduction

- Diabetes mellitus (DM) in pregnancy causes congenital malformation, macrosomia, respiratory distress syndrome, and other abnormalities in neonates.
- And, these offspring have a high risk of developing obesity, impaired glucose tolerance, and type 2 DM in adulthood.
- It has been proposed that DM is caused by activated innate immunity, but whether maternal DM affects the neonatal innate immune system is unknown.
- We aimed to reveal the influence of DM in pregnancy on the toll-like receptor (TLR)-mediated innate immune response in neonates.

Materials and Methods

- Cord blood was collected after full-term vaginal or cesarean delivery and classified into a DM group (n = 8) and non-DM (control) group (n = 7).
- Mononuclear cells were harvested from cord blood by using density gradient centrifugation, after which anti-CD14 magnetic beads were used to isolate monocytes from the mononuclear population.
- After monocytes were cultured with lipopolysaccharide (LPS; TLR4 ligand), Pam3CSK4 (TLR1/TLR2 ligand), zymosan (TLR2/TLR6 ligand), or macrophage activating lipopeptide (MALP; TLR2/TLR6 ligand) for 12 h, the cytokine levels (interleukins) were measured.

Results

Table 1. Clinical characteristics of mothers

<table>
<thead>
<tr>
<th></th>
<th>DM group(n=8)</th>
<th>control group(n=7)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yr)</td>
<td>35 ± 5</td>
<td>33 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 3</td>
<td>19 ± 1</td>
<td>p&lt;0.00</td>
</tr>
<tr>
<td>Gestational weeks at delivery (wks)</td>
<td>38 ± 2</td>
<td>38 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>CS=3,VD=4</td>
<td>CS=4,VD=4</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose** (mg/dl)</td>
<td>126 ± 42</td>
<td>112 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin=6,diet=1</td>
<td></td>
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</tbody>
</table>

Table 2. Clinical characteristics of neonates

- Compared with the control group, the DM group had higher concentrations of IL-8 (P=0.01) and tumor necrosis factor alpha (P=0.02) after monocyte cultures were stimulated with Pam3CSK4 and higher concentrations of IL-8 (P=0.01) after flagellin treatment.
- In contrast, stimulation with lipopolysaccharide, zymosan, or macrophage-activating lipopeptide did not lead to any difference in cytokine profiles between the two groups.

Discussion

- Diabetes mellitus is caused by activated innate immunity.
- The plasma concentration of inflammatory mediators is increased in the insulin-resistant state of obesity and type 2 DM.
- Inflammation modulate insulin resistance in GDM.
- Offspring of women with GDM have a high risk of developing obesity and type 2 DM in adulthood.

Conclusions

Diabetes mellitus in pregnancy induces excessive inflammatory activation in neonates via a TLR5- or TLR1/2-mediated innate immune response.

DM in pregnancy induce a high risk of DM and obesity to neonates in adulthood through activating TLR5 or TLR1/2-mediated signaling.