Mitochondrial Dysfunction Drives a Dysregulated Inflammatory Response in Gestational Diabetes Mellitus

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Introduction

•Our previous research has demonstrated a potential pathogenic role for mitochondrial dysfunction in GDM, through excessive levels of circulating mitochondrial DNA in GDM participants (1).

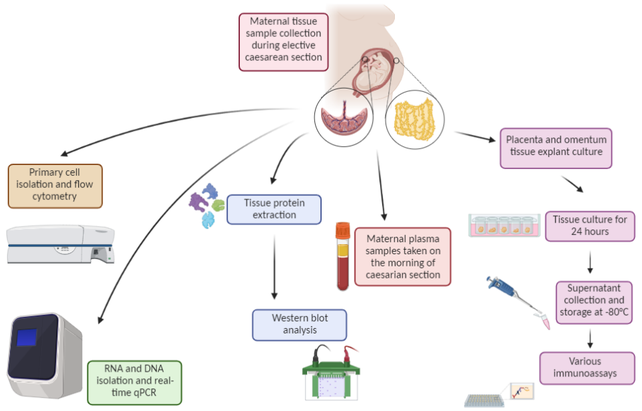
•GDM may be associated with a state of chronic, low-grade inflammation termed “metainflammation” (2).

•Aberrant NLRP3 inflammasome activation, in part modulated by mitochondria dysfunction, has been postulated to contribute to the inflammatory phenotype of gestational diabetes mellitus (GDM) (3).

Aims

1. Characterise systemic and placental tissue mitochondrial dysfunction and inflammation in GDM pathophysiology.
2. Assess the potential role of mitochondrial-targeted antioxidants as potential therapeutic interventions.

Methods



Results

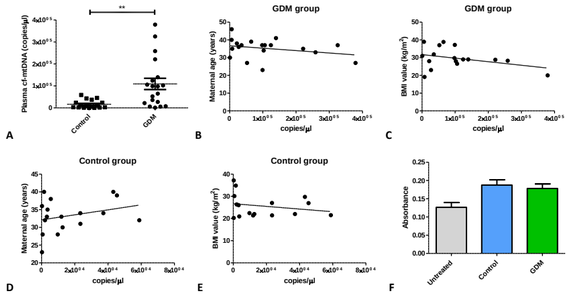


Figure 1. GDM-mediated mitochondrial dysfunction is characterized by significantly higher circulating cf-mtDNA levels in GDM participants. (A) Relative circulating levels of cf-mtDNA were measured (copies/µl). Cf-mtDNA levels did not significantly correlate with **(B)** maternal age in GDM participants, **(C)** BMI in GDM participants, **(D)** maternal age in control participants or **(E)** BMI in control participants. **(F)** 5% plasma-induced TLR9 activation was measured in control (n=20) versus GDM (n=20) samples. Significance levels are shown as: ** p<0.01.

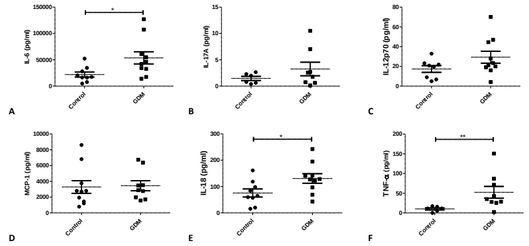


Figure 4. GDM placental tissue secretes higher levels of proinflammatory cytokines. (A) IL-6, **(B)** IL-17A, **(C)** IL-12p70, **(D)** MCP-1, **(E)** IL-18 and **(F)** TNF-α levels were quantified in placental explant culture supernatant from healthy control (n=10) and GDM (n=10) participants. Significance levels are shown as: * p<0.05, ** p<0.01.

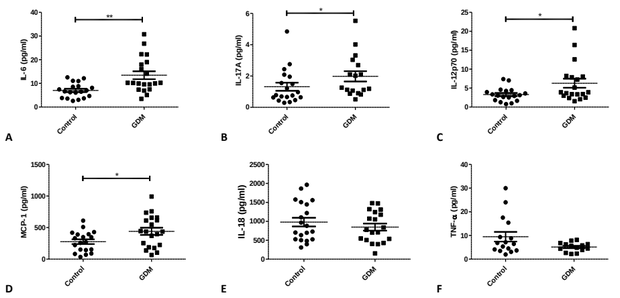


Figure 2. GDM pathophysiology is characterized by significant circulating inflammatory cytokine signalling. (A) IL-6, **(B)** IL-17A, **(C)** IL-12p70, **(D)** MCP-1, **(E)** IL-18 and **(F)** TNF-α levels were quantified in plasma from healthy control (n=20) and GDM (n=20) participants. Significance levels are shown as: * p<0.05, ** p<0.01.

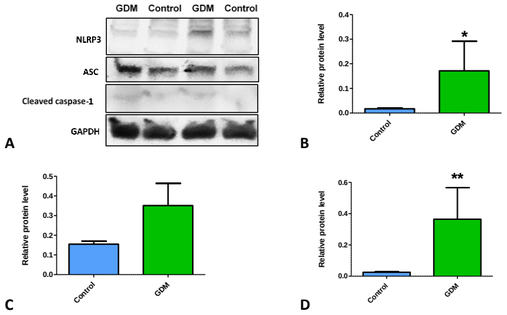


Figure 5. NLRP3 protein expression is upregulated in GDM placenta. (A) Placental tissue protein expression of NLRP3, ASC and Caspase-1 was compared in healthy control placenta (n=8) relative to GDM placenta (n=8), matched by maternal age and BMI. Densitometric analysis was used to quantify protein levels of **(B)** NLRP3, **(C)** ASC and **(D)** cleaved capsase-1 in healthy control and GDM placenta. Significance levels are shown as: * p<0.05, ** p<0.01.

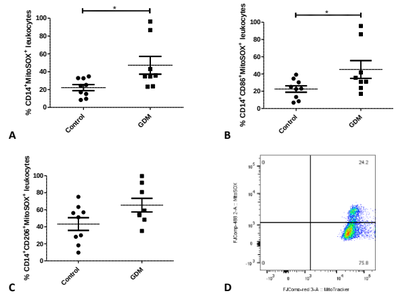


Figure 3. Placental tissue from GDM pregnancies show significantly higher mitochondrial superoxide production in CD14+ cells and CD14+CD86+ cells. Monocyte/macrophage cell phenotype and mitochondrial superoxide production was characterized in control (n=9) and GDM (n=8) placental tissue samples. Population frequencies are shown for **(A)** CD14+MitoSOX+ cells, **(B)** CD14+CD86+MitoSOX+ cells, **(C)** CD14+CD206+MitoSOX+ cells. **(D)** Representative graph. Significance levels are shown as: * p<0.05..

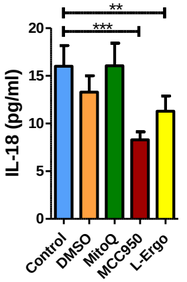


Figure 6. Antioxidant therapy significantly attenuates exaggerated NLRP3 activation in GDM placental tissue. GDM placental explant tissue cultures (n=12) were treated with 1µM MitoQ, 1µM MCC950 and 1mM L-Ergothioneine for 24 hours. The resulting release of IL-18 was quantified. Data was normalized to total protein expression and is represented as mean ± SEM. Significance levels are shown as: ** p<0.01, *** p<0.001.

Conclusions

Mitochondrial dysfunction is evident in GDM pathophysiology. NLRP3 and cleaved caspase-1 inflammasome expression is increased in GDM placenta, independent of maternal age and BMI. Exaggerated NLRP3 activity and concurrent IL-18 release can be attenuated by L-Ergothioneine antioxidant treatment, demonstrating a therapeutic role for targeting mitochondrial dysfunction.

References

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2. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015;36(7):709-715.
3. Zhou F, Li C, Zhang SY. NLRP3 inflammasome: a new therapeutic target for high-risk reproductive disorders? Chin Med J (Engl). 2020;134(1):20-7.