Increased risk factors but not manifestation of disease correlated to placental inflammation

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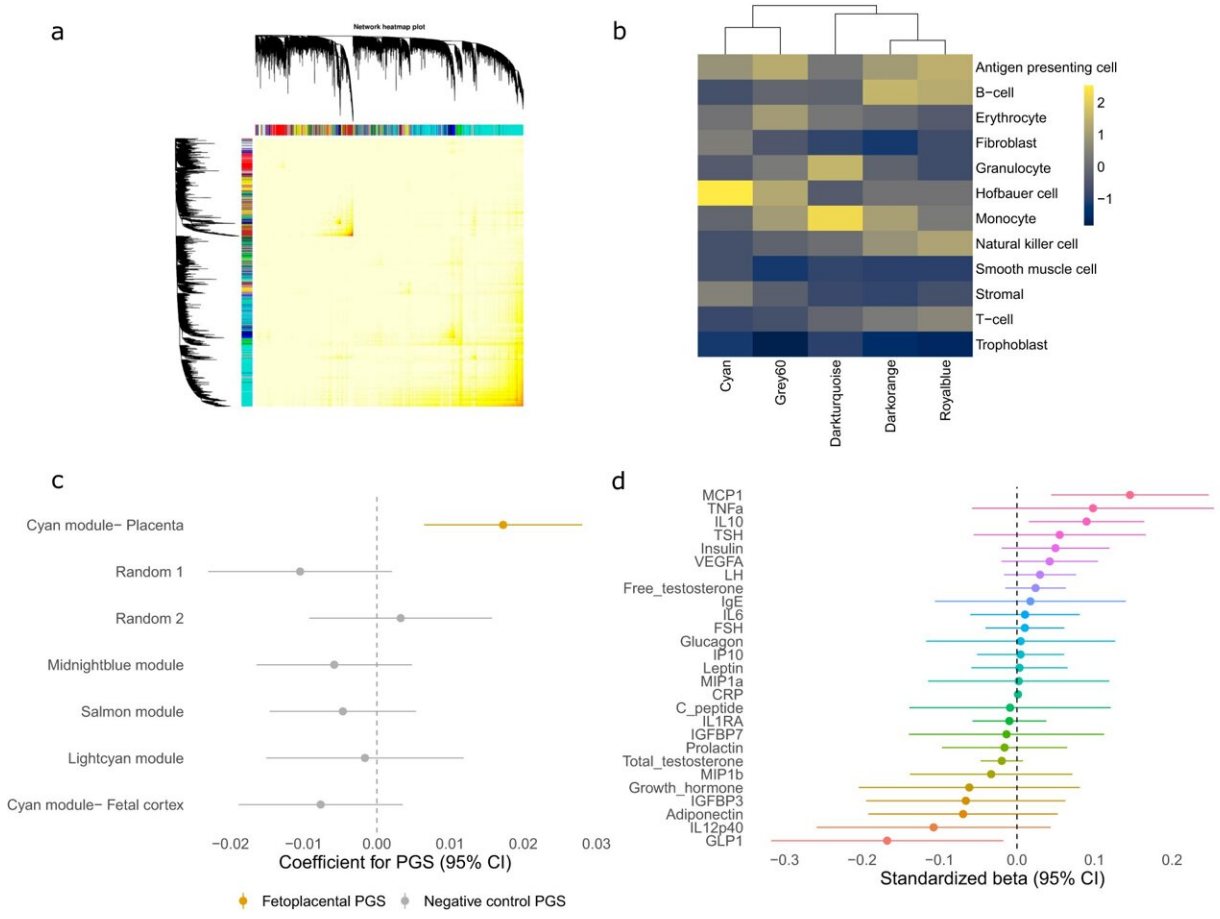

WGCNA of placental villous RNA sequencing data identifies an inflammation-related gene expression module that is highly enriched in Hofbauer cells. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-42300-8

Research led by McGill University, Canada, suggests that disruptions in Hofbauer cell function with preterm birth or intra-amniotic infection may contribute to traits associated with increased risk factors for cardiovascular disease and depression in offspring, despite not finding a direct correlation in outcomes.

In a paper, "Hofbauer cell function in the term placenta associates with adult cardiovascular and depressive outcomes," published in *Nature Communications*, the team used a rigorous and multi-faceted approach involving various molecular, genetic, and statistical techniques to explore the impact of placental inflammation-related gene expression on adult health outcomes in non-pathogenic conditions.

The researchers used cohort data from the Singapore-based Growing Up in Singapore Towards healthy Outcomes (GUSTO) and the UK Biobank. RNA sequencing of 44 placental samples from GUSTO identified an inflammation-related gene co-expression module enriched in Hofbauer cells.

Twenty-eight gene expression modules were identified, with sizes ranging from 72 to 6,794 genes. The cyan module, linked to inflammation and Hofbauer cells, stood out as a candidate for further study as it showed high specificity to placental Hofbauer cells and was enriched with known inflammation-related genes. A polygenic score (fetoplacental PGS) was developed to predict this module's gene expression.

The fetoplacental PGS was significantly linked to 21 traits in a UK biobank study, primarily associated with anthropometric or mental health traits. All anthropometric traits had a positive direction of effect, and all traits within the mental health domain had a negative direction.

The directional trends should put the individuals in higher risk categories

for cardiovascular disease and depression-related outcomes. Interestingly, the UK Biobank study did not find this correlation between fetoplacental PGS and polygenic risk scores for depression or cardiovascular disease.

The lack of a correlation between traits thought to lead to depression or cardiovascular disease outcomes could suggest a protective effect of the cyan module on these outcomes, or it could be highlighting a weakness in the understanding of these correlations, indicating a more nuanced or indirect relationship.

The lone sex-dependent feature identified was a female-specific effect of cyan module genes on reduced risk of suicidality, further distancing the trait-related expectations from the observed results.

The correlations suggest that disruption of Hofbauer cell function due to preterm birth or prenatal infections contributes to increased risk factors for depression and cardiovascular disease later in life, yet no direct correlations were observed on outcomes.

The puzzling results could be the result of genetic disparities between cohorts. While the 44 placental biopsies were conducted in GUSTO from individuals primarily of Chinese, Malay, and Indian ethnicities, outcomes were derived from the UK Biobank, covering a population of 500,000 across the United Kingdom. This difference in population origin and diversity of cohorts may influence the generalizability and applicability of the findings.

One thing science always welcomes is a mystery. When expectations do not match results, it can mean that a better, more complete understanding is waiting to be discovered.

More information: Eamon Fitzgerald et al, Hofbauer cell function in

the term placenta associates with adult cardiovascular and depressive outcomes, *Nature Communications* (2023). DOI: 10.1038/s41467-023-42300-8