

# DIFFERENTIAL miRNA EXPRESSION IN OFFSPRING EXPOSED TO A MATERNAL OBESOGENIC ENVIRONMENT

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## Abstract

An emerging field in obesity research is investigating how exposure to a maternal obesogenic environment in utero may predispose the fetus to developing these conditions later in life. In animal models, fetal exposure to a high fat diet has been shown to have a causal relationship in the development of obesity, metabolic-associated fatty liver disease (MAFLD), high blood pressure, dyslipidemia, cardiovascular impairment, insulin resistance, hyperglycemia, systemic inflammation, and oxidative stress. Fetal cardiometabolic risk factors associated with maternal obesity and high fat diet are thought to be due in part to epigenetic modifications to genes involved in stem cell differentiation, metabolism, and inflammation. Several studies have explored miRNA expression patterns in tissues from offspring exposed to a maternal obesogenic environment. In this literature review, we discussed differential miRNA expression in offspring exposed to maternal obesity in various tissues, that when dysregulated, propagate metabolic disease. We also discussed the known roles of these miRNAs in the context of inflammation, metabolism, and stem cell fate.

### LIVER

*miRNAs regulating many aspects of metabolism are perturbed*

- ↑ miR-185-5p (inhibits SREBP2, regulates cholesterol synthesis and FA metabolism)
- ↓ miR-122 (cholesterol, FA synthesis, and oxidation)
- ↓ miR-370 (inhibits miR-122, inhibits inflammation)
- ↓ miR124, miR-101b (inhibit inflammation)
- ↓ miR-145-3p, miR-183-5p (inhibit SMAD4, which promotes fibrosis and inflammation)
- ↓ miR-615-5p (inhibits IGF-1)
- ↓ miR-130a, miR-186-5p, miR-96-5p (inhibit TCA cycle genes)
- ↓ miR-1285-3p, miR-199a-5p, miR-182-5p (may repress glycolysis, oxidative phosphorylation, and ETC)

### SKELETAL MUSCLE

*Primed for angiogenesis and inflammation*

- ↓ Let-7g (inhibits adipogenesis and inflammation)
- ↓ miR-381 (suppresses  $\beta$ -catenin/Wnt signaling and inflammation)

### PERIPHERAL BLOOD

*Primed for adipogenesis*

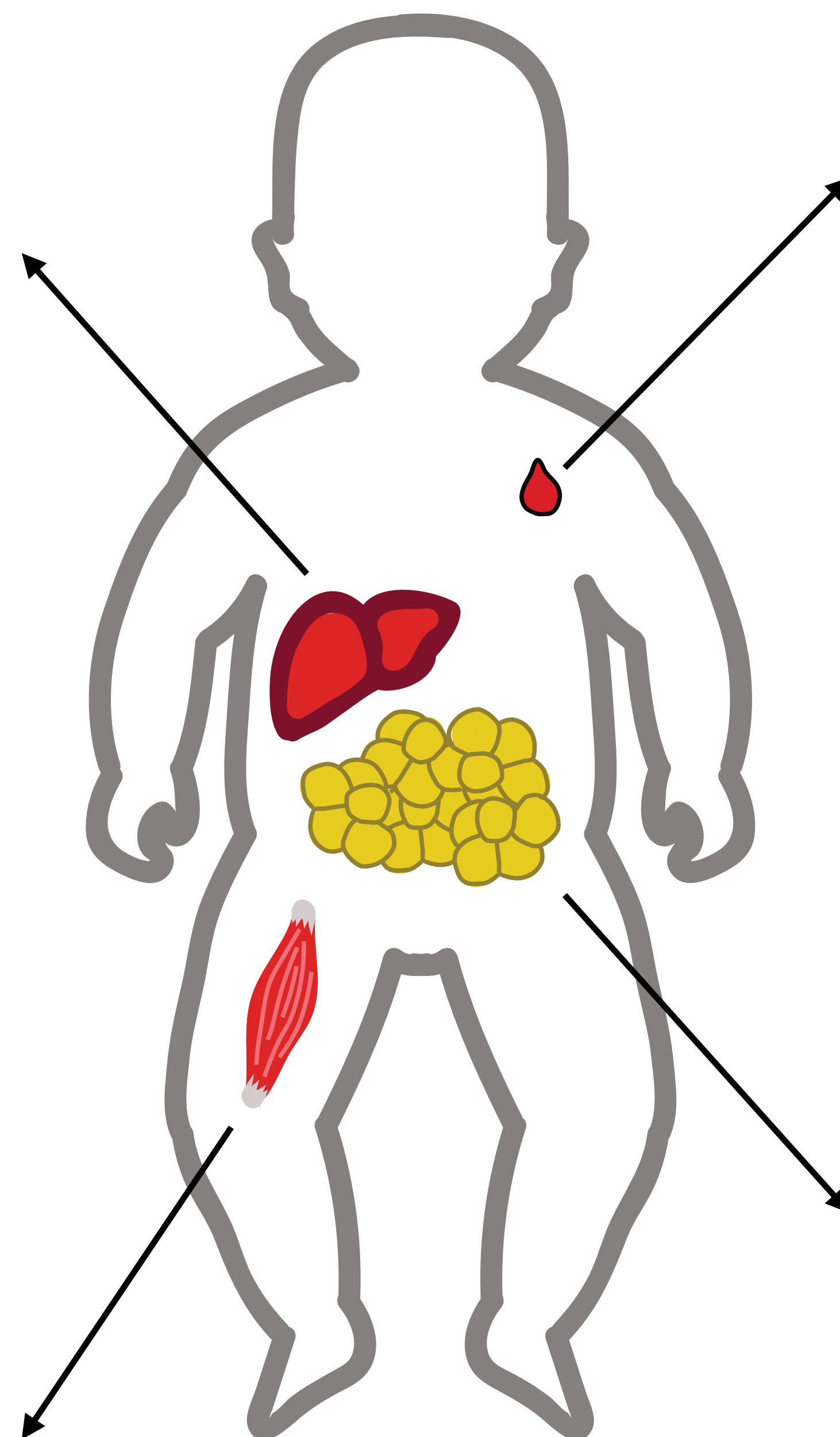
*May show anti-inflammation*

- ↓ miR-181a (inhibits adipogenesis, activates myogenesis)
- ↓ miR-221 (activates Wnt pathway for differentiation and inhibition of adipogenesis)
- ↓ miR-155 (pro-inflammatory)

### ADIPOSE TISSUE

*Primed for inflammation and angiogenesis*

- ↓ miR-706 (promotes inflammation)
- ↓ miR-126 (promotes angiogenesis)



## Conclusion

In this review, we have discussed the animal and human literature on differential expression of miRNAs in adipose, muscle, liver, and blood from offspring exposed to a maternal obesogenic environment and have applied what is known about these miRNAs in the context of stem cell fate, metabolic functioning, and inflammation. Offspring exposed to a maternal obesogenic environment exhibit impaired myogenesis, increased adipogenesis, and lipid accumulation within the liver as well as metabolic dysfunction that is propagated by the chronic, low-grade inflammatory state that is associated with obesity and metabolic disease in adulthood. miRNA expression trends within these tissues seem to support this pathology in many ways. However, there are many studies that suggested miRNAs to have opposite roles than what would be predicted.

→ miRNA expression in **skeletal muscle** and **adipose tissue** suggest it is primed for adipogenesis and inflammation

→ miRNA expression in the **peripheral blood** show it being primed for adipogenesis but may show anti-inflammatory properties

→ In the **liver**, miRNAs appear to propagate inflammation and promote dysregulation of many metabolic pathways, including glycolysis, oxidative phosphorylation, the TCA cycle, and the ETC. However, it seems that activation of some factors, such as SMAD4, may serve in protecting the fetus from sequelae of metabolic disease in response to maternal obesity.

Even though the data is robust for many of these individual miRNAs, their roles in a fetal developmental context remain largely unknown. It is also important to emphasize that the chronic, low-grade inflammatory environment associated with obesity is very difficult to recapitulate in that it is distinct from other inflammatory contexts. Many studies discussed in this review discuss inflammatory roles of miRNAs that may not be directly applicable. Functional knockout and overexpression studies will therefore be necessary to elucidate their functions. It is important to further investigate the role of miRNAs in predisposition to metabolic disease because they serve as unique therapeutic targets to combat this growing health epidemic.