Dysregulated gene expression profile in visceral adipose tissue of juvenile *Wistar* rats with catch-up growth: association with fat expansion and metabolic parameters

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BACKGROUND

Accelerated catch-up growth following intrauterine growth restriction increases the risk of developing visceral adiposity and metabolic syndrome. Animal models of growth restriction during gestation have been developed as a powerful tool to provide insight into the underlying molecular mechanisms thereof.

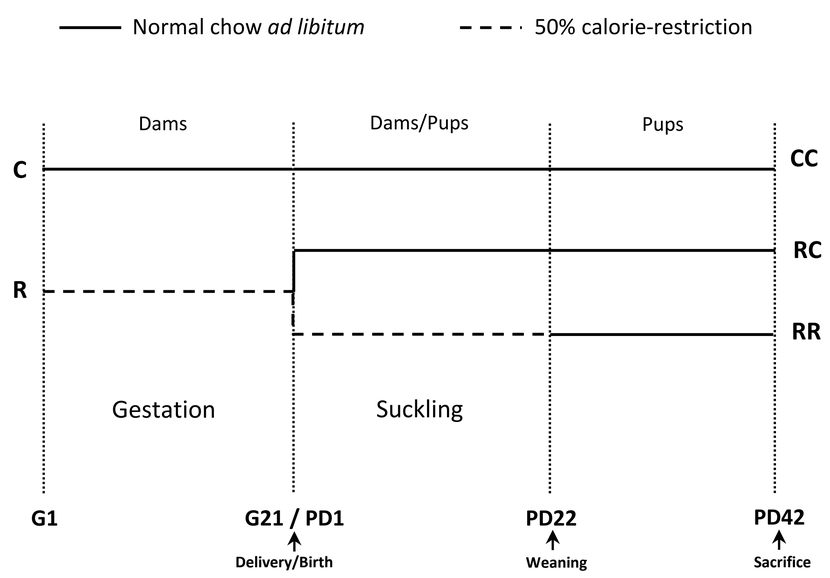
OBJECTIVE

To analyze the patterns of gene expression in the retroperitoneal adipose tissue of rats with intrauterine growth restriction and postnatal catch-up growth.

MATERIAL AND METHODS

A ***Wistar* rat model of catch-up growth following intrauterine growth restriction** was used (Figure). Dams fed *ad libitum* delivered control pups (C) and dams on a 50% calorie-restricted diet during gestation delivered pups with low birth weight (R). Restricted offspring fed a standard rat chow showed catch-up growth (RC) but those kept on a calorie-restricted diet did not (RR).

Microarray studies were performed in the **retroperitoneal adipose tissue at postnatal day 42**. Functional enrichment analysis (Gene Ontology) was performed to study the main representative signaling pathways. The expression of the top twenty ranked genes (yielded by microarray and functional enrichment analysis) were studied by qRT-PCR.



RESULTS

Of the total number of genes (n=23,188), we identified 570 differentially expressed genes [338 upregulated (red) and 232 downregulated (green); **Figure 1**] in the **retroperitoneal adipose tissue of RC vs RR rats** (FDR-p value<0.05 and Fold Change > 3 and <-3).

Functional enrichment analysis revealed a **global up-regulation of genes involved in carbohydrate and lipid metabolism and a down-regulation of genes linked to inflammation and immune response** (**Table 1**).

Five genes representative of these main pathways (***Npr3***, regulation of blood pressure; ***Pnpla3***, lipid metabolic processes; ***Slc2a4***, brown fat cell differentiation; ***Serpina3n***, inflammatory response; ***Serpina12***, positive regulation of PI3K) were confirmed by qRT-PCR (**Figure 2**) and showed associations with several metabolic parameters, including body weight, amount of brown adipose tissue, and serum insulin and lipids (**Table 2**).

Table 1. The main representative signaling pathways and their top ranked genes (Functional enrichment analysis).

	Upregulated genes	Downregulated genes
Lipid Metabolic Process	PCK1, APOD, PNPLA3	-
Immune System Process	-	CR2, ITK, CD79B, CCL19, CCL21
Response to Citokine	SERPINA3N	CCL21, CCL19
Positive Regulation of PI3K	SERPINA12, AGT, IGF1	SEMA4D, CD28
Regulation of Leukocyte Proliferation	NPR3	CR2
Brown fat cell differentiation	UCP1, SLC2A4, ADRB3, PPARG	PLAC8

Figure 1. Volcano plot representing the differentially expressed genes between RC and RR rats (Microarray data).

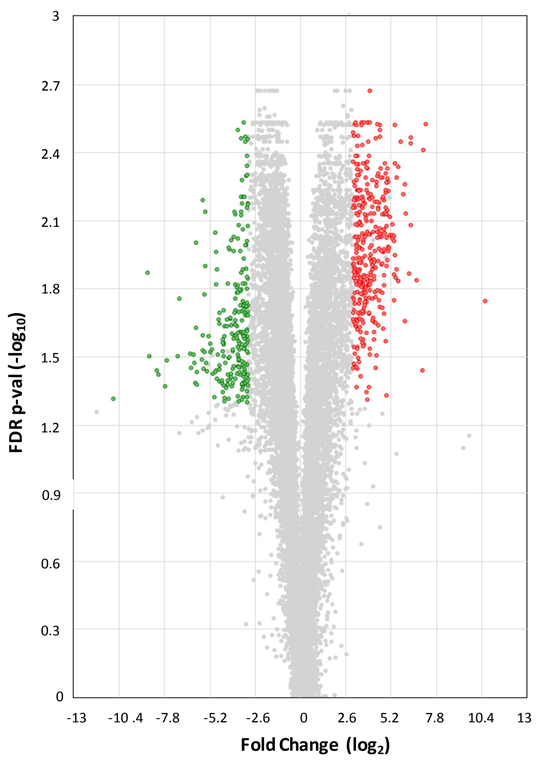


Figure 2. mRNA levels of selected representative genes in RC vs RR rats (qRT-PCR data).

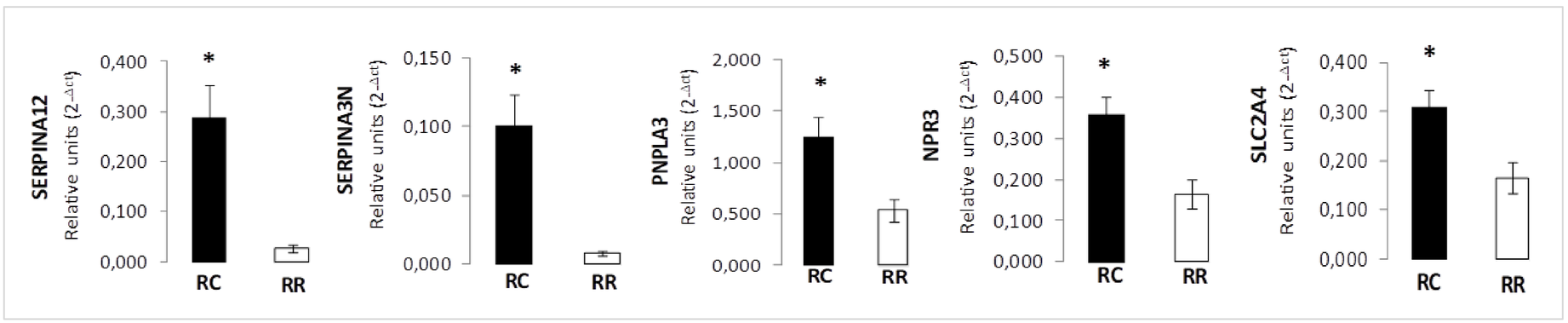


Table 2. Bivariate correlation analysis between differentially expressed genes and metabolic parameters.

N=42	SERPINA12		SERPINA3N		PNPLA3		NPR3		SLC2A4	
	r	p	r	p	r	p	r	p	r	p
Body Weight PD22 (g)	**0,592**	**<0,0001**	**0,674**	**<0,0001**	**0,448**	**0,002**	**0,438**	**0,002**	**0,425**	**0,003**
Body Weight PD42 (g)	**0,550**	**<0,0001**	**0,585**	**<0,0001**	**0,377**	**0,009**	**0,372**	**0,01**	**0,288**	**0,04**
Postnatal Body Weight Gain (g)	**0,547**	**<0,0001**	**0,586**	**<0,0001**	**0,380**	**0,008**	**0,373**	**0,01**	**0,296**	**0,04**
Retroperitoneal adipose tissue (g)	**0,520**	**<0,0001**	**0,499**	**<0,0001**	**0,399**	**0,005**	**0,309**	**0,03**	0,243	0,09
Brown adipose tissue (g)	**0,576**	**<0,0001**	**0,524**	**<0,0001**	**0,492**	**0,001**	**0,377**	**0,01**	**0,326**	**0,02**
Serum Triglycerides (mmol/ L)	**0,428**	**0,01**	**0,584**	**<0,0001**	0,323	0,07	**0,415**	**0,01**	**0,438**	**0,01**
Serum Total Cholesterol (mmol/L)	-0,250	0,16	-0,164	0,36	**-0,391**	**0,02**	-0,258	0,15	**-0,366**	**0,03**
Serum LDL Cholesterol (mmol/L)	**-0,443**	**0,01**	**-0,457**	**0,01**	**-0,442**	**0,01**	**-0,451**	**0,01**	-0,334	0,06

CONCLUSIONS

We have identified the differential gene expression pattern in visceral adipose tissue of juvenile *Wistar* rats with catch-up growth following intrauterine growth restriction. We suggest that **the differential expression of these genes may be involved in visceral fat expansion during catch-up growth** in juvenile rats and in the predisposition of these animals to develop metabolic abnormalities.

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