Transcriptome profiling following treatment with the progesterone receptor modulator mifepristone in breast tissue of healthy premenopausal women – secondary outcomes of a randomized controlled trial

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Conclusions

Transcriptomic profiling and subsequent bioinformatics analyses were performed to explore molecular responses associated with progesterone receptor (PR) antagonism in breast tissue of healthy premenopausal women. We found differentially expressed genes (DEGs) significantly altered in pathways mainly related to extracellular matrix (ECM) organization and remodeling. The present study provides an improved understanding of PR antagonism and its potential breast protective effects but also progesterone action by studying its counteraction in healthy breast tissue.

Introduction

Progesterone has emerged as a major mitogen in healthy breast tissue and may consequently play a key role in breast carcinogenesis. We have previously shown that treatment with a low continuous dose with the PR antagonist mifepristone exert anti-proliferative effects in human breast epithelial cells in vivo. However, the molecular changes relevant to the above observation have never previously been explored.

Materials and methods

Core needle breast biopsies were collected at baseline and after two months of 50 mg mifepristone treatment every other day from healthy pre-menopausal women aged 18-43. The changes on mRNA expression level were screened using next generation sequencing. The DEGs were analyzed using Gene Ontology (GO) and Reactome pathway analyses in the g:Profiler database.

Results

We found 27 DEGs after treatment compared to baseline (Fig.1). The GO analysis revealed DEGs significantly enriched mainly in ECM (Table 1). Similarly, the Reactome pathway analysis revealed significantly enriched pathways mainly related to the ECM (Table 2).

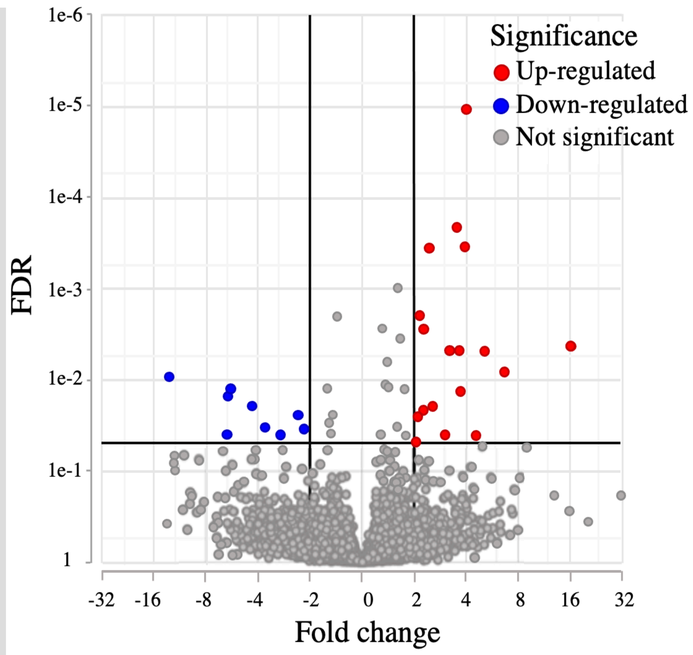

Fig.1: Volcano plot showing the distribution of the differentially expressed genes (DEGs) between breast samples from baseline and after mifepristone treatment. X-axis represent log2 fold change and Y-axis represent logFDR (adjusted p-value).

Term ID	Description	FDR (Padj)
Biological Process		
GO:0030198	Extracellular matrix organization	2.21E-08
GO:0043062	Extracellular structure organization	2.21E-08
GO:0030199	Collagen fibril organization	6.95E-07
GO:0032963	Collagen metabolic process	1.76541E-05
GO:0071230	Cellular response to amino acid stimulus	0.000123191
Cellular Component		
GO:0062023	Collagen-containing extracellular matrix	4.78E-12
GO:0031012	Extracellular matrix	4.59E-11
GO:0098643	Banded collagen fibril	1.13E-08
GO:0005583	Fibrillar collagen trimer	1.13E-08
GO:0098644	Complex of collagen trimers	1.08E-07
Molecular Function		
GO:0048407	Platelet-derived growth factor binding	2.76E-08
GO:0030020	Extracellular matrix structural constituent conferring tensile strength	4.1495E-06
GO:0005201	Extracellular matrix structural constituent	1.75112E-05
GO:0004252	Serine-type endopeptidase activity	1.75112E-05
GO:0017171	Serine hydrolase activity	2.17779E-05

Table 1. The top 15 enriched gene ontology terms of the differentially expressed upregulated genes.

Pathway ID	Name	FDR (Padj)	Genes
R-HSA-1474228	Degradation of the extracellular matrix	1.80E-09	CTSG, TPSAB1, COL1A1, COL1A2, COL3A1, COL5A1, MMP2
R-HSA-1474244	Extracellular matrix organization	2.57E-09	CTSG, TPSAB1, COL1A1, COL1A2, COL3A1, ADAMTS2, COL5A1, MMP2
R-HSA-1650814	Collagen biosynthesis and modifying enzymes	9.22E-08	COL1A1, COL1A2, COL3A1, ADAMTS2, COL5A1
R-HSA-1442490	Collagen degradation	9.22E-08	COL1A1, COL1A2, COL3A1, COL5A1, MMP2
R-HSA-3000170	Syndecan interactions	1.76E-07	COL1A1, COL1A2, COL3A1, COL5A1
R-HSA-1474290	Collagen formation	2.30E-07	COL1A1, COL1A2, COL3A1, ADAMTS2, COL5A1
R-HSA-8874081	MET activates PTK2 signaling	2.30E-07	COL1A1, COL1A2, COL3A1, COL5A1
R-HSA-8875878	MET promotes cell motility	6.69E-07	COL1A1, COL1A2, COL3A1, COL5A1
R-HSA-8948216	Collagen chain trimerization	8.81E-07	COL1A1, COL1A2, COL3A1, COL5A1
R-HSA-3000171	Non-integrin membrane-ECM interactions	2.46E-06	COL1A1, COL1A2, COL3A1, COL5A1

Table 2. The top 10 enriched pathways of the upregulated differentially expressed genes.

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