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Expression of ITGB8 in Epicardial Adipose Tissue is Highly and Directly Correlated with the Severity of Coronary Atherosclerosis

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Comments
Medical student Nancy Lee participated in this study as part of the Senior Scholars research program at the University of Massachusetts Medical School.

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Background

Obesity and its associated cardio-vascular diseases have reached epidemic proportions. Prior studies suggest that in those with increased visceral adiposity, immune cells in visceral adipose tissue (VAT) establish chronic local inflammation that results in ectopic lipid deposition in peripheral organs and insulin resistance.

Epicardial adipose tissue (EAT) has been advanced as a possible direct link between obesity and cardiovascular disease. In patients with coronary artery disease (CAD), EAT has been shown to express increased levels of inflammatory cytokines.

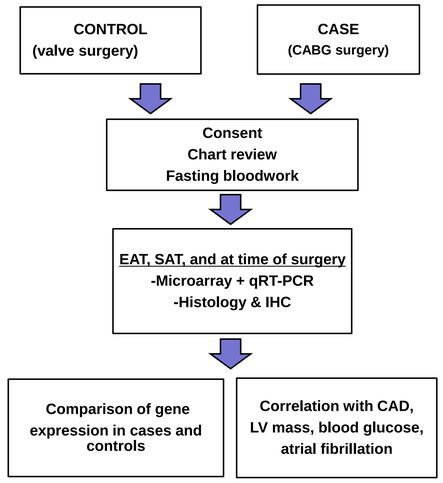
What is not currently understood is whether or not inflammatory gene expression influences the development of atherosclerosis or is a compensatory response to established disease.

Objectives

The purpose of this study was to determine:

- Whether there are differences in gene expression between EAT and subcutaneous adipose tissue (SAT)
- If gene expression in EAT of patients *with* and *without* CAD differs
- If there is a difference, whether these differentially expressed genes participate in the inflammatory pathways.

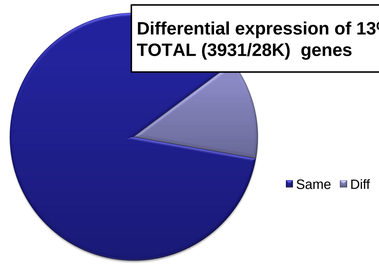
Methods



- Informed consent obtained from **controls *(pts without CAD)*** and **cases *(pts with CAD)*** scheduled for elective cardiothoracic surgery.
- 500 mg EAT and SAT collected at the time of surgery, fixed for microscopy and frozen for RNA extraction.
- RNA was hybridized to Affymetrix Human Gene 1.0 ST chips.
- Genes w/ FC>3 in EAT vs. SAT were identified.
- Gensini scores for participants determined through review of cardiac catheterization data.
- Probe intensities for these resultant genes were then correlated with the severity of atherosclerosis in each patient as determined by the Gensini score.

Results

Is Subcutaneous Fat Different than Epicardial Fat?



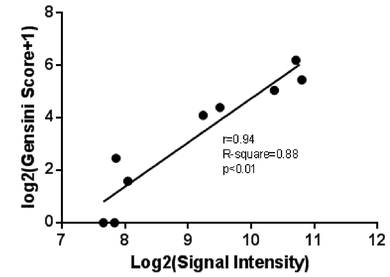
Of these, 35 genes differentially expressed in EAT vs SAT by FC>3 and p<0.05

Name	Symbol	EAT	SAT	FC	P
intelectin 1 (galactofuranose binding)	ITLN1	1854.67	94.54	-17.06	0.000
polycystic kidney and hepatic disease 1 (autosomal recessive)-like 1	PKHD1L1	354.54	42.59	-8.34	0.000
chemokine (C-C motif) ligand 21	CCL21	1153.91	171.44	-6.73	0.000
transcription factor 21	TCF21	421.74	71.43	-5.90	0.000
T-box 20	TBX20	583.09	111.56	-5.23	0.000
haptoglobin /// haptoglobin-related protein	HP /// HPR	294.36	62.14	-4.74	0.000
uroplakin 1B	UPK1B	219.55	47.12	-4.66	0.000
claudin 1	CLDN1	444.40	99.67	-4.46	0.000
serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	SERPINA3	382.53	87.52	-4.37	0.000
sodium channel, voltage-gated, type VII, alpha	SCN7A	278.56	66.15	-4.21	0.001
cysteinyl leukotriene receptor 2	CYSLTR2	249.11	59.59	-4.19	0.000
multimerin 1	MMRN1	304.32	74.13	-4.11	0.001
complement component 7	C7	3565.49	869.29	-4.11	0.001
cadherin 19, type 2	CDH19	233.60	57.42	-4.07	0.000
immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu	IGJ	547.50	136.92	-4.00	0.004
secretory leukocyte peptidase inhibitor	SLPI	536.90	149.97	-3.58	0.001
low density lipoprotein-related protein 2	LRP2	188.17	52.71	-3.57	0.001
proteoglycan 4	PRG4	2957.18	839.11	-3.52	0.000
indolethylamine N-methyltransferase	INMT	1047.75	301.28	-3.48	0.000
integrin, beta 8	ITGB8	243.03	71.21	-3.41	0.000
arachidonate 15-lipoxygenase	ALOX15	232.20	68.83	-3.37	0.000
plectrophin	PTN	237.68	72.48	-3.28	0.000
mesothelin	MSLN	256.40	79.53	-3.21	0.001
transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	TGM2	1216.63	388.91	-3.13	0.000
carboxypeptidase A4	CPA4	194.15	62.47	-3.11	0.004
basonuclin 1	BNC1	268.06	87.53	-3.06	0.000
collagen type VI alpha 6	COL6A6	468.59	152.53	-3.07	0.000
prostaglandin D2 synthase 21kDa (brain)	PTGDS	619.40	202.61	-3.06	0.000
butyrylcholinesterase	BCHE	66.38	21.56	-3.02	0.001
FBJ murine osteosarcoma viral oncogene homolog B	FOSB	264.86	904.08	3.41	0.013
hydroxysteroid (17-beta) dehydrogenase 13	HSD17B13	57.11	193.13	3.52	0.000
chemokine (C-X-C motif) ligand 14	CXCL14	575.84	2178.42	3.78	0.001
corticotropin releasing hormone binding protein	CRHBP	110.56	434.55	3.93	0.000
neuropeptide Y receptor Y1	NPY1R	99.80	497.56	4.99	0.001
neuronatin	NNAT	252.56	1291.48	5.11	0.000

Gene	r-value	p-value
ITGB8	0.94	0.0001
CYSLTR2	0.77	0.0147
ALOX15	0.76	0.0184
COL6A6	0.75	0.0194
MMRN1	0.75	0.0199
LRP2	0.74	0.0232
HPR	0.72	0.0278
CRHBP	0.70	0.0374
IGJ	0.69	0.0386
UCP1	0.68	0.0436
C7	0.67	0.047
TCF21	-0.71	0.0314
TNFRSF1A	-0.73	0.0263
TGM2	-0.80	0.009

Of the 35, 14 are correlated with CAD severity measured by Gensini score

Correlation of Epicardial Adipose Expression of ITGB8 and Severity of CAD



Correlation of Subcutaneous Adipose Expression of ITGB8 and Severity of CAD

Of the 14 genes correlated with CAD severity, EAT expression of *ITGB8* had the strongest positive correlation. Importantly, this relationship did not persist in SAT, suggesting it was an effect specific to EAT.

Conclusion

Expression of ITGB8 was found to be directly correlated with CAD severity. **Integrin αvβ8 (*ITGB8*)** has been previously shown to be expressed by fibroblasts and functions to activate immune-modulating TGFβ. TGFβ signaling has also been correlated with advanced atherosclerosis. We speculate that EAT expression of *ITGB8* may have pro-inflammatory effects, possibly through activation of TGFβ, and stimulating recruitment of dendritic cells or T cells to secondary lymphoid organs in EAT. Whether or not this is the case is a goal of future studies.

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