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

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## Background

**Obesity and its associated cardiovascular 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.

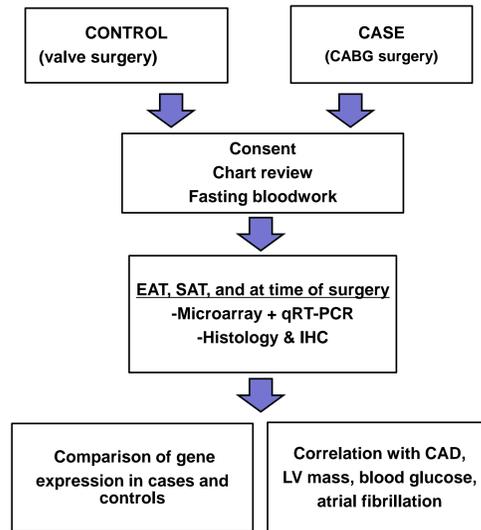
**What is not currently understood is whether or not inflammatory gene expression influences the development of atherosclerosis or is a compensatory response to established disease.**

## 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.

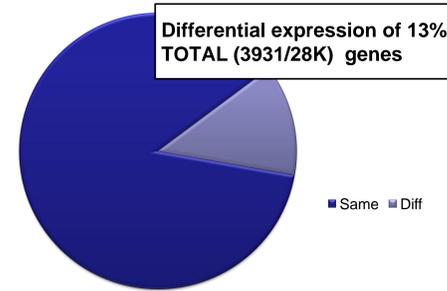
## Methods



- 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.

## 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
Integrin 1 (glycoprotein Ib/IIIa)	ITGB1	1004.67	24.08	41.70	0.000
polyoma virus and herpes simplex 1 (autosomal recessive)-like 1	HPV1L1	1004.64	49.59	20.26	0.000
chemokine (C-C motif) ligand 21	CCL21	1153.91	171.44	6.73	0.000
transcription factor 21	TF21	451.14	114.81	3.93	0.000
1 box 2D	1BX2D	583.09	111.56	5.23	0.000
Integrin alpha 8 (heparin-binding protein)	HPR	284.38	103.14	2.75	0.000
Integrin beta 8	ITGB8	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 antitrypsin, antitrypsin, member 3)	SERP1A3	309.53	67.94	4.57	0.000
sodium channel, voltage-gated, type VII, alpha	SCN7A	278.56	66.15	4.21	0.001
Cytoplasmic leucine receptor 2	CYLR2	349.11	83.28	4.19	0.001
myotubularin 1	MMRN1	324.32	74.13	4.37	0.001
complement component 7	C7	358.49	89.26	4.01	0.001
calcitonin receptor-like receptor 2	CLRLR2	233.90	57.45	4.07	0.001
immunoglobulin lambda polypeptide, linker protein for immunoglobulin alpha and mu	IGJ	547.50	136.92	3.99	0.001
leucocyte endothelin peptidase inhibitor	LEI	138.20	34.91	3.96	0.001
low density lipoprotein-related protein 2	LRP2	188.17	47.71	3.97	0.001
transglutamin 4	TGM4	207.18	52.11	3.99	0.001
indoleamine N-methyltransferase	INMT	1047.75	261.20	3.98	0.000
Integrin beta 8	ITGB8	243.03	61.21	3.97	0.000
arachidonate 15-lipoxygenase	ALOX15	232.20	58.51	3.97	0.000
pancreatin	PN	237.68	59.40	3.99	0.000
transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	TGM2	1216.83	308.91	3.93	0.000
cathepsin B	CTSB	104.13	26.41	3.94	0.000
heparin sulfate proteoglycan 2	HSPG2	201.04	50.73	3.96	0.000
collagen type VI alpha 3	COL6A3	489.59	123.52	3.97	0.000
collagenase 1 (matrix metalloproteinase 13)	MMP13	119.40	29.81	4.00	0.000
butyrylcholinesterase	BChE	66.38	16.55	3.99	0.001
FBI murine osteoarthritis viral oncogene homolog B	FOSE	51.11	12.71	4.02	0.000
hydroxysteroid (17-beta) dehydrogenase 13	HSD17B13	111.11	27.61	4.02	0.000
chemokine (C-C motif) ligand 14	CCL14	170.44	42.54	4.00	0.000
endothelin receptor type B	EDRB	101.11	25.21	4.01	0.000
neuropilin 1 receptor	NP1R	38.01	9.51	4.00	0.000
neuropilin 2 receptor	NP2R	38.01	9.51	4.00	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

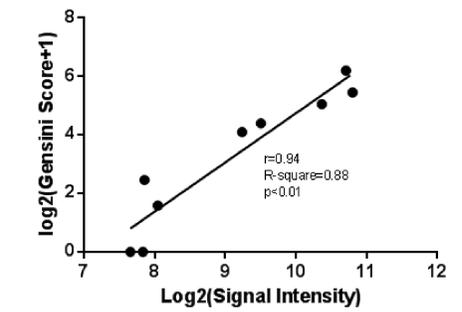
Of the 35, 14 are correlated with CAD severity measured by Gensini score

## Conclusion

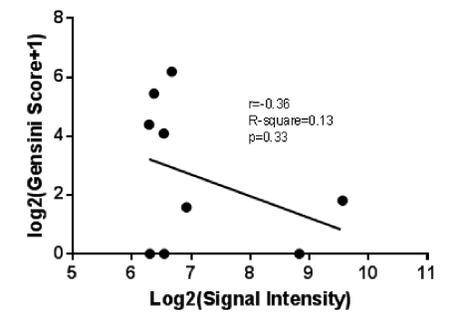
Expression of *ITGB8* was found to be directly correlated with CAD severity. **Integrin  $\alpha$ 8 (ITGB8)** has been previously shown to be expressed by fibroblasts and functions to activate immune-modulating TGF $\beta$ . TGF $\beta$  signaling has also been correlated with advanced atherosclerosis. We speculate that EAT expression of *ITGB8* may have pro-inflammatory effects, possibly through activation of TGF $\beta$ , 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.

## Results

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.

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