Proteins Desmin and VEGFR-1 are associated with coronary calcium scores in diabetic patients without prior cardiovascular disease

A PROTEOMIC ANALYSIS OF FACTOR-64 CLINICAL TRIAL SUBJECTS

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BACKGROUND

Coronary artery calcium (CAC) scores identify underlying coronary artery disease and have been shown to be highly predictive of future cardiac events.

However, a complete understanding of the biological aspects of CAC is lacking.

The purpose of the project was to examine the plasma-based proteomics associated with CAC in a diabetes mellitus (DM) population with no known cardiovascular disease.

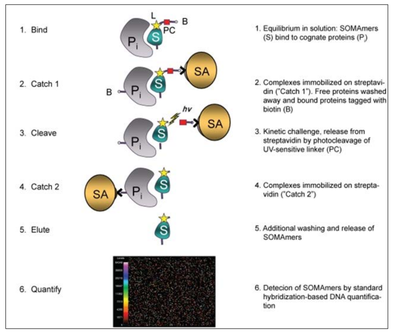
METHODS

Study population:

Subjects enrolled in the FaCTor-64 clinical trial that had a CT with CAC score and had a plasma sample collected at the time of enrollment were studied. FaCTor-64 was a randomized clinical trial examining the use of CT angiography to risk stratify DM patients into directed therapy in order to reduce the risk of death and nonfatal coronary outcomes.

Protein analyses:

The SOMAscan© assay was used to determine plasma levels for nearly 4000 proteins. SOMAscan © assay has been developed by SomaLogic, Inc. using their SOMAmer (Slow Off-rate Modified Aptamer) reagents. SOMAmers are sequences of short single-stranded DNA that incorporate a modifications giving the SOMAmer "protein-like" appendages. These chemical modifications allow for tight binding of a target protein and subsequently the quantification of protein levels.



*Source: SOMAmer-based biomarker discovery to diagnostic and clinical applications: a SOMAmer-based, streamlined multiplex proteomic assay. Kraemer S, et al. PLoS One. 2011;6(10):e26332.

Statistical analyses:

After quality control testing and the elimination of one subject with an extreme CAC (>3400), a total of 128 subjects were available for evaluation. Least squares regression was used for all analyses.

RESULTS

TABLE 1: DEMOGRAPHICS

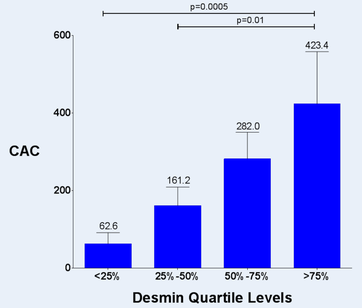
Demographics	n=128
Age, mean ± std	60.0 ± 7.7
Male, No (%)	64 (50.0%)
Caucasian, No (%)	124 (96.9%)
BMI, mean ± std	32.6 ± 6.6
Smoking History, No (%)	25 (19.5%)
Type 2 DM, No (%)	110 (85.9%)
Years with DM	11.1 ± 9.0
DM medication, No (%)	
Insulin	22 (17.2%)
Non-Insulin	78 (60.9%)
Both	28 (21.9%)
Hypertension, No (%)	74 (57.8%)
Hyperlipidemia, No (%)	82 (64.1%)
Sleep Apnea, No (%)	32 (25.0%)
Renal Failure, No (%)	11 (8.6%)

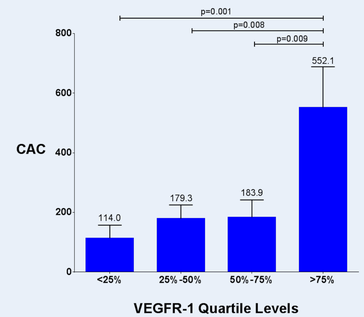
TABLE 2: LEAST SQUARES REGRESSION RESULTS

		Desmin (P17661)	VEGFR-1 (P17948)
Univariate Model	Parameter Estimate	0.21	0.22
	P-value	$1.8x10^{-5}$	$7.1x10^{-9}$
	R-Square	0.14	0.23
Multivariable Model (sex and age included)	Parameter Estimate	0.18	0.18
	P-value	$6.7x10^{-5}$	$3.2x10^{-7}$
	R-Square	0.29	0.34
Full Model (both protein and sex and age)	Parameter Estimate	0.11	0.15
	P-value	0.01	$5.2x10^{-5}$
	R-Square	0.38	

- Two proteins, desmin and VEGFR-1 (vascular endothelial growth factor receptor 1), were significantly associated with CAC. This significance was maintained after adjustment for sex and age.
- A full model, containing both proteins with age and sex, explained 37.7% of the variance of CAC. While both desmin (p=0.01) and VEGFR-1 ($5.2x10^{-05}$) remained significant, the majority of the signal appears to come from VEGFR-1.
- The differences are driven by extreme CAC levels in subjects in the 4th quartile levels for each protein.

FIGURE: CAC LEVELS (MEAN ± SE) BY QUARTILES LEVELS OF DESMIN AND VEGFR-1





CONCLUSIONS

- **Both desmin and VEGFR-1 are associated with increasing CAC.**
- **Our findings with regard to desmin is supported by recent reports of desmin being overly expressed in calcified carotid plaques, perhaps contributing to calcium accumulation.**
- **VEGFR-1 has been linked to atherosclerosis through angiogenesis in the plaque and vessel wall.**
- **The potential role of both desmin and VEGFR-1 in CAC physiology deserves further study.**

Disclosure: SomaScan assay was donated by SomaLogic.