ARIC Manuscript Proposal # 1206

SC Reviewed:	Status:A_ Status:	Priority: _2 Priority:
1.a. Full Title : Association of establicell-markers and cell aggregates (AR)		l platelet and monocyte
b. Abbreviated Title (Length 26 c Risk factors & cell markers	characters):	
2. Writing Group: Writing group members: Aaron Folsom, Nena Matijevic, Diane	e Catellier, Eric Boerwinkle	
I, the first author, confirm that all the manuscript proposalaf [please writing]		
First author: Folsom Address: on file		
Phone: E-mail:	Fax:	
Corresponding/senior author (be sent to both the first author Address:		-
Phone: E-mail:	Fax:	
3. Timeline : We hope to have a draft manuscript b	y March 2007/	

4. Rationale:

The aim of this paper is to report the relation between the established risk factors for atherosclerotic disease and cell markers expressed by circulating blood platelets and leukocytes in the carotid MRI study.

Immune and inflammatory mechanisms are considered to play a key role in the pathogenesis of atherosclerosis. Many inflammatory blood and vascular cell types and their activation markers play a role in the initiation, progression, and all stages of atherosclerosis development. Cell activation and cell-cell interactions result in the production of a cascade of cytokines, chemokines and other proinflammatory molecules that contribute to the disease.

Multiple studies have demonstrated a role of platelets as inflammatory cells; several platelet derived factors, both membrane bound and soluble may be involved in the inflammatory interaction between platelets, leukocytes, and endothelial cells. The platelet-leukocyte cross-talk involves a wide range of mediators such as chemokines, adhesion molecules, reactive oxygen species, and cytokines. Multiple clinical studies reported an association of platelet and leukocyte markers with atherosclerotic disease.

In the carotid MRI study, we measured the expression of a number of blood platelet and leukocyte markers and cell aggregates:

Platelet membrane glycoproteins IIb (CD41) and IIIa (CD61); platelet activation markers P-selectin (CD62P) and CD40L (CD154); platelet-platelet aggregates (PPA); platelet-leukocyte aggregates (platelet-monocyte; platelet-lymphocyte; platelet-granulocytes); monocyte lipopolysacharide (LPS) receptor (CD14); monocyte membrane expression of toll-like receptors TLR2 and TLR4; leukocyte membrane expression of CD45 (leukocyte common antigen) and PSGL-1 (P-selectin glycoprotein ligand-1; CD162); intracellular levels of the two leukocyte enzymes: myeloperoxidase (MPO) and cyclooxygenase-2 (COX-2).

In order to estimate the ability of peripheral blood circulating cellular markers to reflect the inflammatory alterations of the atherosclerotic plaques in carotid atherosclerosis, it is important to analyze the influence of traditional risk factors on the expression of cellular markers. It is important to better understand if there is a potential for confounding between traditional risk factors and cellular markers with respect to atherothrombotic disease. The potential association of cell markers with constitutional, lifestyle and biochemical characteristics of participants must be taken into account when analyzing the role of any of these cellular factors in the development and progression of atherosclerotic diseases.

5. Main Hypothesis/Study Questions:

Are established risk factors associated with expression of blood cell markers in the carotid MRI study?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This is a cross sectional analysis of the carotid MRI data performed at the CSCC.

Exclusions: missing covariates, any cell marker that proved not to be reliable (i.e., r<0.6).

Independent variables: basic risk factors (age, race, gender, LDL-C, HDL-C, lipid med use, systolic BP, antihypertensive med use, diabetes, obesity, cigarette smoking status, alcohol intake, physical activity, BMI, waist to hip ratio, and CRP). All will be from the carotid MRI visit.

Covariates: regular aspirin use, coumadin, others still being considered

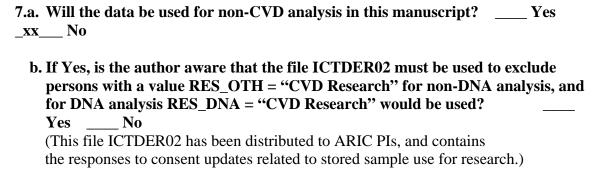
Dependent variables: platelet and leukocyte markers.

Analysis: Because of the design of the carotid MRI study, weighted analyses for complex surveys will be used throughout. The first step will be to review the QC data and remove the assays that are not reliable. Next we will examine the mean values and distributional characteristics of the dependent variables. Next, we will look at correlations among the numerous cell marker variables. If many are highly correlated, a smaller subset might be identified to serve as independent variables.

T tests, ANOVA, or chi-square tests will be used to assess associations of age, sex, or race with dependent variables. If any of these sociodemographic variables are significantly related to cell marker variables, we will model the association of other risk factors with cell markers using linear regression with adjustment for these factors. This modeling approach will also be used to control for potential confounding factors (e.g., aspirin use, coumadin) as needed. The independent variable of interest may be model using a regression spline or smoothing spline if its relationship to the cell marker is nonlinear.

The regression models may be extended to include all predictors found to be significant in univariate analyses described above, to determine which among them are independent predictors of the cell markers.

The challenge of this analysis is the many dependent variables and multiple independent variables, which is probably too much for one paper, unless few associations are evident. We will split out papers as seems appropriate. One logical split is by 1) Platelet markers, 2) Monocyte markers, 3) Cell-cell interactions (platelet-platelet and platelet-leukocyte aggregates).



8.a. Will the DNA data be used in this manuscript?xx No				Yes
Coordin	ating Cent those with	ter must be use	ther DNA data distributed ed, or the file ICTDER02 n NA = "No use/storage DNA	nust be used to
Study manus previously ap ARIC Investig	cript prop proved m gators have	oosals and has fanuscript properaccess to the p	proposal has reviewed the found no overlap between posals either published or so bublications lists under the Society dedu/ARIC/search.php	this proposal and still in active status.
xx	Yes	No		
encouraged t	o ead autho		cript proposals in ARIC (a	
11. a. Is this any ancillary	_		ociated with any ARIC and	cillary studies or use esxx No
I assume ARI	C MRI is r	not ancillary.		
11.b. If yes, is role (u	A. prima B. prima	rily the result or rily based on A	of an ancillary study (list r ARIC data with ancillary d ; list number(s)*	lata playing a minor
*ancillary stud	dies are lis	ted by number a	at http://www.cscc.unc.edu/a	aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.