IP-10 and Cardiovascular Disease in African Americans

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Background and Hypothesis

Immune dysregulation is a common feature of aging-related chronic diseases such as cardiovascular disease (CVD) (1), yet some immune-related pathways have not been extensively studied in the context of CVD risk. Chronic viral infections such as HIV(2) and hepatitis C(3) are associated with increased coronary artery disease risk independent of traditional risk factors, and lead to the induction of antiviral cytokines, such as type I and type II interferons (IFN), which may promote low-grade inflammation, immune dysfunction, and hypercoagulability.(4,5) While IFN is not readily measurable in plasma, a downstream serum protein, interferon gamma-inducible protein 10 (IP-10), may serve as a surrogate chemokine marker for activation of the IFN-1 pathway.

Multiple studies have shown a correlation between IP-10 and CVD, but African Americans have largely been excluded. Here, we examined whether IP-10 was associated with CVD risk factors, subclinical CVD, and incident events in two prospective cohort studies, Jackson Heart Study (JHS) and Reasons for Geographical and Racial Differences in Stroke (REGARDS).

Methods

3,494 African American participants in the Jackson Heart Study and 1,446 in the REGARDS cohort were followed longitudinally with several in-person visits and phone calls to assess a range of measures including health behaviors, medication use, anthropometry, blood pressure, kidney function, diabetes, and CVD biomarkers including IP-10. Imaging was also obtained to detect subclinical CVD.

Linear regression models were used to evaluate the correlation between IP-10 and known CVD risk factors after adjusting for age and sex.

Cox Proportional Hazards models were used to test for correlation between elevated IP-10 and increased incident events including stroke, heart failure, coronary heart disease and all-cause mortality. Multiple levels of covariate adjustment were used.

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Table 1: Age and Sex adjusted associations of IP-10 with CVD risk factors in JHS

	JHS		
	Beta per 1 SD increase in IP-10	SE	P-value
Age (Years)	3.41	0.22	$<1.0x10^{-4}$
Male sex (%)	-0.23	0.04	$<1.0x10^{-4}$
BMI (kg/m²)	0.03	$4.0x10^{-3}$	$<1.0x10^{-4}$
Waist Circumference (cm)	2.20	0.31	$<1.0x10^{-4}$
Current Smoking (%)	-0.33	0.07	$<1.0x10^{-4}$
SBP (mmHg)	-0.18	0.29	0.53
DBP (mmHg)	0.09	0.15	0.55
Hypertension (%)	0.08	0.04	0.05
Type 2 Diabetes (%)	0.08	0.04	0.07
Plasma Glucose (mg/dL)	0.17	0.18	0.36
Statin Medication Use*(%)	-0.05	0.05	0.29
HDL Cholesterol (mg/dL)	-1.90	0.28	$<1.0x10^{-4}$
Triglyceride(mg/dL)	0.05	0.01	$<1.0x10^{-4}$
Total Cholesterol (mg/dL)	-1.85	0.75	0.01
LDL Cholesterol (mg/dL)	-0.89	0.68	0.19
CRP (mg/dL)	0.16	0.03	$<1.0x10^{-4}$

Models are adjusted for age and sex (except for age and sex). BMI, triglycerides, and CRP are ln-transformed prior to analsys. 1 SD IP-10 corresponds to 105 pg/mL in JHS

Table 2: Associations of IP-10 with mortality and incident cardiovascular disease events in JHS

		JHS		
Model		1	2	3
Coronary Heart Disease	Events/N	101/2906		
	HR	0.98	0.98	0.97
	(95% CI)	(0.80, 1.19)	(0.82, 1.17)	(0.81, 1.16)
	p-value	0.81	0.80	0.76
Stroke	Events/N	110/2991		
	HR	1.05	1.07	1.06
	(95% CI)	(0.85, 1.31)	(0.88, 1.31)	(0.88, 1.28)
	p-value	0.64	0.49	0.52
All-Cause Mortality	Events/N	559/3173		
	HR	1.10	1.12	1.12
	(95% CI)	(1.01, 1.19)	(1.03, 1.22)	(1.03, 1.21)
	p-value	0.02	5.8×10^{-3}	7.5×10^{-3}
Heart Failure	Events/N	190/2756		
	HR	1.28	1.26	1.26
	(95% CI)	(1.13, 1.45)	(1.11, 1.42)	(1.11, 1.42)
	p-value	1×10^{-4}	4×10^{-4}	4×10^{-4}

*Hazard ratios (HR) and 95% confidence intervals (Cis) are reported per SD increase in IP-10.

† **Model 1:** Adjusted for age, sex (with additional adjustment for region in REGARDS)

‡ **Model 2:** Model 1 + BMI, blood pressure medications, type 2 diabetes, SBP, total cholesterol, HDL cholesterol, current smoking

§ **Model 3:** Model 2 + CRP

Results

We tested associations between IP-10, an antiviral chemokine, and subclinical cardiovascular disease and incident events in two African American cohorts. IP-10 was modestly associated with higher odds of left ventricular hypertrophy but not with other measures of subclinical cardiovascular disease. IP-10 significantly predicted risk of heart failure and mortality independent of C-reactive protein and traditional cardiovascular disease biomarkers. We found no association between IP-10 and stroke or coronary artery disease.

Discussion

Our study is the first to examine IP-10 specifically in African Americans and is consistent with other studies in both murine and human models of the correlation of IP-10 and pressure overload–induced cardiac dysfunction. These studies show that IP-10 appears to promote CD4+ T helper cell heart infiltration and adverse fibrosis and cardiac remodeling in a CXCR3-/LFA-1/ICAM-1-adhesion pathway.(6,7) This biologic link in conjunction with our findings gives hope that adaptive immunity biomarkers will be useful in diagnosing subclinical CVD in African Americans.

Strengths: evaluation of two large prospective African American Cohorts.
Limitations: lack of viral titers or self-reported chronic viral conditions to test for correlation. Limited HF cases in REGARDS.
Future direction: examine specific causes of death in larger samples to determine IP-10 association with all-cause mortality.

Conclusions

These results suggest a role of IP-10 in heart failure and mortality risk independent of C-reactive protein. Further research is needed to investigate how the body's response to chronic viral infection may mediate heart failure and overall mortality risk in African Americans.

Reference

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