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p53 codon 72 polymorphism and coronary artery disease: Evidence of interaction with ACP_1

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Fulvia Gloria-Bottini[1ACE], Maria Banci[2BDF], Patrizia Saccucci[1BEF], Anna Neri[1BCF], Egidio Bottini[1ACD], Andrea Magrini[1ADG]

[1] Department of Biopathology and Imaging Diagnostics, University of Rome Tor Vergata, Rome, Italy
[2] Department of Cardiology, Valmontone Hospital, Rome, Italy

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Summary

Background: Common biological features between cancer and atherosclerosis suggest possible association of p53 with atherosclerotic diseases, but data on such a relationship are controversial, suggesting interactions with other variables. Acid phosphatase locus 1 (ACP_1) is a polymorphic gene that controls the synthesis of an enzyme involved in important metabolic functions. Since ACP_1 is associated with coronary artery disease (CAD), we searched for possible interactions between this enzyme and p53 codon 72 polymorphism with regard to their effects on susceptibility to CAD.

Material/Methods: The study included 381 patients admitted to the hospital for cardiovascular disease (232 patients with CAD and 149 with other cardiovascular problems) and 97 healthy newborns.

Results: The proportion of subjects carrying the *Pro allele of p53 codon 72 and the high activity *B*C genotype of ACP_1 is higher in CAD (10.3%) than in non-CAD patients (2.0%) and in healthy newborns (6.2%).

Conclusions: The data suggest an interaction between p53 codon 72 and ACP_1 wherein a positive effect of the p53 *Pro allele on susceptibility to CAD occurs, but only in the presence of the ACP_1 genotype characterized by high enzymatic activity.

key words: **p53 • CAD • ACP_1**

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Author's address: Fulvia Gloria-Bottini, Division of Biopathology of Human Population and Environmental Pathology, Department of Biopathology and Imaging Diagnostics, University of Rome Tor Vergata, School of Medicine, Via Montpellier, 00133 Roma, Italy, e-mail: gloria@med.uniroma2.it

Background

Although the inflammatory theory of atherosclerosis is the most prominent, several observations point to common biological features between cancer and atherosclerosis [1–4].

This has suggested a possible relationship between atherosclerosis and p53, a protein well known for its association with cancer [5–10]. At present, however, the data on such a relationship are controversial, suggesting interactions with other variables [11].

The genetic analysis of multifactorial disorders represents a central problem in medical genetics, and the study of single gene factors based on a Mendelian perspective is reductionist and unable to solve the problem. The simultaneous analysis of multiple genes functionally related to the disease, and of environmental factors involved in the susceptibility to a disease, is likely to provide a more productive approach [12].

Recently, we have found an association between CAD and acid phosphatase locus 1 (ACP_1), an enzyme involved in glucose metabolism, cellular growth and cancer development (13). ACP_1 is a polymorphic gene with 3 codominant alleles (*A,*B,*C) at an autosomal locus that controls the synthesis of the cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP). There are 6 genotypes with enzymatic activity, increasing in the order *A/*A<*A/*B<*B/*B=*A/*C<*B/*C<*C/*C; the last genotype is very rare. The enzyme discloses 2 isoforms – F and S – that have different biochemical properties and different concentrations between genotypes; carriers of *C allele have the highest concentration of S isoform [14].

The ACP_1 enzyme dephosphorylates a negative regulatory phosphorylation site in the ZAP-70 tyrosine kinase in T cells, an event that leads to increased activation of this kinase and enhanced signaling from the T cell antigen receptor [15].

Codon 72 in exon 4 of the p53 gene shows a polymorphism characterized by a G to C substitution that determines the change of Arginine to Proline in the protein. The amino acidic change affects biochemical and functional properties of p53: the arginine variant is a stronger apoptosis inducer, while the proline variant is a stronger transcriptional activator. Recent studies point to an involvement of the protein in functions of the immune system [16,17].

In the present study we searched for a possible interaction between ACP_1 and p53 codon 72 concerning their effects on susceptibility to CAD.

Material and Methods

We studied 381 subjects admitted for cardiovascular diseases to the Valmontone Hospital, Rome, Italy – 232 patients with coronary artery disease and 149 with other cardiovascular problems. Tables 1 and 2 show some clinical data for the 2 classes of patients. A small sample of 97 newborn infants was also studied. All subjects were Caucasians.

ACP_1 genotypes were determined as previously described [18] and p53 codon 72 genotype was determined according to the method of De La Calle-Martin et al. [19].

Table 1. Clinical data in subjects admitted to the Hospital for CAD.

Parameter	% Proportion	
Infarction	41.4%	
Major coronary lesions	82.3%	
Bypass	34.2%	
Angioplastic	26.9%	
Gender (female%)	48.1%	
Smoking habit	47.5%	
	Mean	**SD**
Age (years)	67.1	±11.7
Body mass index (kg/m^2)	28.0	±5.2

Table 2. Clinical data in subjects admitted to the Hospital for Cardiovascular Diseases without CAD.

Parameter	% Proportion	
Sex (Female%)	64.1%	
Defects of the hearth valves	31.7%	
Hypertension*	57.2%	
Cardiac hypertrophy**	43.9%	
Dilated heart***	17.1%	
Cardiac arrhythmia#	50.3%	
Smoking habit	41.3%	
	Mean	**SD**
Age (years)	54.1	±17.3
Body mass index (kg/m^2)	26.8	±5.4

* Medicated against hypertension/arterial tension ≥130/85 mm Hg; ** patients with thickness walls ≥ 11mm; *** diameter diastolic left ventricular ≥56 mm; # patients with atrial fibrillation, sinusal arrhythmia, atrial ventricular blocks

Statistical analyses were carried out by SPSS programs [20].

Written informed consent was obtained from patients or from their mothers to participate to this study that was approved by the Hospital Ethics Committee. The study conforms to the Declaration of Helsinki.

Results

Table 3 shows the distribution of p53 codon 72 genotypes in CAD and non-CAD patients in relation to ACP_1 genotypes, grouped according to total enzymatic activity. There is a significant association between ACP_1 and p53 in CAD but not in non-CAD. This interaction depends on the association between high ACP_1 activity *B/*C genotype with *Pro carrier genotypes, which is statistically significant in CAD but not in non-CAD patients. The data suggest a positive effect of *Pro allele of p53 codon 72 on susceptibility to CAD, but only in the presence of the ACP_1 genotype with high enzymatic activity.

Table 4 shows the proportion of the joint genotype "*Pro carrier of p53 codon 72/ *B*C genotype" in CAD, in non-CAD patients, and in newborn infants. The proportion of this joint genotype is higher in CAD than in non-CAD, while

Table 3. Distribution of joint ACP_1-p53 codon 72 genotypes in subjects with coronary artery disease and in patients admitted in Hospital for cardiovascular diseases without CAD.

CAD	*% Proportion of p53 codon 72 genotypes*			
	***Arg/*Arg**	***Arg/*Pro**	***Pro/*Pro**	**Total n°**
ACP_1 genotypes *A/*A + *A/*B (low activity)	57.7%	36.1%	6.2%	97
*B/*B + *A/*C (medium activity)	48.6%	38.1%	13.3%	105
*B/*C (high activity)	20.0%	63.3%	16.7%	30
Test of independence	χ^2	df	p	
Overall	14.676	4	0.005	
Carriers of *Pro allele with high ACP_1 activity 1 *vs.* other joint genotypes	11.420	1	0.000	
NON CAD				
*A/*A + *A/*B (low activity)	56.5%	35.5%	8.1%	62
*B/*B + *A/*C (medium activity)	55.3%	32.9%	11.8%	76
B*/*C (high activity)	72.7%	27.3%	0.0%	11
Test of independence	χ^2	df	p	
Overall 4	2.363	4	0.669	
Carriers of *Pro allele with high ACP_1 activity *vs.* other joint genotypes	1.160	1	0.310	

Table 4. Proportion of the joint genotype *B/*C / *Pro allele carrier in CAD patients, in non-CAD patients and in healthy newborns. The expected proportion calculated on the basis of genotype frequencies in the general population is 6.4%.

	Proportion of subjects carrying the *Pro allele and *B/*C genotype		**Total n°**
CAD patients	10.3%		232
Healthy newborns	6.2%		97
Patients with cardio vascular problems without CAD	2.0%		149
Chi square test of independence	χ^2 9.896	df 2	p 0.007

an intermediate value is observed in newborns. The value observed in newborns corresponds to that expected on the basis of ACP1 and p53 codon 72 genotype frequency in the general population (Figure 1).

We have examined possible effects of the following variables: sex, age, diabetes, hypertension, history of previous infarction and smoking. In the CAD sample no significant effect of these variables was observed on the proportion of *Pro carriers with the *B*C genotype.

Discussion

The results of our study suggest that a relationship between p53 codon 72 polymorphism and CAD may indeed exist and that it is influenced by ACP_1. The joint genotype *Pro carrier/*B/*C in newborns shows an intermediate value between CAD and non-CAD patients. This could be explained by considering that a certain proportion of newborns will have coronary artery disease in adult life. To study the role of genetic factors on susceptibility to CAD, adult subjects with cardiovascular disease without CAD might be a more reliable control as compared to newborns.

These data could be interpreted in favor of the inflammatory theory of atherosclerosis. Recent studies suggest that p53 is involved in autoimmune inflammation [16,17] regulating STAT1 and pro-inflammatory cytokines. On the other hand, ACP_1, through regulation of ZAP-70, could have an important role in immunological processes [15].

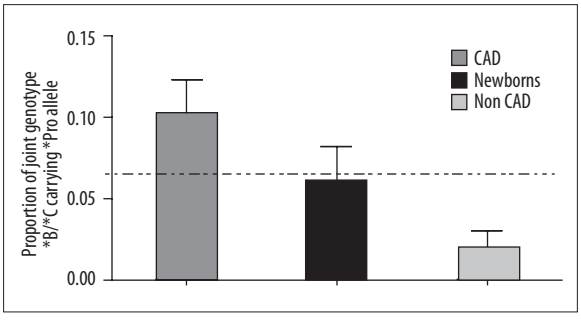

Figure 1. Proportion of the joint genotype "high activity ACP_1 *B/*C carrying *Pro allele of p53 codon 72". The horizontal line corresponds to expected proportion of this genotype in the general population. Chi square of independence: p=0.007.

Overall, it seems that ACP_1 *B/*C subjects carrying the *Pro allele are more vulnerable to CAD than other joint genotypes. *Pro allele of p53 codon 72, with its strong properties of transcriptional activation, could aggravate local coronary inflammatory lesions stimulated by enhanced signalling from T cell antigen receptors due to high ACP_1 activity.

Conclusions

A limitation of the present study is the relatively small size of study samples. Moreover, although no significant effect of several risk factors for CAD have been detected for the proportion of p53 *Pro carriers with *B/*C genotype, in CAD these effects should be carefully evaluated in a larger sample. If confirmed, our observation may have important implications for the evaluation of risk for CAD and could suggest a target for prevention and/or treatment.

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