Short report

Inflammatory bowel disease: Are there gender differences in the genetics of signal transduction? A preliminary study of cytosolic low molecular weight protein tyrosine phosphatase

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The phenotype of cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP or ACP1), an enzyme involved in signal transduction of insulin, PDGF and T-cell receptors, has been determined in 71 patients with Crohn's Disease (CD: 37 males and 34 females), 49 patients with Ulcerative Colitis (UC: 27 males and 22 females) and 358 consecutive newborns (194 males and 164 females). cLMWPTP phenotypes showing a high concentration of F isoforms are associated with CD in females and with UC in males. Since PTPases counteract the effects of protein tyrosines kinases, a high concentration of F isoform of cLMWPTP may influence the mucosal response to pathogenic factors, increasing susceptibility to CD in females and to UC in males.

Abbrevations: IBD, Inflammatory Bowel Disease; CD, Crohn's Disease; UC, Ulcerative Colitis; GF, Growth Factors

1. Introduction

The role of cytokines and growth factors (GF) in the pathogenesis of inflammatory bowel disease (IBD) is currently under active investigation [1–3]. Post-receptorial events, however, are still scarcely considered in IBD literature. Many signal transduction pathways that could have an important role in IBD pathogenesis involve tyrosine phosphorylation phenomena. Protein tyrosine phosphatases (PTPases) are present in these pathways and counteract the effects of receptorial or receptor-associated tyrosine kinases.

In a survey of studies on cytosolic Low Molecular Weight Tyrosine Phosphatse (cLMWPTP or ACP1) in common diseases, one of us has noted a positive association of Crohn's Disease with F isoform of the enzyme [4]. Current interest focuses on gender diferences in immune diseases [5]. Moreover, differences have been described in the susceptibility to Crohn's Disease depending on the sex of the parent showing the

[†]Prof. Pier Giulio Ronchetti died before the manuscript was submitted. His co-authors wish to dedicate this paper to his memory.

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Table 1
Percent distribution (standard error) of cLMWPTP genotypes in subjects with IBD and in controls from the same population

	cLMW-PTP phenotypes						Total
	A	B	C	AB	AC	BC	n
Males							
Crohn's Disease	5.4% (3.7)	43.2% (8.1)	–	37.8% (8.0)	8.1% (4.5)	5.4% (3.7)	37
Ulcerative Colitis	–	70.4% (8.8)	–	22.2% (8.0)	–	7.4% (5.0)	27
Controls (consecutive newborns)	9.8% (2.1)	40.2% (3.5)	–	36.6% (3.5)	3.1% (1.2)	10.3% (2.2)	194
Females							
Crohn's Disease	2.9% (2.9)	79.4% (7.9)	–	17.6% (6.5)	–	–	34
Ulcerative Colitis	18.2% (8.2)	36.4% (10.0)	–	27.3% (9.5)	4.5% (4.4)	13.6% (7.3)	22
Controls (consecutive newborns)	9.1% (7.7)	50.0% (3.9)	1.2% (2.9)	31.7% (3.6)	1.8% (1.0)	6.1% (1.2)	164
Males and females (adult control sample)							
Adult both sexes	8.6% (1.4)	43.9% (2.4)	0.2% (0.2)	31.7% (2.3)	3.4% (0.9)	12.2% (1.6)	417

disease [6]. This prompted us to reconsider our data in more detail. A significant interaction has emerged among cLMWPTP, sex and class of IBD (Crohn's Disease vs Ulcerative Colitis).

2. Subjects and methods

We have studied 71 patients with Crohn's Disease (CD: 37 males and 34 females) and 49 patients with Ulcerative Colitis (UC: 27 males and 22 females) from the population of Rome admitted consecutively to the Division of Gastroenterology of S. Camillo Hospital. For all patients, the diagnosis of CD or UC was performed correlating clinical symptoms with endoscopic findings, mucosal biopsy studies and radiological evaluation of the small and large intestine. The absence of inflammatory intestinal disease other than CD or UC was based on clinical, serological, microbiological and pathological data. Informed consent for participation to the study was obtained for all patients.

We have also studied 358 newborns (194 males and 164 females) delivered consecutively by healthy women in the Maternity Department of University of Rome La Sapienza. For comparison the data on 417 adult blood donors of both sexes studied by Modiano et al. [7] in the population of Rome are also reported.

ACP1 phenotype has been determined by starch gel electrophoresis on red blood cell hemolysates according to Harris and Hopkinson [8]: the acid phosphatase pattern is revealed by a solution of phenolphtalein diphosphate: the addendum of ammonia solution reveals the area where phenolphtalein has been liberated in the areas of gel where ACP1 activity is present. In the European population the presence of three common alleles *A, *B and *C determines the occurrence of six phenotypes: A, AB, B, AC, BC and C. Each of homozygous A, B and C phenotype is composed by two fraction; F and S, corresponding to a fast and slow component of electrophoretic pattern. Heterozygous phenotypes have a pattern corresponding to a mixture of homozygous types.

Chi square analyses have been performed using SPSS package on an IBM PC [9].

3. Results

Table 1 shows the distribution of cLMWPTP phenotypes in CD, in UC and in newborn infants separately. Normal adults (both sexes) from the same population are also shown for comparison. Statistical analyses on these data are reported in Table 2. The distribution of cLMWPTP phenotypes in females with CD is significantly different from that of controls, showing an excess of B phenotype. The distribution of cLMWPTP phenotypes in males with UC is significantly different from that of controls, again showing an excess of B phenotype. In both CD and UC cLMWPTP, distribution in males is significantly different from that of females. Sex differences are not observed in controls.It should be noted that B phenotype shows the highest concen-

Table 2
Distribution of cLMWPTP genotypes in relation to sex and type of IBD. Statistical analyses: A vs B vs AB vs (C + AC + BC)

	Chi square test of independence		
	χ^2	df	p
A) Crohn's Disease			
males vs male newborn control	0.742	3	1.000
males vs adult control	0.947	3	1.000
females vs female newborn control	10.777	3	0.017
females vs adult control	17.160	3	0.000
CD males vs CD females	11.240	3	0.010
B) Ulcerative Colitis			
males vs male newborn control	9.637	3	0.028
males vs adult control	8.141	3	0.056
females vs female newborn control	3.968	3	0.356
females vs adult control	2.563	3	0.632
UC males vs UC females	8.728	3	0.033
C) Healthy Newborns			
males vs females	3.970	3	0.264

tration of F isoform, AB and BC an intermediate one and the other phenotypes (AA, AC and CC) the lowest concentration of this cLMWPTP isoform.

4. Discussion

cLMWPTP (ACP1) is a cytosolic low molecular weight protein tyrosine phosphatase involved in signal transduction of insulin, PDGF and T-cell receptors [10, 11]. cLMW-PTP is a polymorphic enzyme showing strong quantitative variations among phenotypes. It is composed of two isoforms, F and S, which show different concentrations among phenotypes [4].

We have previously reported that CD is significantly associated with dose of *B allele and with F isoform concentration [4]. The present analysis shows that such association is significant for both CD and UC and is dependent on sex being very strong for CD in females and for UC in males. However, considering the relatively small number of subjects studied such association needs to be confirmed in a larger sample.

Intracellular signal transduction is mediated by the balance between kinases and phosphatases and both have a crucial role in metabolism, immunological responses, and cellular growth and multiplication. Genetic variability of kinases and phosphatases involved in these signalling pathways could influence response of receptors to growth factors and cytokines. Both in CD and in UC, a role of increased or decreased levels of growth factors and cytokines and of their signal transduction pathways involving tyrosine kinases has been demonstrated [1–3]. Tyrosine phosphorylation phenomena are also involved in regulation of intestinal barrier permeability [12] and of immune response against pathogens [13]: both of these phenomena have been suggested to be important in IBD pathogenesis [14]. Since PTPases counteract the effect of protein tyrosine kinases, a high concentration of F isoform pf cLMW-PTP may influence the mucosal response to pathogenic factors, increasing susceptibility to CD in females and to UC in males. In particular, as cLMWPTP has been demonstrated to counteract in vitro PDGF signal transduction [15], the relationship between the increased incidence of cLMWPTP phenotypes associated with high F isoform activity in our patients and the low levels of PDGF and PDGF receptors reported in IBD mucosa [3] seems to warrant further investigation.

At present, there is a surge of interest for the genetics of inflammatory bowel disease [16–19]. The presence of CD and UC in the same pedigree has been described [20] and a common genetic factor has been suggested in the pathogenesis of both forms of IBD [21]: in our population cLMWPTP polymorphism seems to be associated with both CD and UC suggesting that one of common genetic determinants of IBD could be located at level of signal transduction pathways involving tyrosine phosphorylation phenomena. It should be made clear that IBD is a multifactorial disorder and it is very likely that many genes contribute to susceptibility to these disorderd [22] that may also be heterogeneous.

Type and degree of immune response differ between men and women [5]. Differences in sex hormones and their receptors, as well as the sexually dimorphic pituitary hormones, could be responsible for gender differences in autoimmunity. These differences might also have important implications for treatment [5].

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