Allotypes and gynecological cancer

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Summary

Purpose: To investigate if gynecologic cancer patients have different immune responses.

Methods: Immunoglobulin heavy chains (G1m, G3m), Kappa light chains (Km) and allotype and phenotype frequencies were examined in 58 patients with gynecologic cancer (ovarian, cervical, endometrial, vulval, vaginal and uterine sarcoma) and a control group of 26 women.

Results: No significant differences were found between the different allotype or phenotype frequencies between the two groups.

Conclusions: Our results indicate that Gm and Km allotypes do not represent susceptibility factors for gynecologic cancer in Caucasians.

Key words: Immunoglobulin allotypes-gynecological cancer-genetics.

Introduction

Antibodies or immunoglobulin are an important component in immune response. There are five classes of immunoglobulins (Kg), IgG, IgA, IgM, IgD, IgE, getting their names from the type of heavy chains they have, which are called γ, α, μ, δ and ε, respectively.

Every Ig molecule has two heavy and two light chains. Light chains are classified in two types κ and λ. Every Ig molecule has two κ and two λ chains irrespective of its class. There are differences between the aminoacid sequences of the heavy chains of each Ig class and between the light chains of the two types.

Each chain has a variable NH_2– domain which is responsible for the recognition of the antigen and a constant COOH– domain responsible for effective molecular function. The constant domains are the same in each class, with the exception of minor differences which are caused by a substitution of only one aminoacid. These differences are related to genetic polymorphism, are called allotypes and are symbolised by Gm.

Allotypes are located on the constant region of the heavy chains IgG1, IgG2, IgG3, IgA2 and IgE and the κ light chains and they are named G1m, G2m, G3m, A2m, Em and Km, respectively.

Allotypes, or genetic markers of immunoglobulins, are the structural differences that are inherited according to the laws of Mendel. As, for example, genetically individuals differ in the antigens of the ABO blood group, the heavy and κ light chains of immunoglobulins differ in their expression of allotypes.

The relation between allotypes and the susceptibility to several types of human cancer is under research. The aim of this study was to investigate the correlations between allotypes and the various types of gynecologic cancer which, to our knowledge, has not yet been studied.

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Patients and Methods

The allotypes of immunoglobulin G (Gm markers), G1m(1), G1m(2), G1m(3), G3m(5), G3m(10), G3m(21), G3m(28) and of the light chain κ Km(1), were designated in the serum of 29 patients with ovarian, 12 with cervical, 8 with endometrial 3 with vulval and 3 with vaginal cancer. Twenty-six healthy women of approximately the same age were used as controls.

The sera were tested for the G1m(1, 2, 3), G3m(5, 10, 21, 28) and Km(1) allotypes by the hemagglutination inhibition technique (HAI) on slides [1], using red blood cells coated with incomplete Rh antisera. The reagents and the nomenclature used are presented in Table 1. The antisera used were derived from the Centre de Recherches sur le Polymorphisme Genetique des Populations Humaines, directed by Dr. Dugouson at Toulouse, France.

The HAI method is simple in principle. If, for example, anti-Gm(1) and a solution of Gm(1) proteins are mixed, the anti-Gm(1) antibody is neutralized. In the second stage, the index stage, anti-Gm(1) is not free and is incapable of agglutinating the red blood cells that are coated with Gm(1) g-globulin. Therefore the ability of anti-Gm(1) to agglutinate red blood cells coated with Gm(1) immunoglobulin is inhibited if the tested solution contains Gm(1) protein, but is not inhibited if it does not contain Gm(1) protein- it is Gm(-1).

Statistical analysis

The x^2. test was employed for the calculation of significant differences between allotypes and phenotypes of patients with gynecological cancer and controls.

Results

The frequencies of the immunoglobulin allotypes (G1m, G3m and Km) observed in gynecologic cancer

Table 1. — *List of reagents used to determine allotypes*

Subclasses	Nomenclature*	Numeric**	Antiseria Anti-allotypes	Homology region	Coating
Heavy Chains Chains	Allotypes		Anti-G1m (1)		
IgG1	G1m (a)	G1m(1)	DON 1/8	CH3	Anti-D GAN/FIS au 1/2
	(x)	(2)	Sub 1/64	CH3	Anti-D GAN/FIS au 1/2
	(f)	(3)	Bon 1/16	CH1	Anti-D LORI P2 au 1/2
			Bon 1/32		Anti-D BEI au 1/2
IgG3	G3m (b1)	(5)	Anti-G3m (5) AG 1/16	CH2	Anti-D EYC au 1/2
	(b5)	(10)	Anti G3m (10)	CH3	
	(g)	(21)	DES 1/32		Anti-D ANT au 1/2
	(g5)	(28)	Anti-G3m (28)	CH3	
Light Chains κ chain	Km (1)	Km (1)	Anti-Km (1) POR 1/8		Anti-D BEI au 1/2

* The nomenclature is that suggested by the WHO (Workshop, Rouen, July 1974)
\+ Only the numeric notation of the two suggested are used (in this work)

Table 2. — *Frequency of immunoglobulin allotype present in patients with gynecologic cancer and healthy individuals*

Ig allotype	Patients with gynecologic cancer (%)	Healthy individuals (%)
G1m(1) (a)	51.7	48.7
G1m(2) (x)	16.1	16.3
G1m(3) (f)	91.3	91.0
G3m(5) (b1)	91.3	90.7
G3m(10) (b5)	89.1	88.3
G3m(21) (g)	49.2	47.5
Gm3(28) (g5)	39.0	42.0
Km(1)	16.4	16.2

patients and healthy individuals are summarized in Table 2.

No significant differences were seen between the numbers of each allotype present in the patients and the controls.

The frequency of eight Gm phenotypes, common in Caucasians, are shown in Table 3, again showing no significant differences between patients and controls.

Discussion - Conclusions

The location of the genes that are responsible for the IgG heavy chains in chromosome 14, band q32.3 is significant because it is within or close to a region of the chromosome that is prone to break and to be involved in rearrangements [2]. Determining the effect of these genetic factors can assist in better understanding the relationship between enviromental factors and the genetic substrate in the susceptibility to cancer.

These fact reinforce the hypothesis that genetic factors (eg. genes that control IgG heavy chains) play some role in human cancer. Genes for the heavy chains of human Ig may have an effect on the abnormal rearrangements of chromosomes or some other non-genetic mechanisms that end in malignant transformation [3, 4].

Table 3. — *Gm and Km phenotypes in patients with gynecologic cancer and healthy controls*

G1m j.. G3m phenotype	Healthy controls (n=26)	Ovarian cancer (n=29)	Cervical cancer (n=12)	Endometrial cancer (n=8)	Vulval cancer (n=3)	Vaginal cancer (n=3)	Uterine sarcoma (n=3)
Gm (3; ..., 5, 10)	53.8	51.0	49.0	49.8	54	52.3	51.2
Gm (1, 3; ..., 5, 10, 21, 28)	19.2	17.2	16.8	18.0	16.5	17.4	19.1
Gm (1, 2, 3; ..., 5, 10, 21, 28)	3.84	2.1	3.1	3.4	4.1	3.9	2.9
Gm (3; ..., 5, 10, 28)	3.8	2.9	3.4	4.1	3.4	2.8	3
Gm (1, ..., 21, 28)	3.8	3.1	41.1	2.1	3.9	2.9	2.7
Gm (1; ...; 5, 10, 21, 28)	3.8	3.0	4.01	3.01	2.9	3.1	2.8
Gm (1, 2; ..., 5, 10, 21, 28)	7.6	5.3	7.0	6.5	6.30	6.3	7.1
Gm (1,2; ..., 5, 10)	3.8	4.01	4.4	3.5	2.9	3.7	4.0
Km + 1	23	20	24	25	24.8	26	25

* All sera were examined for G1m (1, 2, 3) and G3m (5, 10, 21, 28) and Km (1)

The Gm genes may be in linkage disequilibrium with other parts of DNA, such as genes for the V region, which affect the properties (qualitative or quantitative) of the antibodies and change the immune surveillance against malignancy.

Thus, Gm allotypes have been studied as probable genetic markers for human cancer.

Gm phenotypes in the serum of breast cancer patients had a distribution similar to healthy individuals [5]. In contrast, Gm phenotypes 1, 2; 13, 15, 16, 21 of patients with primary hepatoma and lung cancer were significantly elevated when compared with healthy individuals [6]. In patients with nasopharyngeal cancer, two rare phenotypes, Gm 1, 17; 11, 15, 21 and Gm 1, 3; 5, 21 [7] were significantly elevated. In our patients with gynecologic cancer there was no significant difference of various Gm phenotypes between patients and controls. Morever, there was no significant relation between Km markers and the occurrence of gynecologic cancer.

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