IMMUNOLOGY

A γ-Globulin Genetic Factor related to Gm(a) but localized to a Different Portion of the same Heavy Chains

PREVIOUS investigations have indicated that Gm(a)* and Gm(f)* are genetic characters localized in various areas of the major heavy chain class[1-3] of human γG globulins. These determinants, detected as antigens, segregate in most populations, as if controlled by allelic genes, and occur independently in myeloma proteins from Caucasians. A previous report indicated that specific reagents for the human genetic factors can be produced by immunizing rabbits with myeloma proteins[4]. In order to analyse in a more satisfactory way the genetic control of different portions of the heavy chains, it seemed desirable deliberately to immunize with critical protein fragments in order to disclose additional genetic sites believed to be present but not detected by available antisera.

The Fab portion of Gm(a^+) myeloma proteins lacks any detectable genetic factor[5,6] and this was used as the antigen for rabbits. The antisera obtained were absorbed with normal human serum of various phenotypes and were then tested for differential agglutination against a battery of incomplete anti-D coats on human red blood cells. Antisera which appeared specific were investigated further by inhibition with selected proteins[5,6]. In this way a new factor, tentatively called Gm(z)*, was detected.

The Gm(z) genetic factor was found in the Fab portion of papain split FII γ-globulin, while Gm(a) was detected in the Fc portion as previously described[5,6]. All Gm(a^+) myeloma proteins from Caucasians and Negroes were also Gm(z^+) (Table 1). Papain splitting of these doubly positive myeloma proteins showed the Gm(z) determinant in the Fab peak separated by zone electrophoresis, while the Gm(a) factor was present in the faster migrating Fc peak. Pepsin treatment destroyed the Gm(a) determinant and left intact the Gm(z). Inhibition at a concentration as low as 0·008 mg/ml. was obtained for the active fragments. Isolated light chains failed to inhibit even at 2 mg/ml. All preparations of heavy chains from FII and myeloma proteins were inhibitory, but to a lesser degree than the intact protein and Fab fragments. Parallel investigations with Gm(f) indicated that Gm(z) and Gm(f), although on different myeloma proteins, behaved very similarly in the aforementioned experiments and were localized to the Fd portion of the heavy chains. Gm(z) was found only in myeloma proteins of the We(γ_{2b}) sub-group—as was the case for Gm(f).

The phenotype frequencies of various populations are shown in Table 1. In the Caucasian, Negro and Japanese groups, Gm(a) and (z) are concordant, but there are many discordant Gm(a^+z^-) sera in the Chinese and Easter Islanders. The latter groups affirm the non-identity of genetic factors Gm(a) and (z). Further evidence for this difference was obtained from the study of a Chinese myeloma protein which was previously shown to be Gm(a^+f^+) in striking contrast to all Caucasian and Negro myeloma proteins. This protein was Gm(z^-).

The data from these investigations are consistent with the possibility that Gm(z) and (f) segregate as co-dominant alleles. They are the only genetic factors found so far on the Fd portion of the heavy chain[2,3]. None of the more than 300 sera tested were negative for both (z) and (f). A significant finding is that in all the groups investigated (Table 1) the frequencies of both factors and the proportion of heterozygotes are compatible with such allelism—assuming different gene frequencies for Gm(f) and (z). In the Chinese, where the frequency of (f) is high, as would be predicted, (z) is low, whereas in the Negro and Japanese populations the reverse is true. Family investigations of 42 Caucasian and 26 Easter Island progeny support the behaviour of Gm(f) and (z) as alleles.

Table 1. GM PHENOTYPES OF DIFFERENT RACES

Gm type			Races				
a	z	f	Cauc.	Negr.	Jap.	Chin.	East.†
Sera							
+	+	+	41	2	3	58	23
+	+	−	24	19	36	14	13
−	−	+	83	0	0	0	0
+	−	+	0	0	0	53	12
Myeloma proteins*							
+	+	−	5	2			
−	−	+	11				
+	−	+				1	

* Only myeloma proteins of the We(γ_{2b}) class are shown.
† Easter Islanders.

The accumulated evidence indicates that in Caucasians the genes controlling the We-type heavy chain would be Gm^{az} and $Gm^{a\text{-}f}$. In Negroes the predominant gene would be Gm^{az}. On the other hand, in Chinese and the Easter Islanders, the gene Gm^{af} as well as Gm^{az} must be postulated to account for the large number of discordancies between Gm(a) and (z), their phenotype distributions, and the Chinese myeloma protein. The previous suggestion that the Gm^{af} gene arose by an intragenic cross-over[7] is compatible with the present observations, as the association of Gm(z) with Gm(a) disappears when Gm(f) becomes associated with Gm(a).

Two genetic factors are therefore now available which seem to be present on the same heavy chains, but in different areas readily separated by papain splitting. There has been considerable speculation on the possibility that the heavy chains of γ-globulin actually represent two chains under independent genetic control[8]. Some evidence regarding this point has been obtained from the present investigations. Gm(z) located on the Fd fragment seems to be controlled by the same gene as Gm(a) on the Fc fragment. The exact position of Gm(z) on the Fd fragment remains to be determined and the possibility is not ruled out that a separate unit could still exist in another portion of the fragment.

This investigation was supported by the U.S. Public Health Service. We thank Dr. L. Mårtensson for the Japanese sera and the Chinese myeloma protein.

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* The suggested notation of the W.H.O. for Gm(a) is (1); for Gm(f), (4); for Gm(z), (17).

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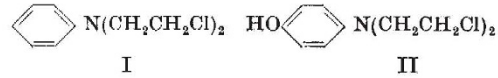
PATHOLOGY

Cure of Mice bearing Advanced Plasma Cell Tumours with Aniline Mustard: the Relationship between Glucuronidase Activity and Tumour Sensitivity

THE unique action of aniline mustard (I) and closely related analogues in curing mice bearing advanced plasma cell tumours (up to 8 g in weight) was recently described[1]. From an investigation of a series of derivatives related to aniline mustard it was postulated that this compound was hydroxylated in the liver to form the highly toxic *p*-hydroxyaniline mustard (II), and then detoxified by conversion to the glucuronide or sulphate. A high glucuronidase or sulphatase activity of the tumour would result in the selective release in the tumour of the toxic *p*-hydroxy derivative:



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