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Multiple Myeloma

Xenobiotic gene polymorphisms and susceptibility to multiple myeloma

Genetic variations in the activity of xenobiotic enzymes may predict susceptibility to multiple myeloma (MM). In a case-control study, 90 Australian Caucasians with MM had significantly higher incidences of GST T1 null, PON1 BB and NAT2 slow acetylation genotypes, but no difference in polymorphism frequencies for GST M1, NAT1, and CYP1A1 when compared to 205 controls.

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All higher species have evolved complex enzyme systems for protection against environmental toxins. The human xenobiotic metabolizing system comprises two main classes of enzymes: phase 1 cytochrome P-450 (CYP) enzymes which bioactivate procarcinogens to genotoxic electrophilic intermediates, and phase 2 enzymes, including glutathione S-transferases μ and τ (GST M1 and GST T1), paraoxonase (PON1) and N-acetyltransferases 1 and 2 (NAT1 and NAT2) which conjugate the intermediates to excitable hydrophilic derivatives, completing the detoxification cycle. It is now widely believed that interindividual differences in susceptibility to malignancy may be mediated in part through variability in the xenobiotic enzyme system. In support of this contention, genetic polymorphisms that result in altered or absent activity of these enzymes have been consistently shown to be risk factors for the development of numerous malignancies, including non-Hodgkin's lymphoma (NHL).[1]

Although epidemiological studies have identified exposure to pesticides and solvents (including dioxin, dichlorodiphenyl-trichloroethane (DDT) and benzene)[2-4] as risk factors for developing MM, no one has investigated the role that differential detoxification of these carcinogens may play in the pathogenesis of the disorder. Furthermore, MM incidence rates are strongly correlated with race,[5] providing evidence for a genetic component to disease susceptibility. Therefore, the aim of this study was to determine whether inheritance of particular polymorphisms in the xenobiotic genes GST M1, GST T1, PONI, NAT1, NAT2, and/or CYP 1A1 are associated with increased risk of MM.

We conducted a case-control study using peripheral blood or bone marrow biopsy specimens from 90 Caucasian individuals (63 males and 27 females), aged 41 to 95 years (median age of 67 years), with a confirmed diagnosis of MM according to the United Kingdom Medical Research Council (MRC UK) definition. All patients were recruited from the Newcastle Mater Misericordiae Hospital, Newcastle, NSW and the Alfred Hospital, Melbourne, VIC, in Australia. The majority of samples were obtained at the time of diagnosis (n=61) or within the first (n=15) or second year (n=9) following diagnosis. The control group consisted of 205 healthy Caucasian volunteer bone marrow donors aged 18 to 65 years. The research protocol was approved by the Hunter Area Research Ethics Committee and informed consent was

Table 1. Comparison of GST T1, GST M1, PON1, NAT1, NAT2, and CYP1A1 polymorphism frequencies in cases and controls (univariate analysis).

Polymorphism		*MM patients n = 90*		*Controls n = 205*		*Odds ratio*	*95% confidence interval*	*p value*
		n[a]	*(%)*	*n*[a]	*(%)*			
GST T1	pos	68	(76)	176	(86)	1.00		
	null	22	(24)	29	(14)	1.96	1.06-3.65	0.04
GST M1	pos	45	(50)	95	(46)	1.00		
	null	45	(50)	110	(54)	0.86	0.53-1.42	0.6
PON1[b]	AA	33	(37)	103	(52)	1.00		
	AB	41	(45)	74	(37)	1.73	0.97-3.10	0.05
	BB	16	(18)	22	(11)	2.27	1.06-4.76	0.04
NAT1[c]	rapid	32	(43)	83	(42)	1.00		
	slow	43	(57)	115	(58)	0.97	0.56-1.67	0.9
NAT2[d]	rapid	31	(34)	98	(50)	1.00		
	slow	59	(66)	98	(50)	1.89	1.14-3.26	0.01
CYP1A1	-/-	69	(78)	159	(82)	1.00		
	-/+, +/+	20	(22)	34	(18)	1.36	0.71-2.50	0.3

[a]Totals vary due to incomplete genotyping data for some individuals. [b]AB vs AA and BB vs AA. [c]NatI rapid acetylators consist of genotypes: 4/10,10/10, 10/11, whilst genotypes 4/4 and 4/11 are considered slow. Odds ratio for slow vs rapid. [d]NAT2 rapid acetylators consist of all genotypes containing allele 1 (ie.,1/1, 1/2, 1/3, 1/4), whereas any other combination of the four alleles produces a slow acetylation phenotype. Odds ratio for slow vs rapid.

Table 2. Adjusted odds ratios (multivariate analysis).

polymorphism		*MM patients n = 90*		*Controls n = 205*		*Odds ratio*	*95% confidence interval*	*p value*
		n[a]	*(%)*	*n*[a]	*(%)*			
GST T1	pos	68	(76)	176	(86)	1.00		
	null	22	(24)	29	(14)	2.47	1.26-4.80	0.008
PON1	AA	33	(37)	103	(52)	1.00		
	BB	16	(18)	22	(11)	2.66	1.20-5.88	0.02
NAT2[b]	rapid	31	(34)	98	(50)	1.00		
	slow	59	(66)	98	(50)	1.93	1.13-3.30	0.02

[a]Totals vary due to incomplete genotyping data for some individuals. [b]NAT2 rapid acetylators consist of all genotypes containing allele 1 (ie.,1/1, 1/2, 1/3, 1/4), whereas any other combination of the four alleles produces a slow acetylation phenotype. Odds ratio for slow vs rapid.

given by all living participants. All genotyping was performed as previously described.[1] Frequencies were compared by Fisher's exact tests (two-tailed) and unconditional multivariate logistic regression incorporating all studied genotypes as co-variables. All statistical analyses were performed using SPSS version 9.0 (SPSS Inc., Chicago, IL, USA).

We found a significant increase in incidences of the GST T1 null, PON1 BB and NAT2 slow acetylation genotypes in MM cases compared with controls (24% vs. 14%, p= 0.04; 18% vs 11%, p=0.04; and 66% vs 50%, p=0.01), each conferring an approximate two-fold increased risk of disease (Table 1). In contrast, the incidences of polymorphisms for GST M1, NAT1 and CYP1A1 did not differ significantly between MM patients and controls. Multivariate analysis (Table 2) revealed that GST T1 null was the most significant risk factor for MM (p=0.008, adjusted OR=2.47, 95% CI, 1.26-4.80), followed by PON1 BB (p=0.02, adjusted OR=2.66; 95% CI, 1.20-5.88) and NAT2 slow acetylation genotypes (p=0.02, adjusted OR=1.93; 95% CI, 1.13-3.30). We found no significant difference between cases and controls when the combined prevalence of any of these three genotypes was assessed together (*data not shown*).

The GST T1 enzyme has been identified as essential for benzene biotransformation[6] and the higher incidence of GST T1 null genotypes among MM sufferers provides biological plausibility to a long suspected association between benzene exposure and development of MM.[7] African Americans are known to have an increased frequency of GST T1 null genotypes compared to Caucasian Americans,[8] and this may at least in part explain why this racial group has double the incidence of MM.[5] However, Asians also have a high population frequency of GST T1 null, and yet generally have much lower rates of MM than do Western societies.[5, 9] Clearly, there are other factors that contribute to the pathogenesis of this disease.

The present study supports the notion that environmental exposure to particular chemicals may contribute to the development of MM, and further suggests that risk of disease may be dependent on inherited polymorphisms in genes responsible for metabolizing these substances. We have previously identified polymorphisms in GST T1 and PON1, but not NAT2, as being associated with increased risk of NHL.[1] The addition of NAT2 as a risk factor for MM highlights the existence of both similarities and differences in the modes of carcinogenesis for these hematologic diseases.

Lisa F. Lincz, Ian Kerridge,* Fiona E. Scorgie* Michael Bailey,° Arno Enno,*# Andrew Spencer@*

**Hunter Hematology Research Group, Newcastle Mater Misericordiae Hospital, Edith Street, Waratah; °Department of Epidemiology & Preventive Medicine, Monash University Inner and Eastern Clinical School, VIC; #Hunter Area Pathology Services, NSW Australia; @Myeloma Research Group, Department of Clinical Hematology and Bone Marrow Transplantation and Department of Medicine, Monash University, Monash University Medical School, The Alfred Hospital, VIC, Australia*

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Key words: multiple myeloma, xenobiotic gene polymorphisms, genetic predisposition to disease, GST T1, PON1, NAT2.

Correspondence: Dr. Lisa Lincz, PhD, Senior Hospital Scientist, Hunter Hematology Research Group, Newcastle Mater Misericordiae Hospital, Locked Bag 7, Hunter Region Mail Centre, Newcastle NSW 2310, Australia, Phone: international +61.2. 49211844. Fax: international +61.2.49602136. E-mail: leukres@hunterlink.net.au

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