ASSOCIATION OF GENETIC POLYMORPHISMS OF MATRIX METALLOPROTEINASES WITH NEW-ONSET DIABETES AFTER TRANSPLANTATION IN RENAL TRANSPLANTATION

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Abstract

Background. New-Onset Diabetes After Transplantation (NODAT) is a serious metabolic complication that may follow renal transplantation. Excess fat deposition requires space, created by adipocyte (hypertrophy and hyperplasia) and extracellular matrix (ECM) remodelling. This process is regulated by several factors, including several adipocyte-derived Matrix metalloproteinases (MMPs) and the adipokine cathepsin, which degrades fibronectin, a key ECM protein. Excess fat, also deposited in visceral organs, generates chronic low-grade inflammation that eventually triggers insulin resistance and the associated diabetes mellitus. Therefore, we examined the association between NODAT and 11 single nucleotide polymorphisms (SNPs) located within the 3 genes of Matrix metalloproteinases (MMPs) which might be related with NODAT.

Methods. A total of 309 renal transplants recipients were included without a history of diabetes. We analyzed the association between NODAT development and a panel of 11 SNPs within 3 genes (MMP1, MMP2, MMP3) of MMPs.

Result (I)

Table 1 Sequences of primers and expected product size.

SNP Locus		Sequence (5′-3′)	Product size (bp)
rs17859821 Promoter	Forward	GTTCCCCATCACAGCTTATCTC	400
	Reverse	TAGAGGTCACAAAGACCCCACT	
rs1132896 Exon_5	Forward	TTCTCTCCTGTCCTCTCTCCAC	352
	Reverse	GTGGAAAGTCTTGGGGACTAGA	
rs1053605 Exon_5	Forward	ATTTGCTTGGACCAGAGAGGT	327
	Reverse	GTGGAAAGTCTTGGGGACTAGA	
rs243849	Forward	ACTGTTGGTGGGAACTCAGAAG	360
Exon_7	Reverse	CAGGATCTAAGCAGGGACCTT	

Table 2 Comparison of clinical characteristics between PTDM and non-PTDM subjects.

	PTDM (n=56)	Non-PTDM (n=255)	p-value
Age (years)	45.11±9.90	38.26±11.17	**<0.001**
Sex (male; female)	30:26	155:100	0.31
Body mass Index (kg/m^2)	22.56±3.32	22.46±3.45	0.85
HLA mismatches (n)	1.02±0.62	1.18±0.66	0.13
Hepatitis C infection (n)	0	6	0.22
Acute rejection (n)	15	43	0.08
Tacrolimus usage (n)	25	77	**0.04**

Result (II)

Table 3 Allele frequencies of four SNPs of *MMP2* gene in PTDM and non-PTDM subjects.

SNP Locus	Allele	PTDM Freq (%)	Non-PTDM Freq (%)	OR (95% CI)	p-value
rs17859821 Promoter	G	85 (80)	370 (72)	0.63 (0.37-1.05)	0.075
	A	21 (20)	146 (28)		
rs1132896 Exon_5	G	82 (76)	418 (81)	1.38 (1.15-2.63)	0.201
	C	26 (24)	96 (19)		
rs1053605 Exon_5	C	90 (83)	450 (87)	1.36 (0.77-2.41)	0.284
	T	18 (17)	66 (13)		
rs243849	C	101 (94)	427 (83)	0.34 (0.15-0.76)	**0.008**
Exon_7	T	7 (6)	87 (17)		

Result (III)

Table 4 Logistic regression analysis of the *MMP2* polymorphisms in PTDM and non-PTDM subjects.

SNP Locus	Genotype	PTDM Freq (%)	Non-PTDM Freq (%)	Codominant OR (95%CI)	p-Value	Dominant OR (95%CI)	p-Value	Recessive OR (95%CI)	p-Value
rs17859821 Promoter	G/G	34 (64.2)	134 (51.9)	0.62 (0.32-1.19)	0.15	0.57 (0.30-1.07)	0.07	0.42 (0.09-1.88)	0.21
	A/G	17 (32.1)	102 (39.5)						
	A/A	2 (3.8)	22 (8.5)						
rs1132896 Exon_5	G/G	34 (63)	169 (65.8)	3.56 (1.10-11.46)	0.11	1.19 (0.64-2.24)	0.58	3.63 (1.15-11.49)	**0.04**
	G/C	14 (25.9)	80 (31.1)						
	C/C	6 (11.1)	8 (3.1)						
rs1053605 Exon_5	C/C	37 (68.5)	196 (76)	1.58 (0.80-3.12)	0.42	1.57 (0.81-3.04)	0.19	1.22 (0.13-11.51)	0.86
	T/C	16 (29.6)	58 (22.5)						
	T/T	1 (1.8)	4 (1.6)						
rs243849 Exon_7	C/C	47 (87)	177 (68.9)	0.30 (0.13-0.72)	**0.002**	0.28 (0.12-0.65)	**0.001**	0.00 (0.00-NA)	0.09
	T/C	7 (13)	73 (28.4)						
	T/T	0 (0)	7 (2.7)						

conclusion

The data suggest that excess fat deposition and ECM remodelling might play a role in the pathogenesis of NODAT in renal transplantation recipients. In particular, significant variations of MMP2 might confer susceptibility to NODAT in patients who receive renal transplants.

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