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Proinflammatory cytokine IFN-γ, lncRNA BANCR and the occurrence of coronary artery disease

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ABSTRACT

Aims: Coronary artery disease (CAD) ranks the leading cause of death globally. Interferon-γ (IFN-γ) gene, along with long noncoding RNA (lncRNA) BRAF-activated noncoding RNA (BANCR), could coordinately function in the occurrence of CAD. We hypothesized that level of IFN-γ, genetic variants of IFN-γ and BANCR gene should be associated with the occurrence of CAD.

Materials and Methods: A case-control study was conducted in Chinese population.

Key findings: We found that serum level of IFN-γ in CAD cases was significantly higher than that in controls ($P < 0.001$). Compared with the first quartile, all of the second (OR: 1.87; 95% CIs: 1.33–2.62), the third (OR: 1.79; 95% CIs: 1.30–2.45), and the fourth (OR: 3.98; 95% CIs: 2.59–6.12) quartiles of serum level of IFN-γ were associated with increased risk of CAD ($P < 0.05$). We found IFN-γ gene (rs2069705 and rs2430561), and 2 variants in lncRNA BANCR (rs6559446 and rs79823312) could increase CAD susceptibility in allelic and dominant model, while IFN-γ rs2069705 and rs2430561, BANCR rs79823312 were also associated with CAD risk in additive model. IFN-γ rs2069705 and rs2430561 were associated with higher level of serum IFN-γ in CAD patients ($P < 0.001$).

Significance: This study confirmed the crucial role of IFN-γ and lncRNA BANCR in the occurrence of CAD, and might serve as the biomarkers of CAD screening and prevention.

1. Introduction

Coronary artery disease (CAD), also known as ischemic heart disease (IHD) and coronary heart disease (CHD), ranks the leading cause of death globally [1–4]. According to the report of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, there were 8930.4 thousand all-age deaths worldwide [1]. Atherosclerosis, a chronic inflammatory lesion with infiltration of mononuclear leukocytes, the proliferation of vascular smooth muscle cells (VSMCs) and the accumulation of extracellular matrix, is the pathological basis of CAD [5–7]. Imbalanced lipid metabolism and accumulation of atherosclerotic plaques could result in the narrowing of the vascular lumen and blocking the blood flow and cardiac ischemia [8,9]. Inflammatory biomarkers play an important role in the initiation and development of atherosclerosis [10–12]. The exploring of inflammatory biomarkers and related genes could help us deep understanding of the mechanism of atherosclerosis, and screening effective biomarkers for CAD.

Proinflammatory cytokine interferon-γ (IFN-γ), a dimerized soluble cytokine which is the only member of the type II class of interferons and a master regulator of atherosclerosis process, plays crucial role in the pathogenesis of CAD [13–17]. It could induce arteriosclerotic changes in the absence of detectable immunocytes by acting on VSMCs to potentiate growth-factor-induced mitogenesis [7]. Long noncoding RNA (lncRNA) BRAF-activated noncoding RNA (BANCR), a 693-bp lncRNA first identified in melanoma cells, was found facilitating VSMC proliferation and migration through JNK pathway [18,19]. Meanwhile, IFN-γ could increase the expression of the lncRNA BANCR, and the increase could be suppressed by blocking STAT1 phosphorylation using JAK inhibitor 1 [20]. The reports above confirmed that IFN-γ and lncRNA BANCR could coordinately function in the occurrence of CAD.

Considering the crucial of IFN-γ and lncRNA BANCR in the atherosclerosis process and the occurrence of CAD, we hypothesized that serum level of IFN-γ, as well as genetic variants of IFN-γ and BANCR gene should be associated with the susceptibility of CAD. Hereby, we conducted a case-control study in a Chinese population to address this issue.

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2. Patients and methods

2.1. Study subjects

The CAD patients were subjects with the symptoms of typical or atypical chest discomfort, and admitted to our cardiology unit and underwent coronary angiography. The diagnostic criterion of CAD was the patients having at least one severe stenosis (> 50%) in a major coronary artery. In current study, we only included subjects with stable angina, and unstable angina as CAD cases. Patients with acute infectious disease, auto immune disorders, inflammatory disease, and cancers were excluded. Controls were recruited from the same population as the cases and had no personal or sibling history of CAD, cancers, auto immune disorders, and were frequency-matched by age and gender. Finally, 890 CAD cases and 900 controls were included in this study. 5 ml fasting blood was collected in EDTA anti-coagulated tubes and centrifuged immediately. The serum was prepared for IFN-γ assay. The Ethical Committee of the Second Hospital of Dalian Medical University approved this research project and written informed consent was obtained. All clinical investigations have been conducted according to the principles described in the Declaration of Helsinki.

2.2. DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Nine tagSNPs (IFN-γ rs2069705, IFN-γ rs2430561, IFN-γ rs1861493, BANCR rs6559446, BANCR rs117180354, BANCR rs79823312, BANCR rs11138012, BANCR rs28800827, BANCR rs10122850) covering the IFN-γ and BANCR gene region were selected using the Haploview 4.2 software basing on1000 genome CHB data (phase 3, minor allele frequency ≥5%, pairwise $r^2 \geq 0.8$). Genotyping was conducted by TaqMan assays (Applied Biosystems [ABI], Foster City, CA) according to the manufacturer's instructions. A randomly selected set of 10% samples was tested in duplicate by different persons, and the concordance rate was 100%.

2.3. IFN-γ assay

Serum level of IFN-γ in CAD patients and controls was measured using the ELISA detection kit (eBioscience, San Diego, CA, USA) following the manufacturer's instructions. Absorbance at 450 nm was measured using microplate reader and concentrations of cytokines were calculated using a linear regression formula.

2.4. Statistical analysis

Demographic variables between the two groups were assessed by chi-square test. Nonnormally distributed continuous variables were presented as median (25th–75th percentile), and Mann–Whitney *U* test were used for comparison. Normally distributed continuous variables were presented as mean ± SD, and independent sample *t*-test were used for comparison. The departures from Hardy–Weinberg Equilibrium for the candidate SNPs in controls were evaluated using goodness-of-fit χ^2 test. The adjusted ORs by age, gender, smoking status, drinking status, and diabetes, 95% CIs, and the corresponding P value for each SNP were calculated using logistic regression analysis. Due to the mean for cases and controls were about 60, thus we stratify patients with 60 years threshold. IFN-γ was also considered as an ordinal variable using quartiles of IFN-γ distribution in control subjects. All calculations were performed using SAS software version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-sided, and significant threshold was set P < 0.05.

Table 1
Clinical demographic characteristics of CAD cases and controls.

Variables	Cases (n = 890)	Controls (n = 900)	P value[a]
Age			
Range	42–77	41–79	
Mean ± sd	59.9 ± 9.99	59.6 ± 10.99	0.546
≥60	408 (45.8%)	420 (46.7%)	0.727
< 60	482 (54.2%)	480 (53.3%)	
Gender			
Male	596 (70.0%)	653 (72.6%)	0.445
Female	294 (30.0%)	347 (27.4%)	
Smoking status			
Smokers	275 (30.9%)	227 (25.2%)	**0.008**
Non-smokers	615 (69.1%)	673 (74.8%)	
Alcohol status			
Drinkers	214 (24.0%)	179 (19.9%)	**0.034**
Non-drinkers	676 (76.0%)	721 (80.1%)	
Diabetes			
Yes	260 (29.2%)	139 (15.4%)	< **0.001**
No	630 (70.8%)	761 (84.6%)	
Hypertension			
Yes	407 (45.7%)	315 (35.0%)	< **0.001**
No	483 (54.3%)	585 (65.0%)	
Heart failure			
Yes	37 (4.6%)	15 (1.7%)	**0.002**
No	853 (95.4%)	885 (98.3%)	
Medications			
Statin	463 (52.0%)	146 (16.2%)	< **0.001**
Aspirin	625 (70.2%)	132 (14.7%)	< **0.001**
IFN-γ (pg/mL)	2.28 (1.75–2.84)	1.90 (1.40–2.34)	< **0.001**

P value in bold means statistically significant.

[a] Demographic variables between the two groups were assessed by chi-square test. Nonnormally distributed continuous variables were presented as median (25th–75th percentile), and Mann–Whitney *U* test were used for comparison. Normally distributed continuous variables were presented as mean ± SD, and independent sample *t*-test were used for comparison.

3. Results

3.1. Characteristics of study subjects

Table 1 presents the clinical demographic characteristics of CAD cases and controls. There is no significant difference for the distribution of age and gender, which means the effectiveness of frequency-matching of controls. The cases are more likely to be smokers, alcohol drinkers, patients of diabetes, hypertension, and heart failure, compared with the controls (P < 0.05).

3.2. Association of serum level of IFN-γ with CAD risk

As shown in Table 1, the distribution of serum level of IFN-γ in CAD cases and controls was significantly different (P < 0.001). When analyzed as an ordinal variable using quartiles of IFN-γ distribution in control subjects, we found quartiles of IFN-γ were significantly associated with increased risk of CAD (Table 2, P < 0.001). Compared with the first quartile, all of the second (OR: 1.87; 95% CIs: 1.33–2.62), the third (OR: 1.79; 95% CIs: 1.30–2.45), and the fourth (OR: 3.98; 95% CIs: 2.59–6.12) quartiles were associated with increased risk of CAD,

Table 2
Distribution of quartiles of IFN-γ in cases and controls.

IFN-γ (pg/mL)	Cases	Controls	OR (95% CIs)[a]	P for trend
Quartile 1 (≤1.40)	92	225	Reference	< 0.001
Quartile 2 (1.40–1.90)	194	225	1.87 (1.33–2.62)	
Quartile 3 (1.90–2.34)	181	225	1.79 (1.30–2.45)	
Quartile 4 (> 2.34)	423	225	3.98 (2.59–6.12)	

[a] Adjusted for age, gender, smoking status, drinking status, Hypertension, Heart failure, diabetes and medications.

Table 3
Associations between candidate genetic variations and risk of CAD.

	CAD cases	Controls	OR (95% CIs)[a]	P value
IFN-γ rs2069705				
Additive model				
GG	493	549	1.00 (Reference)	
AG	334	306	1.26 (1.01–1.58)	0.042
AA	63	45	1.62 (1.07–2.45)	0.022
A vs G			1.28 (1.08–1.53)	0.005
Dominant model				
GG	493	549	1.00 (Reference)	
AG + AA	397	351	1.31 (1.06–1.62)	0.012
IFN-γ rs2430561				
Additive model				
AA	638	696	1.00 (Reference)	
AT	233	195	1.36 (1.07–1.72)	0.013
TT	19	9	2.40 (1.10–5.21)	0.028
T vs A			1.39 (1.13–1.71)	0.002
Dominant model				
AA	638	696	1.00 (Reference)	
AT + TT	252	204	1.4 (1.11–1.76)	0.004
IFN-γ rs1861493				
Additive model				
AA	379	393	1.00 (Reference)	
AG	389	387	1.08 (0.75–1.57)	0.669
GG	122	120	1.10 (0.68–1.77)	0.707
G vs A			1.07 (0.8–1.44)	0.632
Dominant model				
AA	379	393	1.00 (Reference)	
AG + GG	511	507	1.09 (0.78–1.52)	0.628
BANCR rs6559446				
Additive model				
AA	583	630	1.00 (Reference)	
AG	269	243	1.24 (0.98–1.58)	0.075
GG	38	27	1.58 (0.94–2.67)	0.087
G vs A			1.27 (1.04–1.54)	0.018
Dominant model				
AA	583	630	1.00 (Reference)	
AG + GG	307	270	1.28 (1.02–1.6)	0.033
BANCR rs117180354				
Additive model				
GG	805	818	1.00 (Reference)	
AG	83	81	1.08 (0.59–1.98)	0.796
AA	2	1	2.11 (0.2–22.56)	0.536
A vs G			1.11 (0.68–1.79)	0.683
Dominant model				
GG	805	818	1.00 (Reference)	
AG + AA	85	82	1.1 (0.64–1.87)	0.737
BANCR rs79823312				
Additive model				
AA	674	717	1.00 (Reference)	
AG	199	175	1.26 (0.97–1.64)	0.087
GG	17	8	2.35 (1.03–5.36)	0.042
G vs A			1.32 (1.05–1.65)	0.016
Dominant model				
AA	674	717	1.00 (Reference)	
AG + GG	216	183	1.31 (1.02–1.68)	0.036
BANCR rs11138012				
Additive model				
AA	308	327	1.00 (Reference)	
AG	445	449	1.09 (0.78–1.54)	0.607
GG	137	124	1.22 (0.87–1.72)	0.255
G vs A			1.12 (0.91–1.36)	0.284
Dominant model				
AA	308	327	1.00 (Reference)	
AG + GG	582	573	1.12 (0.85–1.48)	0.423
BANCR rs28800827				
Additive model				
GG	353	350	1.00 (Reference)	
AG	435	441	1.02 (0.88–1.18)	0.818
AA	102	109	0.96 (0.84–1.11)	0.617
A vs G			1.01 (0.97–1.04)	0.642
Dominant model				
GG	353	350	1.00 (Reference)	
AG + AA	537	550	1.01 (0.97–1.05)	0.725
BANCR rs10122850				
Additive model				
AA	797	809	1.00 (Reference)	
AT	98	98	1.06 (0.38–2.94)	0.918
TT	5	3	1.76 (0.41–7.53)	0.446
T vs A			1.10 (0.69–1.74)	0.701
Dominant model				
AA	797	809	1.00 (Reference)	
AT + TT	103	101	1.08 (0.59–1.95)	0.807

[a] Adjusted for age, gender, smoking status, drinking status, and diabetes.

when adjusted for age, gender, smoking status, drinking status, Hypertension, Heart failure, diabetes and medications (Table 2).

3.3. Genetic associations of candidate SNPs with CAD risk

As shown in Table 3, all nine tagSNPs analyzed (IFN-γ rs2069705, IFN-γ rs2430561, IFN-γ rs1861493, BANCR rs6559446, BANCR rs117180354, BANCR rs79823312, BANCR rs11138012, BANCR rs28800827, BANCR rs10122850) were in Hardy-Weinberg equilibrium in healthy controls, which indicated that the sampled subjects were representative of the population without any deviation of genotype frequencies ($P > 0.05$). Among them, IFN-γ rs2069705 (OR: 1.28; 95% CIs: 1.08–1.53; P value: 0.005), IFN-γ rs2430561 (OR: 1.39; 95% CIs: 1.13–1.71; P value: 0.002), BANCR rs6559446 (OR: 1.27; 95% CIs: 1.04–1.54; P value: 0.018), and BANCR rs79823312 (OR: 1.32; 95% CIs: 1.05–1.65; P value: 0.016) were significantly associated with increased risk of CAD in allelic model. IFN-γ rs2069705 (AG vs GG: OR = 1.26; 95% CIs = 1.01–1.58; P value = 0.042; AA vs GG: OR = 1.62; 95% CIs = 1.07–2.45; P value = 0.022), IFN-γ rs2430561 (AT vs AA: OR = 1.36; 95% CIs = 1.07–1.72; P value = 0.013; TT vs AA: OR = 2.40; 95% CIs = 1.10–5.21; P value = 0.028), and BANCR rs79823312 (GG vs AA: OR = 2.35; 95% CIs = 1.03–5.36; P value = 0.042) were also associated with CAD risk in additive model. Besides, IFN-γ rs2069705 (OR: 1.31; 95% CIs: 1.06–1.62; P value: 0.012), IFN-γ rs2430561 (OR: 1.40; 95% CIs: 1.11–1.76; P value: 0.004), BANCR rs6559446 (OR: 1.28; 95% CIs: 1.02–1.60; P value: 0.033), and BANCR rs79823312 (OR: 1.31; 95% CIs: 1.02–1.68; P value: 0.036) were significantly associated with increased risk of CAD in dominant model.

3.4. IFN-γ (pg/mL) level in CAD patients with different genotypes of IFN-γ rs2069705 and IFN-γ rs2430561

As shown in Fig. 1, we also compared the difference of serum level of IFN-γ with different genotypes of IFN-γ rs2069705 and IFN-γ rs2430561 in CAD cases. Compared with carriers of homozygotes of major alleles, those of homozygotes of minor alleles and heterozygotes had significantly higher level of serum IFN-γ ($P < 0.001$). We also performed multiple linear regression analysis adjusted for age, gender, smoking status, drinking status, hypertension, heart failure, diabetes and medications, which found minor alleles of IFN-γ rs2069705 and rs2430561 were still significantly associated with higher serum level of IFN-γ ($P < 0.001$).

4. Discussion

CAD is a common and multifactorial disease causing a high incidence of disability and mortality [1,21]. The current study explored associations between serum level of IFN-γ, as well as genetic variants of IFN-γ and BANCR gene and the occurrence of CAD using a case-control study in a Chinese population. Serum level of IFN-γ was significantly

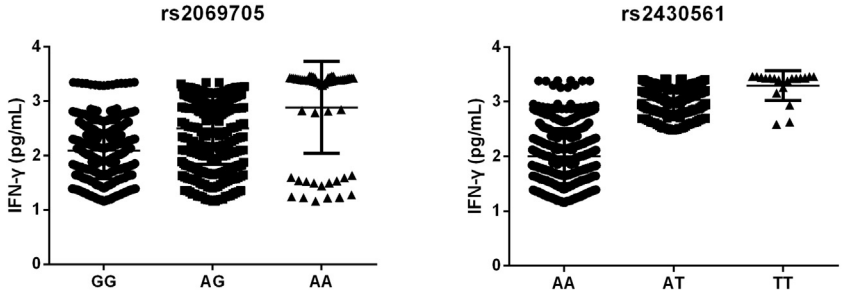

Fig. 1. IFN-γ (pg/mL) level in CAD patients with different genotypes.

associated with increased risk of CAD. Meanwhile, we found IFN-γ gene (rs2069705 and rs2430561), and 2 variants in lncRNA BANCR (rs6559446 and rs79823312) could increase CAD susceptibility in allelic and dominant model, while IFN-γ rs2069705 and rs2430561, BANCR rs79823312 were also associated with CAD risk in additive model. We also identified that carriers of homozygotes of minor alleles and heterozygotes of IFN-γ rs2069705 and rs2430561 had higher level of serum IFN-γ in CAD patients, compared with carriers of homozygotes of major alleles. These findings above further confirmed the crucial role of IFN-γ and lncRNA BANCR in the occurrence of CAD.

Proinflammatory IFN-γ, the main activator of monocytes and macrophages, plays a key role in the regulation of Th1/Th2 ratio in the immune response [22–24]. It has been linked to many disorders, including Atherosclerosis, Alzheimer's disease, infections, and cancers [15,25–27]. Serum level of IFN-γ, which has been identified to be associated with the risk and severity of CAD, has the potential to become a biomarker for diagnosis and prognosis judgement of CAD [28,29]. In current study, we found not only the continuous form, but also the categorical form of serum level of IFN-γ was associated with the occurrence of CAD in a powered sample size of Chinese population. These findings further supported the essential role of inflammation in the etiology of CAD, and enhanced our understanding of the biology of CAD.

The IFN-γ gene owns four exons and three introns, and is located at chromosome 12q24. Previous studies only evaluated the association between IFN-γ rs2430561 and CAD risk, and got inconsistent results, which may be caused by the underpowered sample size [30–32]. In current study, we found IFN-γ rs2430561 was significantly associated with increased serum level of IFN-γ ($P < 0.001$), as well as risk of CAD (OR: 1.39; 95% CIs: 1.13–1.71; P value: 0.002), compared with the major alleles. Using the QUANTO 1.2.4 software, we found the statistical power to detect such an association was 92.9%. IFN-γ rs2069718, which was in linkage disequilibrium with rs2430561 ($r^2 = 1$), showed significant associations with Kawasaki disease [33]. Besides, we also identified that IFN-γ rs2069705 could increase serum level of IFN-γ and risk of CAD. Consistent with our results, Wang et al. found IFN-γ rs2069705 and IFN-γ rs2430561 were significantly associated with sepsis susceptibility [34]. Leng et al. also reported that IFN-γ rs2069705 was associated with increased risk of systemic lupus erythematosus [35].

Growing evidence suggests that lncRNAs play a major role in the occurrence and progression of many diseases and findings in the past decade have contributed to a major breakthrough in finding CAD related lncRNAs [36,37]. BANCR, a novel oncogenic long non-coding RNA in human cancers, was found to facilitate VSMC proliferation, migration, interacting with IFN-γ gene, and coordinately function in the occurrence of CAD [20,38]. Our results, which showed BANCR rs6559446 and rs79823312 could increase susceptibility of CAD in a Chinese population, further supported the crucial role of lncRNA BANCR in the pathogenesis of CAD.

One limitation for the control screening should be mentioned here. Our controls were recruited from the same population as the cases and had no personal or sibling history of CAD, cancers, auto immune disorders. The controls didn't undergo catheterization due to the compliance issue. Absence of family history of CAD and angina symptoms is not sufficient to exclude CAD but might be a justification not to perform catheterization.

5. Conclusion

Conclusively, this study demonstrates that serum level of IFN-γ, two variants in IFN-γ gene (rs2069705 and rs2430561), and 2 variants in lncRNA BANCR (rs6559446 and rs79823312) could increase CAD susceptibility in different genetic models. We also identified that IFN-γ rs2069705 and rs2430561 were associated with higher level of serum IFN-γ in CAD patients. Further studies with larger sample size and conducted in other independent populations will be needed to validate our conclusion.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Author contributions

Bing Xu, Hongli Wang, Na Zhang, and Guiru Li conceived and designed the research; Hongli Wang, Na Zhang, and Guiru Li performed the experiments; Hongli Wang, Na Zhang, and Guiru Li analyzed the data; Hongli Wang, Na Zhang, and Guiru Li contributed reagents/materials/analysis tools; Bing Xu and Hongli Wang, wrote the paper. All authors read and approved the final manuscript.

References

[1] G.B.D.C.o.D. Collaborators, Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018) 1736–1788.
[2] T.F. Luscher, Prevention: some important steps forward, but many unmet needs in a world with cardiovascular disease as the leading cause of death, Eur. Heart J. 37 (42) (2016) 3179–3181.
[3] K.G. Hastings, P.O. Jose, K.I. Kapphahn, A.T. Frank, B.A. Goldstein, C.A. Thompson, K. Eggleston, M.R. Cullen, L.P. Palaniappan, Leading causes of death among Asian American subgroups (2003 – 2011), PLoS One 10 (4) (2015) e0124341.
[4] K. Mc Namara, H. Alzubaidi, J.K. Jackson, Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integr. Pharm. Res. Pract. 8 (2019) 1–11.
[5] N.V.K. Pothineni, S. Subramany, K. Kuriakose, L.F. Shirazi, F. Romeo, P.K. Shah, J.L. Mehta, Infections, atherosclerosis, and coronary heart disease, Eur. Heart J. 38 (43) (2017) 3195–3201.
[6] A.V. Khera, S. Kathiresan, Is coronary atherosclerosis one disease or many? Setting

realistic expectations for precision medicine, Circulation 135 (11) (2017) 1005–1007.
[7] G. Tellides, D.A. Tereb, N.C. Kirkiles-Smith, R.W. Kim, J.H. Wilson, J.S. Schechner, M.I. Lorber, J.S. Pober, Interferon-gamma elicits arteriosclerosis in the absence of leukocytes, Nature 403 (6766) (2000) 207–211.
[8] M. Marzilli, C.N. Merz, W.E. Boden, R.O. Bonow, P.G. Capozza, W.M. Chilian, A.N. DeMaria, G. Guarini, A. Huqi, D. Morrone, M.R. Patel, W.S. Weintraub, Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link!, J. Am. Coll. Cardiol. 60 (11) (2012) 951–956.
[9] C. Weber, H. Noels, Atherosclerosis: current pathogenesis and therapeutic options, Nat. Med. 17 (11) (2011) 1410–1422.
[10] K. Liang, S.R. Dong, H. Peng, Serum levels and clinical significance of IFN-gamma and IL-10 in patients with coronary heart disease, Eur. Rev. Med. Pharmacol. Sci. 20 (7) (2016) 1339–1343.
[11] P.M. Ridker, Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin, Eur. Heart J. 37 (22) (2016) 1720–1722.
[12] E. Casiglia, V. Tikhonoff, Inflammatory and coagulative markers of atherosclerosis, Eur. Heart J. 28 (3) (2007) 271–273.
[13] P.W. Gray, D.V. Goeddel, Structure of the human immune interferon gene, Nature 298 (5877) (1982) 859–863.
[14] P.J. Kusters, E. Lutgens, Cytokines and immune responses in murine atherosclerosis, Methods Mol. Biol. 1339 (2015) 17–40.
[15] N.N. Mehta, H.L. Teague, W.R. Swindell, Y. Baumer, N.L. Ward, X. Xing, B. Baugous, A. Johnston, A.A. Joshi, J. Silverman, D.H. Barnes, L. Wolterink, R.P. Nair, P.E. Stuart, M. Playford, J.J. Voorhees, M.K. Sarkar, J.T. Elder, K. Gallagher, S.K. Ganesh, J.E. Gudjonsson, IFN-gamma and TNF-alpha synergism may provide a link between psoriasis and inflammatory atherogenesis, Sci. Rep. 7 (1) (2017) 13831.
[16] I. Voloshyna, M.J. Littlefield, A.B. Reiss, Atherosclerosis and interferon-gamma: new insights and therapeutic targets, Trends Cardiovasc. Med. 24 (1) (2014) 45–51.
[17] J.E. McLaren, D.P. Ramji, Interferon gamma: a master regulator of atherosclerosis, Cytokine Growth Factor Rev. 20 (2) (2009) 125–135.
[18] N. McCarthy, Epigenetics. Going places with BANCR, Nat. Rev. Cancer 12 (7) (2012) 451.
[19] H. Li, X. Liu, L. Zhang, X. Li, LncRNA BANCR facilitates vascular smooth muscle cell proliferation and migration through JNK pathway, Oncotarget 8 (70) (2017) 114568–114575.
[20] R.K. Kutty, W. Samuel, T. Duncan, O. Postnikova, C. Jaworski, C.N. Nagineni, T.M. Redmond, Proinflammatory cytokine interferon-gamma increases the expression of BANCR, a long non-coding RNA, in retinal pigment epithelial cells, Cytokine 104 (2018) 147–150.
[21] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, S.D. de Ferranti, J. Floyd, M. Fornage, C. Gillespie, C.R. Isasi, M.C. Jimenez, L.C. Jordan, S.E. Judd, D. Lackland, J.H. Lichtman, L. Lisabeth, S. Liu, C.T. Longenecker, R.H. Mackey, K. Matsushita, D. Mozaffarian, M.E. Mussolino, K. Nasir, R.W. Neumar, L. Palaniappan, D.K. Pandey, R.R. Thiagarajan, M.J. Reeves, M. Ritchey, C.J. Rodriguez, G.A. Roth, W.D. Rosamond, C. Sasson, A. Towfighi, C.W. Tsao, M.B. Turner, S.S. Virani, J.H. Voeks, J.Z. Willey, J.T. Wilkins, J.H. Wu, H.M. Alger, S.S. Wong, P. Muntner, Heart disease and stroke statistics-2017 update: a report from the American Heart Association, Circulation 135 (10) (2017) e146–e603.
[22] P. Libby, Inflammation in atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 32 (9) (2012) 2045–2051.
[23] C.M. Blouin, Y. Hamon, P. Gonnord, C. Boularan, J. Kagan, C. Viaris de Lesegno, R. Ruez, S. Mailfert, N. Bertaux, D. Loew, C. Wunder, L. Johannes, G. Vogt, F.X. Contreras, D. Marguet, J.L. Casanova, C. Gales, H.T. He, C. Lamaze, Glycosylation-dependent IFN-gammaR partitioning in lipid and actin nanodomains is critical for JAK activation, Cell 166 (4) (2016) 920–934.
[24] K. Schroder, P.J. Hertzog, T. Ravasi, D.A. Hume, Interferon-gamma: an overview of signals, mechanisms and functions, J. Leukoc. Biol. 75 (2) (2004) 163–189.
[25] G. Kak, M. Raza, B.K. Tiwari, Interferon-gamma (IFN-gamma): exploring its implications in infectious diseases, Biomol. Concepts 9 (1) (2018) 64–79.
[26] M. Mojic, K. Takeda, Y. Hayakawa, The dark side of IFN-gamma: its role in promoting cancer immunoevasion, Int. J. Mol. Sci. 19 (1) (2017).
[27] C. Zheng, X.W. Zhou, J.Z. Wang, The dual roles of cytokines in Alzheimer's disease: update on interleukins, TNF-alpha, TGF-beta and IFN-gamma, Transl. Neurodegener. 5 (2016) 7.
[28] R. Clarke, E. Valdes-Marquez, M. Hill, J. Gordon, M. Farrall, A. Hamsten, H. Watkins, J.C. Hopewell, Plasma cytokines and risk of coronary heart disease in the PROCARDIS study, Open Heart 5 (1) (2018) e000807.
[29] X. Min, M. Lu, S. Tu, X. Wang, C. Zhou, S. Wang, S. Pang, J. Qian, Y. Ge, Y. Guo, D. Xu, K. Cao, Serum cytokine profile in relation to the severity of coronary artery disease, Biomed. Res. Int. 2017 (2017) 4013685.
[30] S. Mastana, S. Prakash, E.C. Akam, M. Kirby, M.R. Lindley, N. Sinha, S. Agrawal, Genetic association of pro-inflammatory cytokine gene polymorphisms with coronary artery disease (CAD) in a North Indian population, Gene 628 (2017) 301–307.
[31] P.R. Garg, K.N. Saraswathy, A.K. Kalla, E. Sinha, P.K. Ghosh, Pro-inflammatory cytokine gene polymorphisms and threat for coronary heart disease in a North Indian Agrawal population, Gene 514 (1) (2013) 69–74.
[32] B.M. Babu, B.P. Reddy, V.H. Priya, A. Munshi, H.S. Rani, G.S. Latha, V.D. Rao, A. Jyothy, Cytokine gene polymorphisms in the susceptibility to acute coronary syndrome, Genet. Test Mol. Biomark. 16 (5) (2012) 359–365.
[33] Y.H. Huang, Y.W. Hsu, H.F. Lu, H.S. Wong, H.R. Yu, H.C. Kuo, F.C. Huang, W.C. Chang, H.C. Kuo, Interferon-gamma genetic polymorphism and expression in Kawasaki disease, Medicine (Baltimore) 95 (17) (2016) e3501.
[34] D. Wang, X. Zhong, D. Huang, R. Chen, G. Bai, Q. Li, B. Yu, Y. Fan, X. Sun, Functional polymorphisms of interferon-gamma affect pneumonia-induced sepsis, PLoS One 9 (1) (2014) e87049.
[35] R.X. Leng, H.F. Pan, J. Liu, X.K. Yang, C. Zhang, S.S. Tao, D.G. Wang, X.M. Li, X.P. Li, W. Yang, D.Q. Ye, Evidence for genetic association of TBX21 and IFNG with systemic lupus erythematosus in a Chinese Han population, Sci. Rep. 6 (2016) 22081.
[36] Y. Lu, X. Meng, L. Wang, X. Wang, Analysis of long non-coding RNA expression profiles identifies functional lncRNAs associated with the progression of acute coronary syndromes, Exp. Ther. Med. 15 (2) (2018) 1376–1384.
[37] D. Yu, C. Tang, P. Liu, W. Qian, L. Sheng, Targeting lncRNAs for cardiovascular therapeutics in coronary artery disease, Curr. Pharm. Des. (2018), https://doi.org/10.2174/1381612824666180108120727 (E-pub ahead of print).
[38] Y. Zou, J. Li, Y. Chen, H. Xiao, F. Zhang, D. Yu, K. Luo, BANCR: a novel oncogenic long non-coding RNA in human cancers, Oncotarget 8 (55) (2017) 94997–95004.