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Association between *PTGER4* polymorphisms and inflammatory bowel disease risk in Caucasian

A meta-analysis

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Abstract

Background: The results from previous studies on association between prostaglandin E receptor 4 (PTGER4) polymorphisms and inflammatory bowel disease (IBD) risk in Caucasian were conflict. The present study aimed to investigate the genetic association by conducting a meta-analysis.

Methods: Systematic literature search was conducted through Wiley Online Library, Chinese National Knowledge Infrastructure (CNKI), and PubMed databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to investigate the associations between rs4613763T/C, 17234657T/G polymorphisms, and IBD risk in Caucasian.

Results: Twenty case-control studies consisting of 18,495 Crohn disease (CD) patients and 4203 ulcerative colitis (UC) patients, as well as 26,063 controls were included in this meta-analysis. The rs4613763T/C polymorphism had obvious influence on CD, UC risk in Caucasian. However, rs17234657T/G polymorphism had obvious influence on CD but not UC in Caucasian.

Conclusion: This meta-analysis suggested that both the rs4613763T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. In addition, rs4613763T/C, polymorphism had obvious influence on risk of UC in Caucasian.

Abbreviations: CD = Crohn disease, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, IBD = inflammatory bowel disease, OR = odds ratio, *PTGER4* = prostaglandin E receptor 4, UC = ulcerative colitis.

Keywords: inflammatory bowel disease, meta-analysis, polymorphism, *PTGER4*

1. Introduction

Inflammatory bowel disease (IBD), a complex chronic inflammatory disorder, is typically classified into 2 clinical syndromes: Crohn disease (CD) and ulcerative colitis (UC). Recently, the incidence rate IBD has been gradually increasing in Europe.[1] Of note, geographic variability in the incidence and prevalence of IBD was found around the world.[1] The majority of IBD patients abdominal pain, vomiting, diarrhea, and other extra-intestinal symptoms, which seriously affects their quality of life.[2] In addition it has been widely accepted that IBD may increase gastrointestinal cancer and cardiovascular disease risk.[3,4] Therefore, IBD patients were at a slightly higher risk of dying than the general population.[3–5]

It was well established the underlying etiology of IBD is multifactorial.[1] Environmental, genetic immune, microbial, and even emotional factors acted as essential players in IBD.[1] Since the first gene CARD15 was demonstrated to be associated with CD in 2001,[6] people gradually realized that genetic predisposition had considerable influence on IBD risk.[7] As we known, disturbed epithelial barrier integrity acts a crucial role in the progression of IBD.[8] Of note, the prostaglandin receptor EP4, encoded by *PTGER4*, has been believed to be essential for maintenance of epithelial barrier integrity.[9] It had been reported that *PTGER4* polymorphisms were associated with ankylosing spondylitis,[10] asthma,[11] rheumatoid arthritis[12] whose genetic predisposition some degree of overlaps with IBD. In 2007, a genome-wide association study (GWAS) identified *PTGER4* contributing to CD susceptibility.[13] Recently, a series of studies investigated the relationship between *PTGER4* polymorphisms and IBD risk in Caucasian, but their results were conflict.[12–28] Therefore, we performed a meta-analysis to strengthen the associations between *PTGER4* polymorphisms and IBD risk in Caucasian.

2. Materials and methods

2.1. Search strategy

Wiley Online Library, PubMed, and Chinese National Knowledge Infrastructure (CNKI) databases were searched up to

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The datasets generated during and/or analyzed during the current study are publicly available.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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January 20, 2019 for studies regarding associations between PTGER4 polymorphism and IBD risk. Both medical subject heading terms and text words in search strategy were as follows: ("Inflammatory bowel disease" or "IBD" or "Crohn's disease" or "ulcerative colitis" or "CD" or "UC") and ("PTGER4" or "prostaglandin receptor EP4") and ("SNP" or "polymorphism" or "variant" or "mutation"). Moreover, additional studies were identified by a full manual search from the reference of selected papers on this topic. Ethical approval was obtained from the Renmin Hospital of Wuhan University Ethics Committee Board.

2.2. Criteria for inclusion and exclusion

The studies eligible should meet following inclusion criteria: case-control studies; studies documented association between *PTGER4* polymorphisms and IBD risk; IBD was clearly diagnosed; the odds ratio (OR) with 95% confidence interval (CI) can be calculated according to information in study; control population was in Hardy-Weinberg equilibrium (HWE); subjects were restricted to Caucasian populations. Accordingly, the exclusion criteria were as follows: duplication of previous publications; not original articles; incomplete genotype data; study on associations between *PTGER4* polymorphisms and other diseases; subjects in studies included are not Caucasians; no control population.

2.3. Data extraction

The author name, region, publication year, number of subjects, minor allele frequencies (MAF), or frequencies of genotypic distributions in cases and controls and other information about the eligible studies was extracted by 2 authors. Any dispute was resolved by a final decision after discussion.

2.4. Statistical analysis

Meta-analysis was performed by STATA, version 11.0 (Stata Corporation, College Station, TX). Pooled ORs and 95% CI were used to estimate potential associations of PTGER4 gene polymorphisms with IBD risk under distinct genetic models. Chi-square-based Q test and I^2 test was used to access heterogeneity between included studies. If $P > .10$ and $I^2 < 50\%$ showed significant heterogeneity, Mantel–Haenszel fixed effect model was executed,[29] otherwise DerSimonian–Laird random effect model was executed.[29,30] Z test was applied to access significance of OR. Egger test was also used in the occurrence of Publication bias.[31] The HWE in the controls within each study was assessed by Pearson chi-squared test. If heterogeneity existed, subgroup analysis should be conducted.[32]

3. Results

3.1. Main characteristics of eligible studies

Forty three records were identified in initial search. After reading titles and abstracts, 7 articles in all records, 21 records were not satisfied inclusion criteria because they were duplicate records (N = 18) or other uncorrelated disease (N = 3). After careful screening, another 8 records were further excluded because they were not case-control studies (N = 4) or not target SNPs (N = 4). Finally, 14 eligible records consisting of 20 case-control studies were identified in this meta-analysis [12–25]. Twenty case-control studies consisting of 18,495 CD patients and 4203 UC patients, as well as 26,063 controls were included in this meta-analysis. The characteristics of all studies included in the meta-analysis is summarized in Table 1.

3.2. Associations between rs4613763 T/C and CD

For rs4613763 T/C polymorphism, 8 case-control studies with 10,193 cases and 10,394 controls were identified. There was significant association found under all genetic models (C vs T: OR = 1.19, 95% CI: 1.05, 1.36, $P = .01$; CC vs TT: OR = 1.30, 95% CI: 1.05, 1.62, $P = .02$; TC vs TT: OR = 1.16, 95% CI: 1.03,

Table 1

Characteristics of studies included in the meta-analysis.

Study	Year	Disease	Country	SNP	Sample size		MAF		HWE
					Case	Control	Case	Control	
Libioulle C	2007	CD	Belgium	rs4613763	547	928	0.191	0.120	0.931
Laukens D	2010	CD	Belgium	rs4613763	1069	697	0.179	0.116	0.103
Danoy P	2010	CD	Australia	rs4613763	2773	2215	0.130	0.130	0.952
Latiano A	2011	CD	Italy	rs4613763	657	548	0.107	0.082	0.337
Latiano A	2011	UC	Italy	rs4613763	692	548	0.114	0.082	0.337
Peter I	2011	CD	USA	rs4613763	369	503	0.080	0.070	0.796
Barrett JC	2008	CD	UK	rs4613763	3230	3952	0.125	0.124	0.993
Amre DK	2010	CD	Canada	rs4613763	406	415	0.160	0.130	0.991
Silverberg MS	2009	UC	Canada	rs4613763	1,052	2,571	0.140	0.110	0.982
Waterman M	2011	CD	Canada	rs4613763	1144	1057	0.133	0.122	0.964
Waterman M	2011	UC	Canada	rs4613763	1230	1057	0.144	0.122	0.964
WTCCC	2007	CD	UK	rs17234657	2000	3000	0.181	0.128	0.980
Parkes M	2007	CD	UK	rs17234657	1747	2933	0.182	0.125	0.356
Parkes M	2007	CD	UK	rs17234657	1116	1853	0.151	0.132	0.081
Jung C	2012	CD	France	rs17234657	798	960	0.150	0.120	0.974
van der Heide F	2010	CD	Netherlands	rs17234657	310	976	0.180	0.130	0.911
Weersma RK	2009	CD	Netherlands	rs17234657	1621	1086	0.170	0.130	0.934
Perdigones N	2010	CD	Spain	rs17234657	709	1369	0.136	0.114	0.657
Perdigones N	2010	UC	Spain	rs17234657	662	1369	0.125	0.114	0.657
Wang MH	2014	UC	USA	rs1174257	566	1436	0.370	0.380	0.980

CD = Crohn disease; UC = ulcerative colitis.

Table 2

Pooled analysis for the associations between rs4613763T/C and risk of CD and UC.

		Test of association		Test of heterogeneity			
Disease	Comparison	OR (95% CI)	*P*	χ^2	I^2 (%)	*P*	Egger test (*P*)
CD	C vs T	1.19[1.05,1.36]	.007	27.55	74.6	.000	.074
CD	CC vs TT	1.30[1.05,1.62]	.018	10.67	34.4	.154	.106
CD	TC vs TT	1.16[1.03,1.30]	.011	17.15	59.2	.016	.066
CD	TC/CC vs TT	1.17[1.04,1.32]	.009	20.01	65.0	.006	.066
CD	CC vs TT/TC	1.26[1.01,1.57]	.038	8.32	15.6	.306	.094
UC	C vs T	1.24[1.12,1.38]	.000	0.43	0.0	.805	.774
UC	CC vs TT	1.54[1.04,2.29]	.031	0.51	0.0	.774	.284
UC	TC vs TT	1.22[1.09,1.37]	.001	0.56	0.0	.756	.508
UC	TC/CC vs TT	1.23[1.10,1.37]	.000	0.46	0.0	.795	.616
UC	CC vs TT/TC	1.47[0.99,2.17]	.056	0.51	0.0	.773	.252

CD = Crohn disease; UC = ulcerative colitis.

1.30, *P* = .01; CC/TC vs TT: OR = 1.17, 95% CI: 1.04, 1.32, *P* = .01; CC vs TC/TT: OR = 1.26, 95% CI: 1.01, 1.57, *P* = .04) (Table 2).

3.3. Associations between rs4613763 T/C and UC

For rs4613763 T/C polymorphism, 3 case-control studies consisting of 2978 cases and 3853 controls were identified. There was significant association found in following genetic models (C vs T: OR = 1.24, 95% CI: 1.12, 1.38, *P* = .00; CC vs TT: OR = 1.54, 95% CI: 1.04, 2.29, *P* = .03; TC vs TT: OR = 1.22, 95% CI: 1.09, 1.37, *P* = .00; CC/TC vs TT: OR = 1.23, 95% CI: 1.10, 1.37, *P* = .00) However, no significant association was found in CC versus TC/TT: OR = 1.47, 95% CI: 0.99, 2.17, *P* = .06 (Table 2).

3.4. Associations between rs17234657T/G and CD

For rs17234657T/G polymorphism, 7 case-control studies consisting of 8302 cases and 12,169 controls were identified. There was significant association found under all genetic models (G vs T: OR = 1.33, 95% CI: 1.26, 1.41, *P* = .00; GG vs TT: OR = 1.97, 95% CI: 1.63, 2.39, *P* = .00; TG vs TT: OR = 1.27, 95% CI: 1.20, 1.36, *P* = .00; GG/TG vs TT: OR = 1.30, 95% CI: 1.22, 1.38, *P* = .00; GG vs TG/TT: OR = 1.83, 95% CI: 1.52, 2.21, *P* = .00) (Table 3).

3.5. Associations between rs17234657T/G and UC

For rs17234657T/G polymorphism, 2 case-control studies consisting of 1228 cases and 1797 controls were included. There was no significant association found under all genetic models (G vs T: OR = 1.01, 95% CI: 0.90, 1.26, *P* = .91; GG vs TT: 0.98, 95% CI: 0.75, 1.30, *P* = .91; TG vs TT: OR = 1.01, 95% CI: 0.88, 1.61, *P* = .00; GG/TG vs TT: OR = 1.01, 95% CI: 0.88, 1.15, *P* = .06; GG vs TG/TT: OR = 0.99, 95% CI: 0.76, 1.28, *P* = .92) (Table 3).

3.6. Publication bias

Egger test was applied to evaluate the publication bias of our meta-analysis. The results of Egger test revealed that there was no publication bias in all analysis (Tables 2 and 3).

4. Discussion

Although the exact of IBD etiology was remains unclear, disturbed intestinal homeostasis was major factor contributing to the pathogenesis and progression of intestinal inflammation in IBD.[33] Prostaglandins are arachidonic acid metabolites produced by the action of the enzymes cyclooxygenase-1 and -2 which have been identified to play a crucial role in maintenance of intestinal homeostasis.[34,35] Moreover, a haplotype of prostaglandin synthase 2/cyclooxygenase 2 has been shown to have a

Table 3

Pooled analysis for the associations between rs17234657T/G and risk of CD and UC.

		Test of association		Test of heterogeneity			
Disease	Comparison	OR (95% CI)	*P*	χ^2	I^2 (%)	*P*	Egger's test (*P*)
CD	G vs T	1.33[1.26,1.41]	.000	9.73	38.3	.136	.215
CD	GG vs TT	1.97[1.63,2.39]	.000	3.38	0.0	.760	.224
CD	TG vs TT	1.27[1.20,1.36]	.000	6.53	8.1	.366	.268
CD	TG/GG vs TT	1.30[1.22,1.38]	.000	7.26	17.3	.298	.246
CD	CC vs TT/TG	1.83[1.52,2.21]	.000	2.37	0.0	.833	.192
UC	G vs T	1.01[0.90,1.26]	.897	0.78	0.0	.333	-
UC	GG vs TT	0.98[0.75,1.30]	.910	1.03	2.6	.311	-
UC	TG vs TT	1.01[0.88,1.61]	.875	0.31	0.0	.576	-
UC	TG/GG vs TT	0.99[0.76,1.28]	.921	0.93	0.0	.336	-
UC	GG vs TT/TG	1.01[0.9,2.17]	.056	0.51	0.0	.333	-

CD = Crohn disease; UC = ulcerative colitis.

strong association with IBD[36] and microsomal prostaglandin E synthase-1 is altered in IBD.[37] Recently, it was reported that Ptger4$^{-/-}$ mice more easily developed severe colitis induced by dextran sodium sulphate while treatment with EP4-selective agonists exerted protective effects against colitis through enhancement of epithelium survival and regeneration.[38–40] EP4 may act a driver of the differentiation of Th1 cells and proliferation of Th17 cells,[41] which play an important role in the pathogenesis of CD.[42]

Genetically, variant in *PTGER4* may lead to functional alterations its production.[13] Recently, numerous studies have indicated that genetic markers of *PTGER4* had effects on inflammatory and autoimmune disease including ankylosing spondylitis,[10] asthma,[11] rheumatoid arthritis[12] whose genetic predisposition overlaps with IBD.[20] Up to now, scientists spent considerable efforts to investigate the relationship between *PTGER4* polymorphism and IBD risk. However, the results of all existing studies are conflict. Considering that subjects in included studies are all Caucasian population, we conducted a meta-analysis to investigate the genetic association.

To our knowledge, this meta-analysis systematically investigated the associations between *PTGER4* polymorphisms and IBD risk in Caucasian population. Twenty case-control studies consisting of 18,495 CD and 4203 UC patients as well as 26,063 controls were included in this meta-analysis. Our synthetic results suggested that the both rs4613763 T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. Moreover, rs4613763 T/C, polymorphism had obvious influence on risk of UC in Caucasian. Up to now, there is few data about how *PTGER4* involving in influencing IBD susceptibility. A possible mechanism is that NF-kB and XBP1 binds to some gene loci in *PTGER4*[43] and then modulates PTGER4 expression,[44] which finally leads to altering IBD susceptibility.

It is worth to note that several genome-wide association studies (GWASs) were included in current meta-analysis.[13,16–18,24–26,28] GWASs, aimed at increasing the reliability of results by comprehensively analyzing different study from different regions, have led to the identification of novel associations that would not otherwise have been identified in individual studies with small sample. The results of our meta-analysis also were consistent with most of GWASs.

It was widely accepted that meta-analysis was a powerful tool to systematically evaluate genetic effect of polymorphism on disease susceptibility.[45,46] Publication bias, also regarded as a "file-drawer problem," was often a major drawback of meta-analyses by compromising their validity.[47] There was no significant publication bias in current analyses. Heterogeneity, known as another important issue in meta-analysis, did not exist. In addition, the sample size is relatively larger. Therefore, our synthetic results are comparatively persuasive and reliable.

Undoubtedly, some limitations in our study still need be careful considered. First, because there was no enough available data, we did not conducted subgroup analysis according to study characteristics, which requires further investigation. Second, the underlying etiology of IBD is extremely complex, but only genetic factors were under our consideration. Last but not least, our studies did not consider potential interaction between gene–gene and gene–environmental interactions had obvious influence on associations between *PTGER4* polymorphisms and IBD risk. Therefore, representativeness bias of the result should be fully valued.

In conclusion, our meta-analysis revealed that both the rs4613763 T/C, rs17234657T/G polymorphisms had obvious influence on risk of CD in Caucasian. In addition, rs4613763 T/C, polymorphism had obvious influence on risk of UC in Caucasian. Given that some limitations exist in our study, further well-designed case-control studies are still warranted to confirm the results of our present meta-analysis.

Author contributions

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References

[1] Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol 2015;50:942–51.
[2] Singh S, Blanchard A, Walker JR, et al. Common symptoms and stressors among individuals with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2011;9:769–75.
[3] Romberg-Camps M, Kuiper E, Schouten L, et al. Mortality in inflammatory bowel disease in the Netherlands 1991-2002: results of a population-based study: the IBD South-Limburg cohort. Inflamm Bowel Dis 2010;16:1397–410.
[4] Manninen P, Karvonen AL, Huhtala H, et al. Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland. J Crohns Colitis 2012;6:524–8.
[5] Ekbom A, Helmick CG, Zack M, et al. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. Gastroenterology 1992;103:954–60.
[6] McGovern DP, van Heel DA, Ahmad T, et al. NOD2 (CARD15), the first susceptibility gene for Crohn's disease. Gut 2001;49:752–4.
[7] Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007;369:1627–40.
[8] Coskun M. Intestinal epithelium in inflammatory bowel disease. Front Med (Lausanne) 2014;1:24–25.
[9] Lejeune M, Leung P, Beck PL, et al. Role of EP4 receptor and prostaglandin transporter in prostaglandin E2-induced alteration in colonic epithelial barrier integrity. Am J Physiol Gastrointest Liver Physiol 2010;299:G1097–105.
[10] Chai W, Lian Z, Chen C, et al. JARID1A, JMY, and PTGER4 polymorphisms are related to ankylosing spondylitis in Chinese Han patients: a case-control study. PLoS One 2013;8:1–8.
[11] Kim SH, Kim YK, Park HW, et al. Association between polymorphisms in prostanoid receptor genes and aspirin-intolerant asthma. Pharmacogenet Genomics 2007;17:295–304.
[12] Perdigones N, Martin E, Robledo G, et al. Study of chromosomal region 5p13.1 in Crohn's disease, ulcerative colitis, and rheumatoid arthritis. Hum Immunol 2010;71:826–8.
[13] Libioulle C, Louis E, Hansoul S, et al. Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. PLoS Genet 2007;3:1–8.
[14] Amre DK, Mack DR, Morgan K, et al. Susceptibility loci reported in genome-wide association studies are associated with Crohn's disease in Canadian children. Aliment Pharmacol Ther 2010;31:1186–91.

[15] Latiano A, Palmieri O, Latiano T, et al. Investigation of multiple susceptibility loci for inflammatory bowel disease in an Italian cohort of patients. PLoS One 2011;6:e22688.
[16] Peter I, Mitchell AA, Ozelius L, et al. Evaluation of 22 genetic variants with Crohn's disease risk in the Ashkenazi Jewish population: a case control study. BMC Med Genet 2011;12:63–9.
[17] Prager M, Buttner J, Buning C. PTGER4 modulating variants in Crohn's disease. Int J Colorectal Dis 2014;29:909–15.
[18] Waterman M, Xu W, Stempak JM, et al. Distinct and overlapping genetic loci in Crohn's disease and ulcerative colitis: correlations with pathogenesis. Inflamm Bowel Dis 2011;17:1936–42.
[19] Wang MH, Fiocchi C, Zhu X, et al. Gene-gene and gene-environment interactions in ulcerative colitis. Hum Genet 2014;133:547–58.
[20] Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.
[21] Jung C, Colombel JF, Lemann M, et al. Genotype/phenotype analyses for 53 Crohn's disease associated genetic polymorphisms. PLoS One 2012;7:1–7.
[22] Silverberg MS, Cho JH, Rioux JD, et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. Nat Genet 2009;41:216–20.
[23] Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40:955–62.
[24] Laukens D, Georges M, Libioulle C, et al. Evidence for significant overlap between common risk variants for Crohn's disease and ankylosing spondylitis. PLoS One 2010;5:1–9.
[25] Danoy P, Pryce K, Hadler J, et al. Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. PLoS Genet 2010;6:1–9.
[26] Parkes M, Barrett JC, Prescott NJ, et al. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. Nat Genet 2007;39:830–2.
[27] van der Heide F, Nolte IM, Kleibeuker JH, et al. Differences in genetic background between active smokers, passive smokers, and non-smokers with Crohn's disease. Am J Gastroenterol 2010;105: 1165–72.
[28] Weersma RK, Stokkers PC, Cleynen I, et al. Confirmation of multiple Crohn's disease susceptibility loci in a large Dutch-Belgian cohort. Am J Gastroenterol 2009;104:630–8.
[29] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[30] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[31] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[32] Scholten RJ, Assendelft WJ, Kostense PJ, et al. [The practice of systematic reviews. V. Heterogeneity between studies and subgroup analysis]. Ned Tijdschr Geneeskd 1999;143:843–8.
[33] Lam G, Apostolopoulos V, Zulli A, et al. NADPH oxidases and inflammatory bowel disease. Curr Med Chem 2015;22:2100–9.
[34] Morteau O. Prostaglandins and inflammation: the cyclooxygenase controversy. Arch Immunol Ther Exp (Warsz) 2000;48:473–80.
[35] Dey I, Lejeune M, Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. Br J Pharmacol 2006;149:611–23.
[36] Cox DG, Crusius JB, Peeters PH, et al. Haplotype of prostaglandin synthase 2/cyclooxygenase 2 is involved in the susceptibility to inflammatory bowel disease. World J Gastroenterol 2005;11:6003–8.
[37] Subbaramaiah K, Yoshimatsu K, Scherl E, et al. Microsomal prostaglandin E synthase-1 is overexpressed in inflammatory bowel disease. Evidence for involvement of the transcription factor Egr-1. J Biol Chem 2004;279:12647–58.
[38] Nitta M, Hirata I, Toshina K, et al. Expression of the EP4 prostaglandin E2 receptor subtype with rat dextran sodium sulphate colitis: colitis suppression by a selective agonist, ONO-AE1-329. Scand J Immunol 2002;56:66–75.
[39] Kabashima K, Saji T, Murata T, et al. The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. J Clin Invest 2002;109:883–93.
[40] Jiang GL, Nieves A, Im WB, et al. The prevention of colitis by E Prostanoid receptor 4 agonist through enhancement of epithelium survival and regeneration. J Pharmacol Exp Ther 2007;320:22–8.
[41] Yao C, Sakata D, Esaki Y, et al. Prostaglandin E2-EP4 signaling promotes immune inflammation through Th1 cell differentiation and Th17 cell expansion. Nat Med 2009;15:633–40.
[42] Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. Gut 2009;58:1152–67.
[43] Glas J, Seiderer J, Czamara D, et al. PTGER4 expression-modulating polymorphisms in the 5p13.1 region predispose to Crohn's disease and affect NF-kappaB and XBP1 binding sites. PLoS One 2012;7:1–12.
[44] Ellson CD, Davidson K, Ferguson GJ, et al. Neutrophils from p40phox-/- mice exhibit severe defects in NADPH oxidase regulation and oxidant-dependent bacterial killing. J Exp Med 2006;203:1927–37.
[45] Kirino Y, Bertsias G, Ishigatsubo Y, et al. Genome-wide association analysis identifies new susceptibility loci for Behcet's disease and epistasis between HLA-B*51 and ERAP1. Nat Genet 2013;45:202–7.
[46] Lu XC, Tao Y, Wu C, et al. Association between variants of the autophagy related gene–IRGM and susceptibility to Crohn's disease and ulcerative colitis: a meta-analysis. PLoS One 2013;8:1–2.
[47] Siddiqi N. Publication bias in epidemiological studies. Cent Eur J Public Health 2011;19:118–20.