Immunobiology 225 (2020) 151876

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Nuclear factor-κB1 and MicroRNA-146a polymorphisms and risk of acute graft versus host disease post allogeneic stem cell transplantation

Ghada I. Mossallam[a,*], Raafat Abdel Fattah[b], Hossam K Mahmoud[b]

[a] Bone Marrow Transplantation Laboratory Unit, National Cancer Institute, Cairo University, Cairo, Egypt
[b] Department of Medical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt Bone Marrow Transplantation Unit, Nasser Institute Hospital for Research and Treatment, Cairo, Egypt

ARTICLE INFO

Keywords:
NF-κB
MiR-146
Acute graft versus host disease
Haematopoeitic stem cell transplantation

ABSTRACT

Acute graft-versus-host disease (aGVHD) is a severe inflammatory complication of haematopoeitic stem cell transplantation. The nuclear factor- Kappa Beta (NF-κB) signaling pathway regulates T cell activation. The NF-κB controls the expression of microRNA-146a (miR-146a) that in turn regulates NF-κB activation through a negative feedback loop. We aim to analyze the association between NF-κB1 encoding p50 (rs28362491, −94 in.ertion/deletion ATTG) and miR-146a (rs2910164, G > C) polymorphisms and risk of aGVHD. Genotyping was performed for 135 HLA-matched donors using polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP).The incidence of aGVHD grades II-IV was 24/135 (17.8 %). NF-κB1 genotype and cytomegalovirus infection were significantly associated with risk of aGVHD II-IV (p = 0.022, HR = 3.17, 95 % CI:1.18-8.51 and p = 0.048, HR = 2.56, 95 % CI:1.01–6.52, respectively). In multivariate analysis, NF-κB1homozygous deletion/deletion genotype was the only independent risk factor associated with aGVHD II-IV (p = 0.013, HR = 3.50, 95 % CI:1.30–9.44). No significant association could be observed between miR-146a polymorphism and aGVHD. Combined NF-κB1 and miR146a genotype analysis warrants investigation in a larger cohort. Our preliminary data do not support the association between miR146a and aGVHD, but suggest an association between NF-κB1 and risk of aGVHD that may pave the way for the development of a novel targeted therapy if proved in a larger cohort.

1. Introduction

Allogeneic haematopoietic stem cell transplantation (AHSCT) is an effective treatment modality for many malignant and non malignant haematological disorders. Nevertheless, the development of acute graft versus host disease (aGVHD) in up to 35–50 % of patients constitutes a major cause of morbidity and transplant-related mortality (TRM) that necessitates appropriate intervention and prevention (Jacobsohn, 2007). aGVHD is a severe inflammatory complication of AHSCT (Zeiser and Blazar, 2017). T cell activation plays a crucial role in its pathogenesis and represents a major target for the developing immunosuppressive approaches (Zhang et al., 2018).

The functional interaction between the nuclear factor of kappa light polypeptide gene enhancer in B-cells (NF-κB) signaling pathway and microRNAs (miRNAs) is essential for the regulation of inflammation. T-cell activation induces a variety of proinflammatory and immunemodulatory responses. NF-κB controls the initiation and resolution of inflammation by promoting the synthesis of pro-inflammatory cytokines and chemokines at the induction of inflammation while suppressing upregulated inflammatory genes upon termination (Ghosh and Hayden, 2008; Lawrence and Fong, 2010). The induced expression of miR-146a following T cell activation depends on NF-κB signaling. In turn, miR-146a negatively regulates activated T cells (Yang et al., 2012b).

The NF-κB family of transcription factors comprises five subunits, RelA (p65), NF-κB1 (p50 and p105), NF-κB2 (p52 and p100), c-Rel, and RelB that regulate gene expression by forming homodimers and heterodimers complexes with distinctive functions in the immune response (Cartwright et al., 2016, Zeligs et al., 2016). The T cell receptor (TCR) and Toll-like receptor (TLR) engagement and the exposure to proinflammatory cytokines such as tumor necrosis factor (TNF) activate the classical canonical NF-κB signaling pathway through the adaptor molecule tumor necrosis factor receptor-associated factor 6 (TRAF6) allowing translocation of different NF-κB subunits into the nucleus and their binding to the promoters of target genes (Liu et al., 2017, Pereira and Oakley, 2008, Sun et al., 2004).

* Corresponding author at: National Cancer Institute, Cairo University, Fom El-Khalig Square, Kasr El-Aini St., 11796 Cairo, Egypt.
E-mail address: ghada.mossallam@nci.cu.edu.eg (G.I. Mossallam).

https://doi.org/10.1016/j.imbio.2019.11.011
Received 23 August 2019; Received in revised form 18 November 2019; Accepted 26 November 2019
Available online 27 November 2019

The NF-κB1 gene is located on chromosome 4q24 and encodes the regulatory p50 subunit and its isoform p105. p50 lacks transcriptional activity, and therefore promotes transcription only by forming heterodimer with other subunits, of which p65 (RelA) is the most abundant one activated by the canonical NF-κB pathway (Oeckinghaus and Ghosh, 2009). p50 homodimers repress transcription of proinflammatory genes by promoting chromatin condensation by combining with histone deacetylase1 (p50/p50/HDAC1) and competing for NF-κB binding sites (Cartwright et al., 2016, Elsharkawy et al., 2010, Zhong et al., 2002). While Bcl-3 maintains repression by the p50 homodimer by forming of a stable repressor complex through inhibition of ubiquitination (Cartwright et al., 2016, Oeckinghaus and Ghosh, 2009).

MiR-146a, a member of miR-146 family, encoded by a gene located on chromosome 5, plays a role in controlling inflammatory immune responses by signaling modulation (Esteller, 2011, Tahamtan et al., 2018, Testa et al., 2017, Zheng et al., 2017). MiR-146a negatively regulates T cells by targeting the TRAF6 and interleukin-1 receptor associated kinase 1 (IRAK1) adaptor molecules in the NF-κB signaling pathway through a negative feedback loop (Ma et al., 2011, Testa et al., 2017).

Dysregulation of NF-κB1 and miR-146a activity is associated with inflammatory disorders. A functional insertion/deletion polymorphism (-94 insertion/deletion ATTG) (rs28362491) in the promoter of the NF-κB1 associated with reduced promoter activity has been studied in many inflammatory and autoimmune diseases (Borm et al., 2005, Hegazy et al., 2001, Karban et al., 2004, Li et al., 2008, Sun and Zhang, 2007). The miR-146a rs2910164 G > C single nucleotide polymorphism (SNP) located in the stem region of pre-miR-146a is associated with decreased expression of its mature form and was reported to be associated with susceptibility to aGVHD and many autoimmune diseases (Li et al., 2015, Stickel et al., 2014, Stickel et al., 2017).

We investigated the role played by the NF-κB signaling pathway in the pathogenesis of aGVHD by studying the association between NF-κB1 (rs28362491, −94 in./del ATTG) and miR-146a (rs2910164, G > C) polymorphisms and the risk of aGVHD development.

2. Material and methods

2.1. Patients

This retrospective study included 135 patients with haematological malignancies [89 acute myeloid leukemia (AML), 28 acute lymphoblastic leukemia (ALL), 13 chronic myeloid leukemia (CML) and 5 myelodysplastic syndrome (MDS)] who underwent HLA-identical sibling-donor allogeneic haematopoietic stem cell transplantation between 20015 and 2018 at Nasser Institute Hospital for Research and Treatment, Ministry of Health, Egypt. The median age of patients was 30 years (range: 4–57) and that of donors was 32 years (range: 10–56). The patients were 82 (60.7 %) males and 53 (39.3 %) females. The study was approved by the National Cancer Institute institutional review board. All patients provided written informed consent according to the Declaration of Helsinki. Acute GVHD was graded according to the Glucksberg scale (Glucksberg et al., 1974).

Conditioning regimens and GVHD prophylaxis

The conditioning regimens shown in Table 1 included busalfan (BU), fludarabine (FLU), cyclophosphamide (CY), melphalan (MELPH), and total body irradiation (TBI). The use of different regimens varied according to different diseases (BU/CY, FLU/BU, FLU/MELPH and FLU/CY for AML, MDS and CML and TBI/CY for ALL). GVHD prophylaxis consisted of combinations of cyclosporine A (CSA), methotrexate (MTX), mycophenolate mofetil (MMF) and post transplant cyclophosphamide (Table 1).

2.2. Methods

Genotyping

Table 1
Patients' characteristics.

Patient characteristics	Number (%)
Age*	30(4–57)
Gender	
• Male	82(60.7)
• Female	53(39.3)
Disease at transplantation	
• Acute myeloid leukemia	89(65.9)
• Acute lymphoblastic leukemia	28(20.8)
• Chronic myeloid leukemia	13(9.6)
• Myelodysplatic syndrome	5(3.7)
Gender mismatch between recipient and donor	
• Female to male	34(25.2)
• Other combinations	101(74.8)
Conditioning regimen	
• Busulfan/Cyclophosphamide	81(60)
Fludarabin-based	43(31.9)
Fludarabin/ Alkylating agent	9(6.7)
Fludarabin/ Busulfan	31(23)
Fludarabin/ Cyclophosphamide	3(2.2)
• TBI/ Cyclophosphamide	11(8.1)
GVHD prophylaxis	
• Cyclosporine, Methotrexate	109(80.7)
• Cyclosporine, Mycophenolate mofetil	10(7.4)
• Cyclosporine, post Cyclophosphamide	16(11.9)
CMV infection (by PCR)	
• Yes	18(13.3)
• No	117(86.7)
Acute graft versus host disease (aGVHD)	
Grade	
• Grade 0-I	111(82.2)
• Grade II-IV	24(17.8)
Site	
Skin	7/24(29.4)
GIT	13/24(53)
Liver	4/24(17.6)

Abbreviations: TBI: Total body irradiation, CMV: Cytomegalovirus.
* median (range).

Genomic DNA was extracted from peripheral blood cells obtained from donors using minicolumn DNA purification kit (Qiagen, Hilden, Germany).Genotyping of NF-κB1 (rs28362491, −94 in./del ATTG) and miR-146a (rs2910164, G > C) SNPs was performed for the HLA-matched related donors using the polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) method as described previously (Gautam et al., 2017, Zeng et al., 2010).

2.3. Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as median range as appropriate. Qualitative data were expressed as frequency and percentage. For normally distributed quantitative data, comparison between two groups was done using Student t-test. Association between development of aGVHD and different genotypes was done using Kaplan-Meier survival analysis and the risk (hazard ratio) was estimated using Cox-proportional hazard model for univariate and multivariate analysis with 95 % confidence interval (CI). All tests were two-tailed. A p-value < 0.05 was considered significant.

3. Results

Patient characteristics are summarized in Table 1. The incidence of

Table 2
NF-kB1 (rs283624 91) and miR-146a (rs2910164) genotypes and development of acute graft versus host disease.

Gene	n	No. of aGVHD	Cumulative proportion at 100 days	p-value	HR	95 % CI
Whole Group	135	24	81.1			
NF-κB1						
Additive Model						
ins/ins	58	8	85.5 %	0.065	1	
ins/del	66	11	82.0 %		1.27	0.51-3.17
del/del	11	5	54.5 %		3.63	1.18-11.11
Recessive model						
ins/ins	58	8	85.5 %	0.280	1	
ins/del + del/del	77	16	77.8 %		1.60	0.68-3.73
Dominant Model						
ins/ins + ins/del	124	19	83.6 %	0.022	1	
del/del	11	5	54.5 %		3.17	1.18-8.51
MiR-146a						
Additive Model						
GG	43	7	82.9 %	0.915	1	
GC	74	13	81.0 %		1.13	0.45-2.83
CC	18	4	77.8 %		1.30	0.38-4.44
Recessive Model						
GG	43	7	82.9 %	0.732	1	
CG + CC	92	17	80.3 %		1.17	0.48-2.81
Dominant Model						
GG + CG	117	20	81.7 %	0.738	1	
CC	18	4	77.8 %		1.12	0.41-3.51

HR: Hazard Ratio, CI: Confidence Interval, aGVHD: acute graft-versus-host disease, ins: insertion, del: deletion.

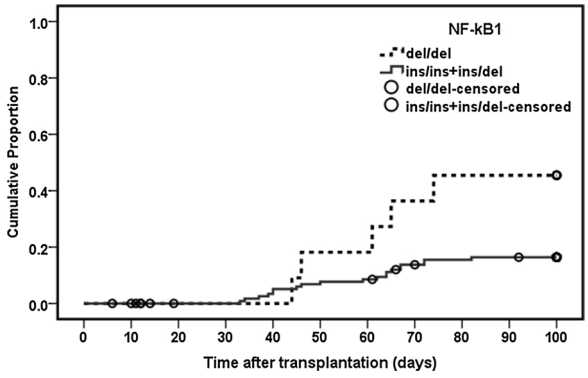

Fig. 1. The cumulative incidence of acute GVHD according to NF-kB1 genotypes.

aGVHD grade II–IV was 24/135 (17.8 %) (Table1). The gastrointestinal tract (GIT) was the commonest affected organ followed by the skin and the liver (Table 1). Eleven patients (8.1 %) died before 100 days of transplantation without developing aGVHD. The distribution of donors NF-κB1 (rs283624 91) and miR-146a (rs2910164) genotypes is present in Table 2 and was in Hardy Weinberg equilibrium. Association of donors NF-kB1 (rs283624 91) and miR-146a (rs2910164) genotypes with risk of aGVHDII-IV is shown in Table 2. Recipients of donors carrying NF-κB1 homozygous del/del genotype had a statistically significant increased risk of aGVHD grade II–IV compared to those carrying insertion/insertion (ins/ins) or ins/del genotypes (p = 0.022, HR = 3.17, 95 % CI:1.18-8.51). The cumulative incidence of grade II-IV aGVHD post-transplantation according to del/del versus del/ins or ins/ins genotype is shown in Fig. 1. Analysis of other risk factors for aGVHD including patient age, donor-recipient gender combination, conditioning regimen, GVHD prophylaxis and cytomegalovirus infection by PCR is shown in Table 3. Cytomegalovirus infection showed significant association with increased risk of aGVHD in univariate analysis. On multivariate analysis, NF-κB1 genotype was the only independent factor that significantly affected risk of aGVHD (p = 0.013, HR: 3.50, 95 % CI: 1.30–9.44). Statistical significance was not maintained for cytomegalovirus infection (p = 0.190, HR: 1.92, 95 % CI: 0.72–5.08).

No significant association was found between donor miR-146a genotype and the risk of aGVHD II-IV as shown in Table 2 (p = 0.738, HR: 1.12, 95 %CI: 0.41–3.51). Statistical analysis of combined NF-κB1 p50 and miR-146a genotypes could not be performed, however we observed lower incidence of aGVHD in patients with donors carrying combined mir-146a GG and p50 in./ins genotypes compared those carrying mir146GG genotype combined with p50 in./del and del/del genotypes [1/17 (5.9 %) versus 6/19 (31.6 %)].

Table 3
Relation of risk factors of acute graft versus host disease.

Risk factor	Univariate			Multivariate		
	p-value	HR	95 % CI	p-value	HR	95 % CI
NF-κB1 del/del vs ins/ins and ins/del	0.022	3.17	1.18-8.51	0.013	3.50	1.30-9.44
Patient age > 40 years vs ≤ 40 years	0.584	1.35	0.46-3.95			
Gender mismatch between recipient and donor Female donor to male recipient vs others combinations	0.899	1.06	0.42-2.68			
Conditioning regimen TBI /CY vs others	0.576	.565	0.08-4.18			
GVHD prophylaxis CSA,MTX vs CSA,MMF or CSA, post CY	0.085	5.82	0.79-43.16	0.077	6.11	0.82-45.30
CMV infection by PCR CMV vs No CMV	0.048	2.56	1.01-6.52	0.190	1.92	0.72-5.08

HR: Hazard ratio, CI: Confidence interval.
TBI:Total body irradiation; CY:cyclophpsphamide; CSA:Cyclosporine; MTX :Methotrexate; CSA:Cyclosporine; MMF: Mycophenolate mofetil; post CY: post Cyclophosphamide.

4. Discussion

Acute GVHD is a severe inflammatory complication of AHSCT. The functional interaction between the NF-κB signaling pathway and miRNAs is essential for the regulation of inflammation.

In our cohort, the NF-κB1 (rs28362491, −94 in./del ATTG) p50 del/del genotype was an independent risk factor for the development of aGVHD II-IV. Association of the del allele with chronic inflammatory disorders and autoimmune diseases for instance ulcerative colitis, rheumatoid arthritis, multiple sclerosis and psoriasis has been reported by many groups (Bogunia-Kubik et al., 2016, Borm et al., 2005, Karban et al., 2004, Li et al., 2008, Oakley et al., 2005, Salim et al., 2013). The NF-κB1 del allele is associated with reduced expression of p50 gene and p50/p105 protein production (Hegazy et al., 2001). Diminished inhibitory p50/p50 homodimer/ HDAC1 complex and p50/Bcl-3 protein interaction is expected to be associated with potent activation of transcription of proinflammatory cytokines such as TNFα (Bogunia-Kubik et al., 2016, Collins et al., 2015, Elsharkawy et al., 2010; Pereira and Oakley, 2008). TNFα produced by activated T cells mediates inflammation and tissue damage in the course of aGVHD (Choi et al., 2008). Higher TNFα levels produce more severe GVHD and are associated with increased incidence of TRM (Choi et al., 2008, Levine, 2011). Inhibition of TNFα by the use monoclonal antibodies or competitors of the TNF-α -receptor has been introduced in the treatment of steroid-refractory GVHD (Levine, 2011, Wolff et al., 2005). Study of these biological drugs in rheumatoid arthritis in relation to NF-kB1 genotype showed poor response in patients with the ins variant in one study and favorable response in patients with del allele in an another one (Gębura et al., 2017, Oakley et al., 2005). Glucocortecoids are the front-line therapy for GVHD. Schäfer et al., 2014 et al. reported failure of the hydrocortisone to inhibit the lipopolysaccharide induced translocation of NF-kB1 in patients with septic shock carrying the deletion allele. These suggested NF-κB1 inflammation- modulating effects warrant further investigation in aGVHD.

The change in the level of p50 subunit can also alter the balance between other dimers involved in the NF-κB signaling pathway leading to immune dysregulation. In the study conducted by Karban et al., 2004, the association between NF-κB1 del allele and ulcerative colitis was attributed not only to a decrease in the inhibitory p50/p50 homodimer, but also to a reduction in the inflammatory p50/p65 heterodimer and associated weakened innate immune response and invasion by the intestinal bacteria. Reduced p50/p65 heterodimer may also diminish protection of the small intestine from the radiation-induced damage as reported by Wang et al., 2004.

In contrast to our finding, the ins variant has been shown to be associated with risk of Behcet's disease and psoriasis in the Turkish population (Li et al., 2008, Yenmis et al., 2015). Ethnic variation in the association the del allele with susceptibility to autoimmune and inflammatory diseases was demonstrated by Zou et al., 2011, in their metaanalysis.

In our study, we did not find significant association between donor miR-146a rs2910164 polymorphism and aGVHD. Contrary to our finding, previous studies have revealed an association between miR-146a polymorphism in both donors and recipients with risk and severity of aGVHD. Associations were attributed to deregulated TRAF6/ NF-kB and JAK–STAT/CIITA/MHCII signaling pathways, in T cells and dendretic cells, respectively (Stickel et al., 2014, Stickel et al., 2017). The expression level of miR-146a post transplantation affected the incidence of aGVHD in the study conducted by Atarod et al., 2016. Ethnic variation has been reported in the anti-inflammatory function of miR-146a and its role in the pathogenesis of various autoimmune diseases, where, association with rheumatoid arthritis, and systemic lupus erythematosus has been observed by some ethnic groups and not by the others (Bogunia-Kubik et al., 2016, Ji et al., 2014, Jiménez-Morales et al., 2012, Yang et al., 2012a). Previous Egyptian studies showed controversy in the association of miR-146a with rheumatoid arthritis (El-Shal et al., 2013, Shaker et al., 2018). Given the negative feedback relationship between miR146a and NF-κB, we tried to investigate the combined effect of miR146a and NF-κB1 genotypes on the risk of aGVHD. The observed lower frequency of aGVHD in patients with donors carrying combined miR-146a GG and p50 in./ins genotypes compared to those carrying miR146GG, p50 in./del and del/del genotypes underlines the dominant role of NF-κB1 in the activation of miR-146a. On the other hand, in the absence of the p50 subunit, the negative feedback on NF-κB activation may be missed since miR-146a is down-regulated (Rusca et al., 2012). This suggested combined effect needs to be confirmed in a larger cohort.

Redundancy in the functions of various danger signals, cytokines and chemokines released during aGVHD may affect response to targeted therapies. Novel strategies rely on the inhibition of signaling pathways in T cells (Teshima et al., 2016, Zeiser, 2018). As global inhibition of the NF-κB signaling may be associated with risk of relapse and TRM, designing therapeutic agents should be more specific and selective, taking into account the different roles played by various subunits and the balance between them (Roman-Blas and Jimenez, 2006).

Ongoing researches involving p50 as anti-inflammatory and anticancer therapy by either restoring the NF-κB1 nucleotide sequence through gene editing or strengthening p50 homodimer:DNA complexes by using Bcl-3 peptide mimetics may pave the way for the development of a novel target therapy for aGVHD (Collins et al., 2015, Concetti and Wilson, 2018, Poveda et al., 2017).

In conclusion, our preliminary data do not support the association between miR-146a and aGVHD, but report for the first time an association between NF-κB1 polymorphism and risk of aGVHD and highlight its role in the modulation of inflammation. Identification of patients at risk of developing aGVHD allows early therapeutic intervention. NF-κB1 may also represent a potential novel therapeutic target for aGVHD. More research is needed to confirm our finding in a larger cohort in various populations.

CRediT authorship contribution statement

Ghada I. Mossallam: Formal analysis, Investigation, Methodology, Writing - original draft. **Raafat Abdel Fattah:** Investigation, Data curation. **Hossam K Mahmoud:** Supervision.

Declaration of Competing Interest

No conflict of interest

References

Atarod, S., Ahmed, M.M., Lendrem, C., Pearce, K.F., Cope, W., Norden, J., Wang, X.N., Collin, M., Dickinson, A.M., 2016. miR-146a and miR-155 expression levels in acute graft-versus-host disease incidence. Front Immunol. Mar 8 (7), 56. https://doi.org/10.3389/fimmu.2016.00056. eCollection 2016.

Bogunia-Kubik, K., Wysoczańska, B., Piątek, D., Iwaszko, M., Ciechomska, M., Świerkot, J., 2016. Significance of polymorphism and expression of miR-146a and NFkB1 genetic variants in patients with rheumatoid arthritis. Arch Immunol. Ther. Exp. (Warsz) 64 (December (Suppl 1)), 131–136. https://doi.org/10.1007/s00005-016-0443-5. Epub 2017 Jan 12.

Borm, M.E., van Bodegraven, A.A., Mulder, C.J., Kraal, G., Bouma, G.A., 2005. NFKB1 promoter polymorphism is involved in susceptibility to ulcerative colitis. Int. J. Immunogenet. 32, 401–405.

Cartwright, T., Perkins, N.D., Wilson, C.L., 2016. NFKB1: a suppressor of inflammation, ageing and cancer. FEBS J. 283 (May (10)), 1812–1822. https://doi.org/10.1111/febs.13627. Epub 2016 Jan 13.

Choi, S.W., Kitko, C.L., Braun, T., Paczesny, S., Yanik, G., Mineishi, S., Krijanovski, O., Jones, D., Whitfield, J., Cooke, K., Hutchinson, R.J., Ferrara, J.L., Levine, J.E., 2008. Change in plasma tumor necrosis factor receptor 1 levels in the first week after myeloablative allogeneic transplantation correlates with severity and incidence of GVHD and survival. Blood 112 (August (4)), 1539–1542. https://doi.org/10.1182/blood-2008-02-138867. Epub 2008 May 23.

Collins, P.E., Grassia, G., Colleran, A., Kiely, P.A., Ialenti, A., Maffia, P., Carmody, R.J., 2015. Mapping the interactionof B cell leukemia 3 (BCL-3) and nuclear factor kappaB (NF-kappaB) p50 identifies a BCL-3-mimetic anti-inflammatory peptide. J. Biol.

Chem. 290, 15687–15696.
Concetti, J., Wilson, C.L., 2018. NFKB1 and cancer: friend or foe? Cells 7 (September (9)), E133. https://doi.org/10.3390/cells7090133.
El-Shal, A.S., Aly, N.M., Galil, S.M., Moustafa, M.A., Kandel, W.A., 2013. Association of microRNAs genes polymorphisms with rheumatoid arthritis in Egyptian female patients. Joint Bone Spine 80 (December (6)), 626–631. https://doi.org/10.1016/j.jbspin.2013.03.005. Epub 2013 Jun 2.
Elsharkawy, A.M., Oakley, F., Lin, F., Packham, G., Mann, D.A., Mann, J., 2010. The NF-kappaB p50:p50:HDAC 1 repressor complex orchestrates transcriptional inhibition of multiple pro-inflammatory genes. J. Hepatol. 53 (September (3)), 519–527. https://doi.org/10.1016/j.jhep.2010.03.025. Epub 2010 Jun 2.
Esteller, M., 2011. Non-coding RNAs in human disease. Nat. Rev. Genet. 12 (12), 861–874.
Gautam, A., Gupta, S., Mehndiratta, M., Sharma, M., Singh, K., Kalra, O.P., Agarwal, S., Gambhir, J.K., 2017. Association of *NFKB1* gene polymorphism (rs28362491) with levels of inflammatory biomarkers and susceptibility to diabetic nephropathy in Asian Indians. World J. Diabetes 15 (February 8(2)), 66–73. https://doi.org/10.4239/wjd.v8.i2.66.
Gębura, K., Świerkot, J., Wysoczańska, B., Korman, L., Nowak, B., Wiland, P., Bogunia-Kubik, K., 2017. Polymorphisms within genes involved in regulation of the NF-κB pathway in patients with rheumatoid arthritis. Int. J. Mol. Sci. 18 (July (7)), E1432. https://doi.org/10.3390/ijms18071432.
Ghosh, S., Hayden, M.S., 2008. New regulators of NF-kappaB in inflammation. Nat. Rev. Immunol. 8, 837–848.
Glucksberg, H., Storb, R., Fefer, A., et al., 1974. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 18, 295–304.
Hegazy, D.M., O'Reilly, D.A., Yang, B.M., Hodgkinson, A.D., Millward, B.A., Demaine, A.G., 2001. NFκB polymorphisms and susceptibility to type 1 diabetes. Genes Immun. 2 (6), 304–308.
Jacobsohn, D.A., 2007. Vogelsang GB. Acute graft versus host disease. Orphanet J. Rare Dis. 2 (September 4), 35.
Ji, J.D., Cha, E.S., Lee, W.J., 2014. Association of miR-146a polymorphisms with systemic lupus erythematosus: a meta-analysis. Lupus 23 (September (10)), 1023–1030. https://doi.org/10.1177/0961203314534512. Epub 2014 May 6.
Jiménez-Morales, S., Gamboa-Becerra, R., Baca, V., Del Río-Navarro, B.E., López-Ley, D.Y., Velázquez-Cruz, R., Saldaña-Alvarez, Y., Salas-Martínez, G., Orozco, L., 2012. MiR-146a polymorphism is associated with asthma but not with systemic lupus erythematosus and juvenile rheumatoid arthritis in Mexican patients. Tissue Antigens 80 (October (4)), 317–321. https://doi.org/10.1111/j.1399-0039.2012.01929.x. Epub 2012 Jul 24.
Karban, A.S., Okazaki, T., Panhuysen, C.I., Gallegos, T., Potter, J.J., Bailey-Wilson, J.E., Silverberg, M.S., Duerr, R.H., Cho, J.H., Gregersen, P.K., Wu, Y., Achkar, J.P., Dassopoulos, T., Mezey, E., Bayless, T.M., Nouvet, F.J., Brant, S.R., 2004. Functional annotation of a novel NFKB1 promoter polymorphism that increases risk for ulcerative colitis. Hum. Mol. Genet. 2004 (13), 35–45.
Lawrence, T., Fong, C., 2010. The resolution of inflammation: anti-inflammatory roles for NF-kappaB. Int. J. Biochem. Cell Biol. 42 (April (4)), 519–523. https://doi.org/10.1016/j.biocel.2009.12.016. Epub 2009 Dec 22.
Levine, J.E., 2011. Implications of TNF-α in the pathogenesis and management of GVHD. Int. J. Hematol. 93 (May (5)), 571–577. https://doi.org/10.1007/s12185-011-0803-1. Epub 2011 Mar 8.
Li, C., Fu, W., Zhang, Y., Zhou, L., Mao, Z., Lv, W., Li, J., Zhou, Y., 2015. Meta-analysis of microRNA-146a rs2910164 G&C polymorphism association with autoimmune diseases susceptibility, an update based on 24 studies. PLoS One 10 (April (4)), e0121918. https://doi.org/10.1371/journal.pone.0121918. eCollection 2015.
Li, H., Gao, L., Shen, Z., Li, C.Y., Li, K., Li, M., Lv, Y.J., Li, C.X., Gao, T.W., Liu, Y.F., 2008. Association study of NFKB1 and SUMO4 polymorphisms in Chinese patients with psoriasis vulgaris. Arch. Dermatol. Res. 300 (September (8)), 425–433. https://doi.org/10.1007/s00403-008-0843-4. Epub 2008 Mar 11.
Liu, T., Zhang, L., Joo, D., Sun, S.C., 2017. NF-κB signaling in inflammation. Signal Transduct. Target. Ther. 2, 17023. https://doi.org/10.1038/sigtrans.23. Epub 2017 Jul 14.
Ma, X., Becker Buscaglia, L.E., Barker, J.R., Li, Y., 2011. MicroRNAs in NF-kappaB signaling. J. Mol. Cell Biol. 3 (June (3)), 159–166. https://doi.org/10.1093/jmcb/mjr007. Epub 2011 Apr 18.
Oakley, F., Mann, J., Nailard, S., Smart, D.E., Mungalsingh, N., Constandinou, C., Ali, S., Wilson, S.J., Millward-Sadler, H., Iredale, J.P., Mann, D.A., 2005. Nuclear factor-kappaB1 (p50) limits the inflammatory and fibrogenic responses to chronic injury. Am. J. Pathol. 166, 695–708.
Oeckinghaus, A., Ghosh, S., 2009. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb. Perspect. Biol. 1 (October (4)), a000034. https://doi.org/10.1101/cshperspect.a000034.
Pereira, S.G., Oakley, F., 2008. Nuclear factor-kappaB1: regulation and function. Int. J. Biochem. Cell Biol. 40, 1425–1430.
Poveda, J., Sanz, A.B., Carrasco, S., Ruiz-Ortega, M., Cannata-Ortiz, P., Sanchez-Niño, M.D., Ortiz, A., 2017. Bcl3: a regulator of NF-κB inducible by TWEAK in acute kidney injury with anti-inflammatory and antiapoptotic properties in tubular cells. Exp. Mol. Med. 49 (July (7)), e352. https://doi.org/10.1038/emm.2017.89.
Roman-Blas, J.A., Jimenez, S.A., 2006. NF-kappaB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. Osteoarthr. Cartil. 14 (September (9)), 839–848 Epub 2006 May 26.
Rusca, N., Dehò, L., Montagner, S., Zielinski, C.E., Sica, A., Sallusto, F., Monticelli, S., 2012. MiR-146a and NF-κB1 regulate mast cell survival and T lymphocyte differentiation. Mol Cell Biol. 32 (November (21)), 4432–4444. https://doi.org/10.1128/MCB.00824-12. Epub 2012 Aug 27.
Salim, P.H., Jobim, M., Bredemeier, M., Chies, J.A., Brenol, J.C., Jobim, L.F., Xavier, R.M., 2013. Interleukin-10 gene promoter and NFKB1 promoter insertion/deletion polymorphisms in systemic sclerosis. Scand. J. Immunol. 77 (February (2)), 162–168. https://doi.org/10.1111/sji.12020.
Schäfer, S.T., Gessner, S., Scherag, A., Rump, K., Frey, U.H., Siffert, W., Westendorf, A.M., Steinmann, J., Peters, J., Adamzik, M., 2014. Hydrocortisone fails to abolish NF-κB1 protein nuclear translocation in deletion allele carriers of the NFKB1 promoter polymorphism (-94ins/delATTG) and is associated with increased 30-day mortality in septic shock. PLoS One 9 (August (8)), e104953. https://doi.org/10.1371/journal.pone.0104953. eCollection 2014. Erratum in: PLoS One. 2014;9(10):e112369.
Shaker, O.G., El Boghdady, N.A., El Sayed, A.E., 2018. Association of MiRNA-146a, MiRNA-499, IRAK1 and PADI4 polymorphisms with rheumatoid arthritis in egyptian population. Cell. Physiol. Biochem. 46 (6), 2239–2249. https://doi.org/10.1159/000489592. Epub 2018 May 3.
Stickel, N., Prinz, G., Pfeifer, D., Hasselblatt, P., Schmitt-Graeff, A., Follo, M., Thimme, R., Finke, J., Duyster, J., Salzer, U., Zeiser, R., 2014. MiR-146a regulates the TRAF6/TNF-axis in donor T cells during GVHD. Blood 124 (October (16)), 2586–2595. https://doi.org/10.1182/blood-2014-04-569046. Epub 2014 Sep 9.
Stickel, N., Hanke, K., Marschner, D., Prinz, G., Köhler, M., Melchinger, W., Pfeifer, D., Schmitt-Graeff, A., Brummer, T., Heine, A., Brossart, P., Wolf, D., von Bubnoff, N., Finke, J., Duyster, J., Ferrara, J., Salzer, U., Zeiser, R., 2017. MicroRNA-146a reduces MHC-II expression via targeting JAK/STAT signaling in dendritic cells after stem cell transplantation. Leukemia. 31 (December (12)), 2732–2741. https://doi.org/10.1038/leu.2017.137. Epub 2017 May 9.
Sun, L., Deng, L., Ea, C.K., Xia, Z.P., Chen, Z.J., 2004. The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1in T lymphocytes. Mol. Cell 14 (3), 289–301.
Sun, X.F., Zhang, H., 2007. NFKB and NFKBI polymorphisms in relation to susceptibility of tumour and other diseases. Histol. Histopathol. 22 (December (12)), 1387–1398. https://doi.org/10.14670/HH-22.1387.
Tahamtan, A., Teymoori-Rad, M., Nakstad, B., Salimi, V., 2018. Anti-inflammatory MicroRNAs and their potential for inflammatory diseases treatment. Front Immunol. 9 (June 25), 1377. https://doi.org/10.3389/fimmu.2018.01377.
Teshima, T., Reddy, P., Zeiser, R., 2016. Acute graft-versus-Host disease: novel biological insights. Biol. Blood Marrow Transplant. 22 (January (1)), 11–16. https://doi.org/10.1016/j.bbmt.2015.10.001. Epub 2015 Oct 26.
Testa, U., Pelosi, E., Castelli, G., Labbaye, C., 2017. miR-146 and miR-155: two key modulators of immune response and tumor development. Noncoding RNA 3 (June (3)), E22. https://doi.org/10.3390/ncrna3030022.
Wang, Y., Meng, A., Lang, H., Brown, S.A., Konopa, J.L., Kindy, M.S., Schmiedt, R.A., Thompson, J.S., Zhou, D., 2004. Activation of nuclear factor κB in vivo selectively protects the murine small intestine against ionizing radiation-induced damage. Cancer Res. 64, 6240–6246.
Wolff, D., Roessler, V., Steiner, B., Wilhelm, S., Weirich, V., Brenmoehl, J., Leithaeuser, M., Hofmeister, N., Junghanss, C., Casper, J., Hartung, G., Holler, E., Freund, M., 2005. Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. Bone Marrow Transplant. 35 (May (10)), 1003–1010.
Yang, B., Chen, J., Li, Y., Zhang, J., Li, D., Huang, Z., Cai, B., Li, L., Shi, Y., Ying, B., Wang, L., 2012a. Association of polymorphisms in pre-miRNA with inflammatory biomarkers in rheumatoid arthritis in the Chinese Han population. Hum. Immunol. 73 (January (1)), 101–106. https://doi.org/10.1016/j.humimm.2011.10.005. Epub 2011 Oct 12.
Yang, L., Boldin, M.P., Yu, Y., Liu, C.S., Ea, C.K., Ramakrishnan, P., Taganov, K.D., Zhao, J.L., Baltimore, D., 2012b. miR-146a controls the resolution of T cell responses in mice. J. Exp. Med. 209, 1655–1670 [PubMed: 22891274].
Yenmis, G., Oner, T., Cam, C., Koc, A., Kucuk, O.S., Yakicier, M.C., Dizman, D., Kanigur Sultuybek, G., 2015. Association of NFKB1 and NFKBIA polymorphisms in relation to susceptibility of Behçet's disease. Scand. J. Immunol. 81 (January (1)), 81–86. https://doi.org/10.1111/sji.12251.
Zeiser, R., Blazar, B.R., 2017. Acute graft-versus-host disease - biologic process, prevention, and therapy. N. Engl. J. Med. 377 (November (22)), 2167–2179. https://doi.org/10.1056/NEJMra1609337.
Zeiser, R., 2018. Biology-driven developments in the therapy of acute graft-versus-host disease. Hematology Am. Soc. Hematol. Educ. Program 2018 (November (1)), 236–241. https://doi.org/10.1182/asheducation-2018.1.236.
Zeligs, K.P., Neuman, M.K., Annunziata, C.M., 2016. Molecular pathways: the balance between Cancer and the immune system challenges the therapeutic specificity of targeting nuclear Factor-κB signaling for Cancer treatment. Clin. Cancer Res. 22 (September (17)), 4302–4308. https://doi.org/10.1158/1078-0432.CCR-15-1374. Epub 2016 Jul 15.
Zeng, Y., Sun, Q.M., Liu, N.N., Dong, G.H., Chen, J., Yang, L., Wang, B., 2010. Correlation between pre-miR-146a C/G polymorphism and gastric cancer risk in Chinese population. World J. Gastroenterol. 16 (July (28)), 3578–3583.
Zhang, L., Yu, J., Wei, W., 2018. Advance in targeted immunotherapy for graft-versus-Host disease. Front. Immunol. 9 (May 16), 1087. https://doi.org/10.3389/fimmu.2018.01087. eCollection 2018. Review.
Zheng, C.Z., Shu, Y.B., Luo, Y.L., Luo, J., 2017. The role of miR-146a in modulating TRAF6-induced inflammation during lupus nephritis. Eur. Rev. Med. Pharmacol. Sci. 21 (March (5)), 1041–1048.
Zhong, H., May, M.J., Jimi, E., Ghosh, S., 2002. The phosphorylation status of nuclear NF-kB determines its association with CBP/p300 or HDAC-1. Mol. Cell 625–636.
Zou, Y.F., Wang, F., Feng, X.L., Tao, J.H., Zhu, J.M., Pan, F.M., Su, H., 2011. Association of NFKB1 -94ins/delATTG promoter polymorphism with susceptibility to autoimmune and inflammatory diseases: a meta-analysis. Tissue Antigens 77 (January (1)), 9–17. https://doi.org/10.1111/j.1399-0039.2010.01559.x. Epub 2010 Sep 6.