Short Conceptual Overview

Natalia Cullell, Elena Muiño, Caty Carrera, Nuria Torres, Jerzy Krupinski and Israel Fernandez-Cadenas*

Role of TRAF3 in neurological and cardiovascular diseases: an overview of recent studies

DOI 10.1515/bmc-2017-0008
Received February 23, 2017; accepted June 10, 2017

Abstract: Tumour necrosis factor receptor-associated factor 3 (TRAF3) is a member of the TRAF adaptor protein family, which exerts different effects on the cell depending on the receptor to which it binds and the cell type in which it is expressed. TRAF3 is a major regulator of the innate immune response. To perform its functions properly, *TRAF3* is transcriptionally and epigenetically regulated. At the transcriptional level, *TRAF3* expression has been associated with neurological and cardiovascular diseases including stroke, among other pathologies. Epigenetic modifications of *TRAF3* have been observed at the histone and DNA levels. It has been observed that acetylation of *TRAF3*, as well as other NF-κβ target genes, is associated with cardiac hypertrophy. Furthermore, *TRAF3* methylation has been associated with vascular recurrence after ischemic stroke in patients treated with clopidogrel. In this overview, we summarise the most interesting studies related to transcriptional and epigenetic regulation of *TRAF3* focusing on those studies performed in neurological and cardiovascular diseases.

***Corresponding author: Israel Fernandez-Cadenas,** Stroke Pharmacogenomics and Genetics Laboratory, Fundació Docència i Recerca Mútua Terrassa, Hospital Mútua de Terrassa, C/Sant Antoni 19, E-08221, Terrassa, Barcelona, Spain, e-mail: israelcadenas@yahoo.es
Natalia Cullell, Elena Muiño and Nuria Torres: Stroke Pharmacogenomics and Genetics Laboratory, Fundació Docència i Recerca Mutua Terrassa, Hospital Mutua de Terrassa, C/Sant Antoni 19, E-08221 Terrassa (Barcelona), Spain. http://orcid.org/0000-0001-5118-1014 (N. Cullell)
Caty Carrera: Stroke Pharmacogenomics and Genetics Laboratory, Fundació Docència i Recerca Mutua Terrassa, Hospital Mutua de Terrassa, C/Sant Antoni 19, E-08221 Terrassa (Barcelona), Spain; and Neurovascular Research Laboratory, Universitat Autònoma de Barcelona, Vall d'Hebron Institute of Research (VHIR), Passeig de la Vall d'Hebron 119-129, E-08035 Barcelona, Spain
Jerzy Krupinski: Neurology Service, Hospital Mútua de Terrassa, Pl. Dr. Robert, 5, E-08221 Terrassa (Barcelona), Spain; and School of Healthcare Science, Manchester Metropolitan University, Chester Street, Manchester M1 5GD, UK

Keywords: epigenetics; EWAS; genetics; stroke; TRAF3.

Introduction

The tumour necrosis factor receptor-associated factor (TRAF) family is composed of adaptor proteins which mediate different transduction signal pathways through different receptors: tumour necrosis factor receptors (TNFRs), toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs) and other cytokine receptors (1–3). These receptors mediate transduction signals of cell survival, proliferation, differentiation, activation and migration. There are seven members of the TRAF family (TRAF 1–7). TRAF2, 3 and 6 are expressed in almost all cell types and tissues, whereas TRAF1, 4 and 5 have a more restrictive expression pattern. Structurally (Figure 1), all the TRAF members have a TRAF domain in the C-terminal. The TRAF domain is divided into TRAF-N and TRAF-C. The TRAF-N domain is helical and is folded into a coiled coil to allow oligomerisation of TRAF proteins. The TRAF-C domain promotes oligomerisation and interaction with cytoplasmic factors. TRAF7 does not have a TRAF-C domain; instead, it has seven WD40 domains. All TRAFs have a RING-finger domain in the N-terminal, except TRAF1, plus a variable number of zinc finger motifs. TRAF2, 3, 5 and 6 have five zinc fingers, TRAF1 has only one zinc finger and TRAF4 has seven zinc fingers (4, 5). The RING and zinc finger domains are necessary for the transduction of signals (6) participating in the activation of the kinases cascade (7).

The most studied pathways activated by TRAF members are NF-κβ and AP-1 transcription factor pathways (8). NF-κβ is related with cell proliferation, survival and differentiation. TRAFs are also involved in immunological and inflammatory responses through the induction of the transcription factors NF-κβ and interferon-regulatory factor (IRF) (4, 9). AP-1 is a dimeric transcription factor not only related with proliferation and survival signals but also with apoptotic and stress signals (7).

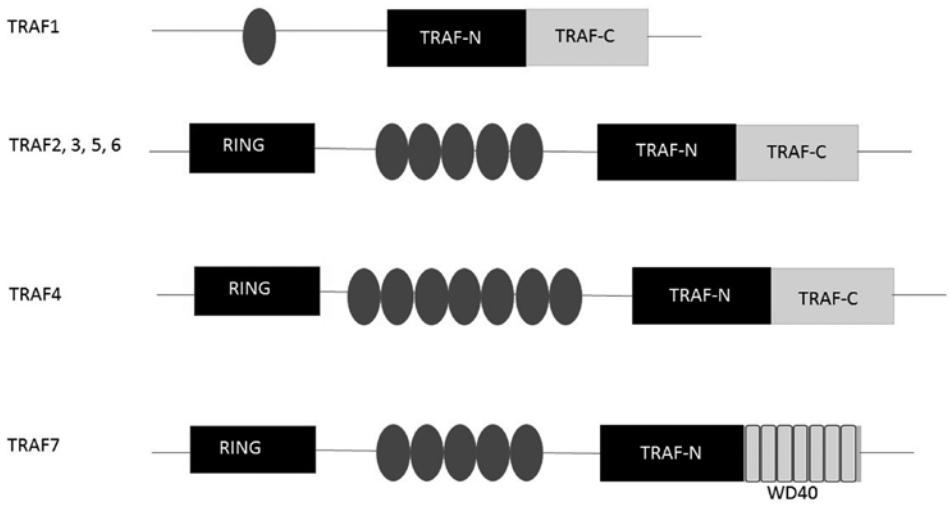

Figure 1: TRAF structures. In the N-terminal, all TRAF members contain a RING-finger domain (RING), except TRAF1. In the C-terminal, all TRAF members have the TRAF domain, divided into TRAF-N and TRAF-C domains. TRAF7 does not contain the TRAF-C domain. Instead, it has seven WD40 domains. Between the N-terminal and C-terminal, all the members contain zinc finger motifs, represented as ovals. The number of zinc fingers is different among TRAF members.

The different members of the TRAF family have divergent and non-redundant roles, but they also have overlapping roles in the control of cellular processes and the regulation of multiple signal transduction pathways (4).

TRAF3 regulates multiple pathways through its interaction with receptors, adaptors, kinases and regulatory proteins (10, 11). The main pathways regulated by TRAF3 are the canonical and non-canonical NF-κβ pathway (12) and the JNK pathway (13).

TRAF3 is an inhibitor of the non-canonical NF-κβ activation induced by the lymphotoxin-β receptor (LTβR) and the canonical NF-κβ pathway, thus inhibiting the inflammatory response (Table 1) (8, 12).

TRAF3 is a critical regulator of the antiviral innate response and interferon (IFN) I production (8). As TRAF3 controls the innate and adaptive immune responses, its deficiency implies the development of immunodeficiency syndromes (Table 1) (12). TRAF3 degradation plays an important role in activating the canonical and non-canonical NF-κβ pathways leading to the production of IFN. However, in other cases, TRAF3 exerts the opposite effect in the regulation of NF-κβ activation (14).

TRAF3 is a negative regulator of JNK but in some circumstances, for instance, when TRAF3 is myristoylated, it can be a positive regulator of JNK. After a stroke, JNK is important in regulating inflammation and neuronal survival (Table 1) (13).

One example of JNK positive regulation mediated by TRAF3 is produced when latent membrane protein 1 (LMP1) encoded by the Epstein-Barr virus (EBV) is active. TRAF3 is necessary for sustained B cells activation mediated by LMP1 through the downstream activation of JNK and NF-κβ (Table 1) (14).

Table 1: TRAF3 functions at the cellular level, main affected pathways and pathologies associated with each function.

TRAF3 functions		
Cellular effects (references)	**Main affected pathways**	**Pathologies**
Inflammatory response inhibition (8, 12, 13, 19)	NF-κβ and JNK	Atherosclerosis, myocardial hypertrophy
Innate and adaptive immune response regulation (8, 12)	NF-κβ	Immunodeficiency syndromes, HIV and other viral infections
Apoptosis activation (13, 15, 16)	NF-κβ, JNK and Rac-1	Stroke, SCI
B cell activation (14)	NF-κβ and JNK	Multiple myeloma, EBV infection
Microglia activation (17)	MAPK and NF-κβ	Multiple sclerosis
Osteoclastogenesis (21)	NF-κβ	Osteoporosis
Platelet aggregation (23)		Vascular recurrence in patients treated with clopidogrel

HIV, human immunodeficiency virus; SCI, spinal cord injury; EBV, Epstein-Barr virus.

In addition, CD40, a TNF receptor, and LMP1 share TRAF3 for signal transduction in the activation of B cells (14). Interestingly, mutations which inactivate TRAF3 are associated with B cell diseases, especially multiple myeloma (15).

TRAF3 also mediates apoptosis in some cellular types. In some studies, it has been shown that TRAF3 has a proapoptotic effect when it binds to CD40. It has also proapoptotic effects when it binds to the JNK upstream kinase ASK1 (16).

TRAF3 expression

The expression and mRNA levels of *TRAF3* are regulated under different conditions. In stroke, TRAF3 is associated with neuronal death (11, 13), although other associations with other neurological conditions such as spinal cord injury (SCI) (15) and multiple sclerosis (17) have also been observed. In cardiovascular disease, an altered expression of TRAF3 is related with cardiac hypertrophy (10), atherosclerosis (18, 19) and arterial injury (20).

TRAF3 and neurological deterioration

In a study performed using a mouse model of stroke with middle cerebral artery occlusion (MCAO), TRAF3 was found overexpressed in neurons from the hippocampus, cortex and striatum after ischaemia/reperfusion injury. This overexpression was associated with neuronal loss and larger infarct size. The authors found that TRAF3 interacts with TAK1 at the C-terminal domain and facilitates its phosphorylation and activation, which activates the NF-κβ, Rac-1/NADPH oxidase and c-Jun kinase/c-Jun pathways. The interaction of TRAF3 with TAK1 was responsible for the neuronal death produced in MCAO mice. Inhibition of TRAF3 or TAK1 suppressed this neuronal death (13). TRAF3 increased Rac-I phosphorylation and thereby, NADPH mRNA was overexpressed (13). Higher levels of antiapoptotic proteins (BCL-2) from the apoptotic mitochondrial signalling pathway were observed compared with the levels of proapoptotic proteins (Fas, FasL, Bax and Bad) in *TRAF3* knockout mice. Overexpression of TRAF3 reversed this effect, confirming that TRAF3 plays a role in the suppression of antiapoptotic protein expression and activation of proapoptotic protein expression (13).

Another study observed the same association between TRAF3 and neuronal death and infarct size (Table 1) (11). The authors observed that the inhibition of TRAF3 expression by miR-455 binding reduced infarct size in mice brains after MCAO and suppressed neuronal death in cortical neuronal culture after oxygen-glucose deprivation (11). After MCAO, levels of miR-455 decreased, increasing TRAF3 expression, which in turn increased neuronal death and, thereby, infarct size (11).

This association of TRAF3 with neuronal death and infarct size after ischaemia in mouse models of stroke has led some authors to postulate its potential role as a drug target to reduce poor outcomes after ischaemic stroke (13).

TRAF3 and neurological diseases

TRAF3 was observed to be upregulated in SCI in mice, with a peak on day 1 after the injury. SCI is mediated by two steps. In the first one, tissue detrition and necrosis occurs after the external injury. The second one involves an apoptotic process, oedema formation, electrolytic imbalance, ischaemia and inflammation, among other processes (15).

Upregulation of TRAF3 and its peak on day 1 was correlated with overexpression of proapoptotic proteins from the apoptotic mitochondrial pathway. It was also associated with increased active caspase 3 and phosphorylated JNK, and at the same time with a decrease in antiapoptotic proteins (Table 1). In accordance with these findings, TRAF3 affects JNK phosphorylation and activation to induce cellular apoptosis, a common phenotype after SCI. Whether this molecular mechanism can be generalised to other central nervous system injuries has yet to be evaluated (15).

Another study found that TRAF3 expression was crucial for the Peli1-induced microglia activation in an experimental model of multiple sclerosis (17). Peli1 is an E3 ubiquitin ligase highly expressed in microglia, which regulates microglia activation through the regulation of a signalling pathway which leads to TRAF3 degradation (Table 1) (17).

TRAF3 and cardiovascular disease

Cardiac hypertrophy is an early condition of heart failure and different stimuli lead to this condition, such as hypertension or ischaemia. TRAF3 was identified in a study with mice and failing human hearts as a regulator of cardiac hypertrophy in response to high pressure levels (10). As expected, *TRAF3* knockout mice had significantly lower cardiac hypertrophy, fibrosis and dysfunction (10). In contrast, transgenic mice with an overexpression of

TRAF3 had increased hypertrophy, fibrosis and heart dysfunction (10). It seems that the mechanism by which TRAF3 mediates the development of hypertrophy is through binding with TBK1 and subsequent TBK1 phosphorylation (10).

TRAF3 was also found upregulated in murine and human atheromatous plaques compared with fibrous plaques (18). When *TRAF3* was silenced in isolated human and murine endothelial cells, IL-6, MCP-1 and IL-8 were overexpressed. These results support the inhibitory role of TRAF3 in CD40L-induced proinflammatory gene expression (Table 1). The stimulation of endothelial cells with IL-1β and TNFα also induced the expression of TRAF3 (18). Similarly, atherosclerosis was related with CD40 stimulation in another study (19). It was found that the atheroprotective property of shear stress is mediated by TRAF3 upregulation in isolated human endothelial cells (19).

Another study evaluated the role of CD40 and TRAF proteins in the underlying mechanism of restenosis (neointima formation) after artery injury in mice (20). The authors observed upregulation of CD40, TRAF proteins, including TRAF3, NF-κβ p65 and phospho-NF-κβ p65 in the injured carotid artery (20).

TRAF3 and other conditions

Other conditions in which TRAF3 expression is affected are osteoclastogenesis (21) and viral infection, such as human immunodeficiency virus (HIV) infection (12).

One study evaluated the role of TRAF3 in osteoclastogenesis induced by the cytokine RANKL (Table 1) (21). The authors found that TRAF3 limited osteoclast formation induced by RANKL, through inhibition of the canonical and non-canonical NF-κβ pathways (21).

In viral infection (12, 22), increased expression of miR-32 was correlated with the levels of HIV-1 Tat protein (associated with HIV-associated neurological disorder). Interestingly, the target of miR-32 is TRAF3. This interaction inhibits TRAF3 expression in microglial cells, enabling the production of IFN through IRF7 activation (Table 1) (12).

TRAF3 epigenetics

Epigenetic modifications are stable, heritable and reversible changes which are modulated by multiple factors such as genetics, environment and different phenotypes (22). Different pathologies, such as cardiovascular diseases, are associated with epigenetic alterations (23, 24).

Different epigenetic modifications such as histone modifications, DNA methylation and mechanisms acting on RNA, mainly microRNAs (miRNAs), can modulate gene transcription (23, 24).

The main histone modification is histone acetylation. Histones are the basic unit of the nucleosomes. The N-terminal tails of histones are modified by histone acetyl transferases (HATs) and histone deacetylases (HDACs), which acetylate and deacetylate, respectively. Acetylation is usually associated with gene activation while deacetylation is usually associated with gene inactivation (25).

DNA methylation consists of the addition of a methyl group to the 5′ carbon of a cytosine, mainly in the context of cytosine and guanine dinucleotide (CpG site) (24). DNA methylation is usually associated with transcription repression, in contrast with unmethylated DNA, usually associated with active transcription (23–25).

MiRNAs are small molecules consisting of 20–25 nucleotides which are bound to the RNA-induced silencing complex (RISC) to target specific mRNA sequences, mainly in the 3′ UTR, to inhibit their transcription (23). As mentioned above, *TRAF3* expression could be regulated by an miRNA, miR-455 (11).

TRAF3 was found to be epigenetically regulated in three conditions: cardiac hypertrophy (25), acute lymphoblastic leukaemia (ALL) (26) and vascular recurrence in patients treated with clopidogrel (22).

In a study analysing the role of acetylation/deacetylation in myocardial hypertrophy, the authors found an altered acetylation pattern in mice with myocardial hypertrophy compared with controls. It was observed that cardiac hypertrophy was associated with increased acetylation and activation of *TRAF3* and other NF-κβ target genes. HDAC inhibition was associated with an anti-inflammatory effect and, therefore, with cardio-protection through histone deacetylation and inactivation of NF-κβ target genes, including *TRAF3* (25).

Regarding the epigenetic regulation of *TRAF3* in ALL, the genome-wide methylation profile was analysed in ALL using methylated CpG island recovery assay followed by next-generation sequencing (26). Then, the authors performed whole-transcriptome analysis and integrated this data with the methylation data. The study found more than 25 000 differentially methylated regions (DMRs). The authors found DMRs in ‘enhancer-like’ regions, in which altered methylation was associated with altered expression in neighbouring genes. Among these genes, *TRAF3* was downregulated by hypermethylation of an ‘enhancer-like’ region (26).

In addition, *TRAF3* methylation has been associated with vascular recurrence after ischaemic stroke in patients treated with clopidogrel. Patients suffering ischaemic stroke present a higher risk of suffering new cardiovascular events. To prevent vascular recurrence, antiplatelet agents such as clopidogrel are administered in these higher risk patients. However, despite antiplatelet treatment, 10%–20% of the patients develop a recurrent vascular event. Using an epigenome-wide association study (EWAS) in 42 patients, 21 with vascular recurrence and 21 without vascular recurrence, and analysing over 480 000 DNA methylation sites, it was observed that lower methylation levels of *TRAF3* were associated with a higher risk of new vascular events. These results were replicated in a new cohort of 191 patients. In addition, the methylation levels of *TRAF3* were associated with platelet aggregation activity (22).

Conclusions

To summarise, TRAF3 is regulated in multiple ways affecting disease status. TRAF3 undergoes regulation at the mRNA level as well as at the DNA and histone levels by epigenetic modification.

It is important to highlight the relevant role of transcriptional regulation of *TRAF3*, which is caused primarily by epigenetic modifications. These modifications affect the regulation of TRAF3 exerted on atherothrombotic processes, and are associated with vascular recurrence in patients treated with clopidogrel and the formation of atheromatous plaques. These findings suggest that epigenetics could play an important role in cardiovascular diseases, and particularly in TRAF3 regulation, and this should be further studied.

The critical role of TRAF3 in multiple diseases makes it a good candidate as a target for treatment therapies, such as treatment of neurological deterioration after ischaemic stroke.

Compared with the large number of studies on the expression level of *TRAF3*, little is known about the epigenetics of *TRAF3*. In the future, functional analyses studying the effects of *TRAF3* epigenetic modifications are necessary.

List of abbreviations

TRAF3	tumour necrosis factor receptor-associated factor 3
TNFR	tumour necrosis factor receptors
TLRs	toll-like receptors
RLRs	RIG-I-like receptors
NLRs	NOD-like receptors
IRF	interferon-regulatory factor
LTβR	lymphotoxin-β receptor
IFN	interferon
LMP1	latent membrane protein 1
EBV	Epstein-Barr virus
MCAO	middle cerebral artery occlusion
SCI	spinal cord injury
HIV	human immunodeficiency virus
miRNAs	microRNAs
HAT	histone acetyl transferases
HDAC	histone deacetylases
RISC	RNA-induced silencing complex
ALL	lymphoblastic leukaemia
DMRs	differentially methylated regions
EWAS	epigenome-wide association study.

Acknowledgements: This work was supported by a grant from the Carlos III Institute of Health (PI15/01978) and by Boehringer Ingelheim funding. We thank the International Stroke Genetics Consortium (ISGC), the Spanish Stroke Genetics Consortium (www.genestroke.com) and the RETICS Network INVICTUS, which The Neurovascular Pharmacogenomics and Genetics Laboratory are part of.

References

1. Yang XD, Sun SC. Targeting signaling factors for degradation, an emerging mechanism for TRAF functions. Immunol Rev 2015; 266: 56–71.
2. So T, Nagashima H, Ishii N. TNF receptor-associated factor (TRAF) signaling network in CD4(+) T-lymphocytes. Tohoku J Exp Med 2015; 236: 139–54.
3. Xie P. TRAF molecules in cell signaling and in human diseases. J Mol Signal 2013; 8: 7.
4. Wang Y, Zhang P, Liu Y, Cheng G. TRAF-mediated regulation of immune and inflammatory responses. Sci China Life Sci 2010; 53: 159–68.
5. Inoue J, Ishida T, Tsukamoto N, Kobayashi N, Naito A, Azuma S, Yamamoto T. Tumor necrosis factor receptor-associated factor (TRAF) family: adapter proteins that mediate cytokine signaling. Exp Cell Res 2000; 254: 14–24.
6. Bishop GA, Hostager BS, Brown KD. Mechanisms of TNF receptor-associated factor (TRAF) regulation in B lymphocytes. J Leukoc Biol 2002; 72: 19–23.
7. Ha H, Han D, Choi Y. TRAF-mediated TNFR-family signaling. Current Protocols in Immunology. 2009. Chapter 11:Unit11.9D.
8. He JQ, Oganesyan G, Saha SK, Zarnegar B, Cheng G. TRAF3 and Its Biological Function. In: TNF Receptor Associated Factors (TRAFs). New York, NY: Springer New York, 2007: 48–59.
9. Gerondakis S, Fulford TS, Messina NL, Grumont RJ. NF-κB control of T cell development. Nat Immunol 2014; 15: 15–25.
10. Jiang X, Deng K-Q, Luo Y, Jiang D-S, Gao L, Zhang X-F, Zhang P, Zhao G-N, Zhu X, Li H. Tumor necrosis factor receptor-associated

factor 3 is a positive regulator of pathological cardiac hypertrophy. Hypertens (Dallas, Tex 1979) 2015; 66: 356–67.
11. Yao S, Tang B, Li G, Fan R, Cao F. miR-455 inhibits neuronal cell death by targeting TRAF3 in cerebral ischemic stroke. Neuropsychiatr Dis Treat 2016; 12: 3083–92.
12. Mishra R, Chhatbar C, Singh SK. HIV-1 Tat C-mediated regulation of tumor necrosis factor receptor-associated factor-3 by microRNA 32 in human microglia. J Neuroinflammation 2012; 9: 131.
13. Gong J, Li Z-Z, Guo S, Zhang X-J, Zhang P, Zhao G-N, Gao L, Zhang Y, Zheng A, Zhang X-F, Xiang M, Li H. Neuron-specific tumor necrosis factor receptor–associated factor 3 is a central regulator of neuronal death in acute ischemic strokenovelty and significance. Hypertension 2015; 66: 604–16.
14. Xie P, Hostager BS, Bishop GA. Requirement for TRAF3 in signaling by LMP1 but not CD40 in B lymphocytes. J Exp Med 2004; 199: 661–71.
15. Wu Y, Zheng M, Wang S, Song C, Wang C, Xiao Y, Xu L, Xu X. Spatiotemporal pattern of TRAF3 expression after rat spinal cord injury. J Mol Histol 2014; 45: 541–53.
16. Gu H, Yu J, Dong D, Zhou Q, Wang J-Y, Yang P. The miR-322-TRAF3 circuit mediates the pro-apoptotic effect of high glucose on neural stem cells. Toxicol Sci 2015; 144: 186–96.
17. Xiao Y, Jin J, Chang M, Chang J-H, Hu H, Zhou X, Brittain GC, Stansberg C, Torkildsen Ø, Wang X, Brink R, Cheng X, Sun S-C. Peli1 promotes microglia-mediated CNS inflammation by regulating Traf3 degradation. Nat Med 2013; 19: 595–602.
18. Zirlik A, Bavendiek U, Libby P, MacFarlane L, Gerdes N, Jagielska J, Ernst S, Aikawa M, Nakano H, Tsitsikov E, Schönbeck U. TRAF-1, -2, -3, -5, and -6 are induced in atherosclerotic plaques and differentially mediate proinflammatory functions of CD40L in endothelial cells. Arterioscler Thromb Vasc Biol 2007; 27: 1101–7.
19. Urbich C, Mallat Z, Tedgui A, Clauss M, Zeiher AM, Dimmeler S. Upregulation of TRAF-3 by shear stress blocks CD40-mediated endothelial activation. J Clin Invest 2001; 108: 1451–8.
20. Song Z, Jin R, Yu S, Rivet JJ, Smyth SS, Nanda A, Granger DN, Li G. CD40 is essential in the upregulation of TRAF proteins and NF-kappaB-dependent proinflammatory gene expression after arterial injury. Zernecke A, editor. PLoS One. 2011; 6: e23239.
21. Xiu Y, Xu H, Zhao C, Li J, Morita Y, Yao Z, Xing L, Boyce BF. Chloroquine reduces osteoclastogenesis in murine osteoporosis by preventing TRAF3 degradation. J Clin Invest 2014; 124: 297–310.
22. Gallego-Fabrega C, Carrera C, Reny J-L, Fontana P, Slowik A, Pera J, Pezzini A, Serrano-Heras G, Segura T, Martí-Fàbregas J, Muiño E, Cullell N, Montaner J, Krupinski J, Fernandez-Cadenas I. TRAF3 epigenetic regulation is associated with vascular recurrence in patients with ischemic stroke. Stroke. 2016; 47: 1180–6.
23. Udali S, Guarini P, Moruzzi S, Choi SW, Friso S. Cardiovascular epigenetics: from DNA methylation to microRNAs. Vol. 34, Mol Aspects Med 2013; 34: 883–901.
24. Zhang Y, Zeng C. Role of DNA methylation in cardiovascular diseases. Clin Exp Hypertens 2016;38: 261–7.
25. Ooi JYY, Tuano NK, Rafehi H, Gao XM, Ziemann M, Du XJ, El-Osta A. HDAC inhibition attenuates cardiac hypertrophy by acetylation and deacetylation of target genes. Epigenetics 2015; 10: 418–30.
26. Almamun M, Levinson BT, Van Swaay AC, Johnson NT, McKay SD, Arthur GL, Davis JW, Taylor KH. Integrated methylome and transcriptome analysis reveals novel regulatory elements in pediatric acute lymphoblastic leukemia. Epigenetics 2015; 10: 882–90.