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Review Article

The Roll of Nfkb in Aneurysms-A Mini Review

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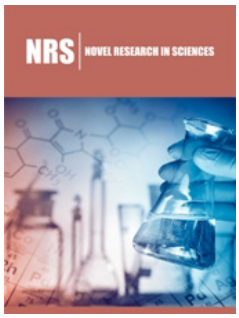

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Introduction

The transcription factor nuclear factor-κappa B (NF-κB) regulates cell growth and maturation on the one hand, and NF-κB is a component of signaling pathways of immune defense and inflammation on the other. After its activation, it migrates from the cytoplasm of the cell to the nucleus. Activated via a variety of stimuli such as viruses, bacteria, cytokines, free radicals, carcinogens, tumor promoters, and endotoxins, NF-κB regulates the expression of nearly 400 different genes, including enzymes (COX-2 and iNOS), cytokines (TNF, IL-1, IL-6, IL-8, and chemokines), which influence the production of adhesion molecules, cell cycle regulatory molecules, viral proteins, and angiogenic factors. The reciprocal influence of NF-κB and the genes activated by NF-κB is highly complex. For example, TNF-α activates NF-κB, which itself transcriptionally induces TNF-α. A similarly complex induction pathway exists between NF-κB and COX-2 prostaglandin E2-EP2-NF-κB pathway. COX-2 induced by hemodynamic stress induces and produces prostaglandin E2, which further induces NF-κB. Constitutive NFkB activation is involved in the pathogenesis of cancer, diabetes, allergy, rheumatoid arthritis, Crohn's disease, cardiovascular disease, atherosclerosis, and other diseases. Among others, its role in various aneurysms has been highlighted. The present work provides some complex interactions of NF-κB in the context of various aneurysms.

General inflammatory response

In the pathogenesis of aneurysms, vascular inflammation starting from activated stromal cells represents a major pathomechanism [1]. In this process, the cytokines IL-6, IL-1β, and the MCP-1 chemokine receptor CCR2 appear to play a central role [2-4]. In contrast, deficiency of AT1aR (Ang-II type 1a receptor), pattern recognition receptor TLR4 (Toll-like receptor 4), and adaptor protein MyD8836 exerts a protective effect, suggesting the key role of proinflammatory transcription factor NF-κB/RelA [5,6]. In the Ang II model of AAA, an interaction between proliferating resident adventitial fibroblasts with infiltrating monocytes has been shown several times. This activates an ECM destruction-promoting cytokine amplification loop. Therefore, loss of vascular integrity and aortic dilatation is preceded by adventitial inflammation [7]. A subpopulation of fibroblasts, namely the specialized myofibroblasts and Col1A-expressing synthetic VSMCs, plays an important role in fibrosis and

formation/remodeling of the aortic ECM [8,9]. Ang II leads to RelA activation and IL-6 production in both the adventitial and medial layers of the abdominal aorta [10].

Endothelial NF-κB signaling

Endothelial NF-κB signaling not only promotes leukocyte-endothelium interaction in the vasa vasorum, a necessary step toward Ang II-induced aneurysms [11]. A significant association of the common 1166C variant of the angiotensin II type 1a receptor gene with AAA was demonstrated in 3 independent, geographically distinct but ethnically similar case-control cohorts [12]. The AGTR1 1166C risk association is not with peripheral or coronary artery disease. Although AAA and atherosclerotic occlusive pAVD represent distinct pathophysiological entities, a large association of MMP9 C-1562T SNP and AGTR1 1166C genotypes was found between AAA and patients with peripheral arterial disease [13].

NF-κB and the perivascular adipose tissue (PVAT)

A growing interest in large artery disease is the transcriptome of Perivascular Adipose Tissue (PVAT), as this plays a basic role in the regulation of vascular physiology and its dysfunction influences the development of dilated and atherosclerotic aortic disease [14-19]. Only by focusing research not only on the aortic wall but also on the perivascular adipose tissue has it been possible to gain insight into the complicated pathomechanism of AAA development. In this regard, an altered immune response in the perivascular adipose tissue represents a crucial pathogenetic element for the development of AAA [20-22]. Reconstruction of regulatory networks shows that the combination of multiple pathobiological factors (disease genes, hubs) in complex relationships with each other lead to the development of AAA [23]. Thus, in addition to SPIB and TBP (i.e., "hub" TFs), NFKB1 has been identified as the major regulator of the resulting gene regulatory network because it exhibits the greatest connectivity with co-expressed genes associated with diseased PVAT [22]. Most importantly, on the one hand, the NFKB1 transcriptional cluster leads to positive regulation of lymphocyte proliferation and, together with TBP, to the expression of genes involved in the innate immune response, i.e., Toll-Like Receptor (TLR) signaling [22,24,25].

In addition, NFKB1, REL, and RELA may affect T-cell proliferation, macrophage infiltration, and osteoclastogenic dehydration in different ways. At the end of this activation chain is the inflammatory response in vascular smooth muscle cells and mesenchymal cells [26-30]. In addition, the protein kinases MAPK1 and GSK3B and the nuclear receptor RXRA (a type of retinoid X receptor) play critical roles in the pathogenesis of AAA. Directly, MAPKs and GSK3s are mainly involved in innate immunity including TLR-related signaling, including TLR-related signaling that modulates the activity of matrix metalloproteinases during AAA formation [31,32]. Regulation of the ERK1 and ERK2 cascade in the perivascular adipose tissue transcriptome via the NFKB1, SPIB, and TBP transcriptional clusters highlights the role of NFKB1 and protein kinases in aneurysm formation [33,34]. Although inhibition of angiotensin type 1 receptor in vascular smooth muscle cells by activation of retinoid X receptors (RXR activation) may influence AAA development, this mechanism is not considered to be important [35-37]. Other protein kinases, albeit with less importance in the regulatory network, such as histone deacetylase 1 (HDCA1), may also directly interact with NFKB1 and with TBP to influence AAA development [38,39]. In close interaction, perivascular adipocytes secrete soluble factors e.g., adipokines, chemokines, or proinflammatory, which may lead to NF-kB activation [40,41].

NF-κB and hub genes

Molecular Complex Detection (MCODE) identified a total of 55 hub genes, of which the genes for positive regulation of cytosolic calcium ion concentration, lymphocyte activation, and regulation of cytosolic calcium ion concentration were found to be the most important for the development of AAA [42]. The hub genes in MCODE 6, hsa04064, R-HSA-5668541, and R-HSA-5676594 can activate the NF-kappa B pathway via tumor necrosis factor (TNF) [42,43]. The other three genes lymphotoxin-α and -β (LTA=TNF-β and LTB) and TNF receptor-associated factor 3 (TRAF3) can lead to NF-kappa B activation [44-46]. Angiotension II (Ang II) is able to increase the expression of phospho-p65 P65 subunit of NF-kB, which itself has been shown to induce a pro-inflammatory state leading to the increased expression of MMP9, MCP1, VCAM1, ICAM1, and IL1beta [47-49]. Direct interaction of FKBP11 with the NF-kB p65 subunit promotes endothelial inflammation through secretion of pro-inflammatory cytokines [49].

NF-κB and ALOX5

The reciprocal action of ALOX5 and Nfkb contributes significantly to the formation of AAA. ALOX5 encodes the enzyme arachidonate-5-lipoxygenase in the eicosanoid synthesis pathway, which, in conjunction with the ALOX5AP protein [24], catalyzes the conversion of 5-HPETE to leukotriene A4 (LTA4) [50]. This in turn promotes proinflammatory leukotriene biosynthesis [51]. Increasing leukotriene B4 signaling increases immune cell infiltration [52]. Cathepsin K (CTSK) is also modulated by ALOX5, which directly affects AAA development through collagen turnover, T-cell proliferation, and apoptosis [53-55]. Down-regulation of miRNA-125b-5p and miR-193a-3p in AAA tissues leads to up-regulation of the ALOX5 gene, which initiates primary aortic wall inflammation in AAA development via leukotriene production [56,57]. As a general inflammatory response, increased expression of 5-LOX, NF-κB, and iNOS has already been found in ischemic cerebral ischemia [58-60]. Inhibition of NF-κB luciferase activity in vitro and translocation of p65 to the nucleus by the 5-LOX inhibitor BW-B 70C reinforces the hypothesis that 5-LOX/NF-κB signaling results from its direct interaction with the p65 subunit of NF-κB [57,61,62]. Decreased iNOS expression by BW-B 70C argues for primary activation of 5-LOX upon inflammation, which then initiates NF-κB and iNOS expression [57].

NF-κB and cyclooxygenase 2 (COX-2)

Cyclooxygenase 2 (COX-2), known as prostaglandin synthase-2, catalyzes the isomerization of the COX product prostaglandin H2 to prostaglandin E2, which itself initiates nuclear factor-κB expression

via activation from the endothelial prostaglandin receptor [61-67]. On the one hand, COX-2 expression is initiated by the involvement of protein kinase C (PKC), Ras, and Wnt signaling pathways through the activation of mitogen-activated protein kinase (MAPK), kinase family proteins such as extracellular-signal-regulated kinas (ERK), C-Jun N-terminal cinase (JNK), and p38 [68-72]. On the other hand, DNA binding sites for transcription factors NF-κB, AP1, cAMP response element-binding protein (CREB C/EBP), NF-IL6, MEF2, and transcription factor 4/LEF1 in the COX-2 promoter indicate their functional regulation of COX-2 transcription [73,74]. Nuclear factor-κB (NF-κB) plays a key role in both the initiation and progression of intracerebral aneurysms, in which macrophage recruitment via activation of inflammatory genes [75], vascular cell adhesion protein (VCAM)-1 and monocyte chemoattractant protein (MCP)-1 trigger endothelial dysfunction and initiate endothelial cell membrane (ECM) degradation through interleukin [IL]-1β-mediated downregulation of procollagen genes [76-80]. Besides, tumor necrosis factor-α, mitogen-activated protein kinases, ANRIL, also called CDKN2B-AS, CDKN2A/B, Krüppel-like factor 2, caspase recruitment domain family, member 8, etc., contribute a major part in the development of cerebral aneurysms [81-99].

NF-κB polymorphisms

Several NFKB polymorphisms can lead to the initiation of cardiovascular disease. One of the best known and regulating NF-κB expression and activity polymorphisms within the promoter of the NFKB1 gene is -94 ins/del ATTG rs28362491 [100], which show increased susceptibility to atherosclerosis. The (rs696) polymorhism in the 3'UTR region of the NFKBIA gene leads to an alteration in the expression of IκBα protein, an inhibitory version of NF-κB protein, which is also encoded by NFKB1A [101]. In apolipoprotein E (ApoE)-deficient mice, expression of the NF-κB inhibitor IκBα-superrepressor (DNIκBα) resulted in inhibition of atheromatous plaque development [102].

NF-κB and microRNAs

The role of microRNAs (mi RNAs) in the regulation of gene expression involved in inflammation is moving to the center of the etiology of cardiovascular disease [103,104]. In particular, mi-146a, an NF-κB target gene, is thought to play an essential role in inflammatory cardiovascular disease [105]. Single nucleotide polymorphisms (SNPs) of pre-miR-146a, for example, can modify the expression level of mature miRNA-146a and influence the progression of cardiovascular disease [106-108]. Based on this assumption, downregulation of miR-146a expression via interleukin-1 receptor-associated kinase 1 (IRAK-1), TNF receptor-associated factor 6 (TRAF6), and toll-like receptor -4 (TLR-4) by angiotensin receptor blockers and statins has been suggested [109,110]. A similar effect with delay of miR-146a expression has been attributed to estrogens and progesterone [111,112]. This may provide an explanation for the gender difference in the occurrence of aneurysms. Drugs in the statin group may have led to suppression of both miR-126-3p and miR-146a expression levels, thereby preventing aortic disease [113].

Other miRs have also been implicated in the very complex AAA development. Whereas miR-146a-5p is overexpressed in AAA tissue samples, miR 146a regulates inflammation in the AAA via CARD10 [114]. MiR-144-3p regulates ABCA1 in macrophages and influences the production of proinflammatory cytokines and thus plaque morphology through inhibition from reverse cholesterol transport [115-119]. In this context, the expressions of individual miR in AAA tissues and plasma of patients with AAA are controversial and also different. In this regard, some research groups found downregulation of miR-133b, miR-29b-3p, and miR-27b-3p in AAA tissues [120-124], whereas other authors found upregulation of the same [113,125]. Different plasma and AAA tissue levels of miR were pointed out several times for miR-221-3p and miR-27b-3p, among others [112,113,126-129]. However, miR-195 and miR-29b can also suppress AAA development via the TNF-α/NF-κB and VEGF/PI3K/Akt signaling pathways [130-132]. Surprisingly, the missing -94Ins/DelATTG promoter polymorphism in the transcription factor NF-Kb in patients with popliteal aneurysm has been recently reported, opening new molecular biological aspects in the development of aneurysms [133].

Conclusion

Nfkb as one of the main factors is involved in AAA development in many mutual complex processes, based on which new therapy approaches are being tested.

Conflict of Interest

I hereby declare that there were no financial or other interests in the execution and evaluation of this work.

References

1. Brasier AR (2010) The nuclear factor-kappaB-interleukin-6 signalling pathway mediating vascular inflammation. Cardiovasc Res 86(2): 211-218.
2. Tieu BC, Lee C, Sun H, Lejeune W, Recinos A, et al. (2009) An adventitial IL-6/MCP1 amplification loop accelerates macrophage-mediated vascular inflammation leading to aortic dissection in mice. J Clin Invest 119(12): 3637-3651.
3. Luchtefeld M, Grote K, Grothusen C, Bley S, Bandlow N, et al. (2005) Angiotensin II induces MMP-2 in a p47phox-dependent manner. Biochem Biophys Res Commun 328(1): 183-188.
4. Daugherty A, Rateri DL, Charo IF, Owens AP, Howatt DA, et al. (2010) Angiotensin II infusion promotes ascending aortic aneurysms: attenuation by CCR2 deficiency in apoE-/- mice. Clin Sci 118(11): 681-689.
5. Liu J, Sawada H, Howatt DA, Moorleghen JJ, Vsevolozhskaya O, et al. (2020) Hypercholesterolemia accelerates both the initiation and progression of angiotensin ii-induced abdominal aortic aneurysms. Ann Vasc Med Res 6(2): 1099.
6. Owens AP, Rateri DL, Howatt DA, Moore KJ, Tobias PS, et al. (2011) MyD88 deficiency attenuates angiotensin II-induced abdominal aortic aneurysm formation independent of signaling through toll-like receptors 2 and 4. Arterioscler Thromb Vasc Biol 31(12): 2813-2819.
7. Trachet B, Aslanidou L, Piersigilli A, Fraga RA, Sordet J, et al. (2017) Angiotensin II infusion into Apo E-/- mice: a model for aortic dissection rather than abdominal aortic aneurysm? Cardiovasc Research 113(10): 1230-1242.

8. Ponticos M, Smith BD (2014) Extracellular matrix synthesis in vascular disease: Hypertension, and atherosclerosis. J Biomed Res 28(1): 25-39.

9. Larsson E, Lean SE, Mecham RP, Lindahl P, Nelander S (2008) Do two mutually exclusive gene modules define the phenotypic diversity of mammalian smooth muscle? Mol Genet Genomics 280(2): 127-137.

10. Recinos A, LeJeune WS, Sun H, Lee CY, Tieu BC, et al. (2007) Angiotensin II induces IL-6 expression and the Jak-STAT3 pathway in aortic adventitia of LDL receptor-deficient mice. Atherosclerosis 194(1): 125-133.

11. Saito T, Hasegawa Y, Ishigaki Y, Yamada T, Gao J, et al. (2013) Importance of endothelial NF-κB signalling in vascular remodelling and aortic aneurysm formation. Cardiovasc Res 97: 106-114.

12. Jones GT, Thompson AR, Bockxmeer FM, Hafez H, Cooper JA, et al. (2008) Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arteriosclerosis, Thrombosis, and Vascular Biology 28(4): 764-770.

13. Zhang MM, Chang XW, Hao XQ, Wang H, Xie X, et al. (2018) Association between matrix metalloproteinase 9 C-1562T polymorphism and the risk of coronary artery disease: an update systematic review and meta-analysis. Oncotarget 9(10): 9468-9479.

14. Piacentini L, Werba JP, Bono E, Saccu C, Tremoli E, et al. (2019) Genome-wide expression profiling unveils autoimmune response signatures in the perivascular adipose tissue of abdominal aortic aneurysm. Arter Thromb Vasc Biol 39(2): 237-249.

15. Piacentini L, Saccu C, Bono E, Tremoli E, Spirito R, et al. (2020) Gene-expression profiles of abdominal perivascular adipose tissue distinguish aortic occlusive from stenotic atherosclerotic lesions and denote different pathogenetic pathways. Sci Rep 10: 6245.

16. Rajsheker S, Manka D, Blomkalns AL, Chatterjee TK, Stoll LL, et al. (2010) Crosstalk between perivascular adipose tissue and blood vessels. Curr Opin Pharmacol 10(2): 191-196.

17. Brown NK, Zhou Z, Zhang J, Zeng R, Wu J, et al. (2014) Perivascular adipose tissue in vascular function and disease: A review of current research and animal models. Arterioscler Thromb Vasc Biol 34(8): 1621-1630.

18. Liu Y, Sun Y, Hu C, Liu J, Gao A, et al. (2020) Perivascular adipose tissue as an indication, contributor to, and therapeutic target for atherosclerosis. Front Physiol 11: 615503.

19. Queiroz M, Sena CM (2020) Perivascular adipose tissue in age-related vascular disease. Ageing Res Rev 59: 101040.

20. Horimatsu T, Kim HW, Weintraub NL (2017) The role of perivascular adipose tissue in non-atherosclerotic vascular disease. Front Physiol 8: 969.

21. Estrelinha M, Hinterseher I, Kuivaniemi H (2014) Gene expression studies in human abdominal aortic aneurysm. Rev Vasc Med 2(3): 77-82.

22. Piacentini L , Chiesa M, Colombo GI (2020) Gene regulatory network analysis of perivascular adipose tissue of abdominal aortic aneurysm identifies master regulators of key pathogenetic pathways. Biomedicines. 8(8): 288.

23. Hao T, Wang Q, Zhao L, Wu D, Wang E, et al. (2018) Analyzing of molecular networks for human diseases and drug discovery. Curr Top Med Chem 18(12): 1007-1014.

24. Gerondakis S, Siebenlist U (2010) Roles of the NF-B pathway in lymphocyte development and function. Cold Spring Harb Perspect Biol 2(5): a000182.

25. Kawasaki T, Kawai IT (2014) Toll-like receptor signaling pathways. Front Immunol 5: 461.

26. Liu T, Zhang L, Joo D, Sun SC (2017) NF-κB signaling in inflammation. Signal Transduct Target Ther 2: 17023.

27. Shiraya S, Miwa K, Aoki M, Miyak, T, Oishi M, et al. (2006) Hypertension accelerated experimental abdominal aortic aneurysm through upregulation of nuclear factor b and Ets. Hypertension 48(4): 628-636.

28. Takei Y, Tanaka T, Kent KC, Yamanouchi D (2016) Osteoclastogenic dierentiation of macrophages in the development of abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 36(9): 1962-1971.

29. Cui R, Tieu B, Recinos A, Tilton RG, Brasier AR (2006) RhoA mediates angiotensin II-induced phospho-Ser536 nuclear factor kappaB/RelA subunit exchange on the interleukin-6 promoter in VSMCs. Circ Res 99(7): 723-730.

30. Ijaz T, Sun H, Pinchuk IV, Milewicz DM, Tilton RG, et al. (2017) Deletion of NF-B/RelA in angiotensin II-sensitive mesenchymal cells blocks aortic vascular inflammation and abdominal aortic aneurysm formation. Arterioscler Thromb Vasc Biol 37(10): 1881-1890.

31. Neece BT, Sharma K, Lawrence GW, Lawrence KS, Klink VP (2019) The mitogen activated protein kinase (MAPK) gene family functions as a cohort during the Glycine max defense response to *Heterodera glycines*. Plant Physiology and Biochemistry 137: 25-41.

32. Ghosh A, Musto PD, Ehrlichman LK, Sadiq O, Evoy B, et al. (2012) The role of extracellular signal-related kinase during abdominal aortic aneurysm formation. J Am Coll Surg 215(5): 668-680.

33. Homeister L, Diekmann M, Brand K, Huber R (2020) GSK3: A kinase balancing promotion and resolution of inflammation. Cells 9(4): 820.

34. Neels JG, Khodja RH, Chinetti G (2020) Nuclear receptors in abdominal aortic aneurysms. Atherosclerosis 297: 87-95.

35. Qing H, Jones KL, Heywood EB, Lu H, Daugherty A, et al. (2017) Deletion of the NR_4A nuclear receptor NOR_1 in hematopoietic stem cells reduces inflammation but not abdominal aortic aneurysm formation. BMC Cardiovasc Disord 17(1): 271.

36. Das S, Senapati P, Chen Z, Reddy MA, Ganguly R, et al. (2017) Regulation of angiotensin II actions by enhancers and super-enhancers in vascular smooth muscle cells. Nat Commun 8(1): 1467.

37. Czimmerer Z, Halasz L, Nagy L (2020) Unorthodox transcriptional mechanisms of lipid-sensing nuclear receptors in macrophages: are we opening a new chapter? Front Endocrinol 11: 609099.

38. Galán M, Varona S, Orriols M, Rodríguez J, Aguiló S, et al. (2016) Induction of histone deacetylases (HDACs) in human abdominal aortic aneurysm: Therapeutic potential of HDAC inhibitors. Dis Model Mech 9(5): 541-552.

39. Ellmeier W, Seiser C (2018) Histone deacetylase function in $CD4^+$ T cells. Nat Rev Immunol 18(10): 617-634.

40. Kim HW, Chantemèle EJB, Weintraub NL (2019) Perivascular adipocytes in vascular disease. Arterioscler Thromb and Vasc Biol 39(11): 2220-2227.

41. Huh JY, Park YJ, Ham M, Kim JB (2014) Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol Cells 37(5): 365-371.

42. Siwei B, Ruiqi L, Linfeng H, Jingyi L, Jun G (2021) Bioinformatics analysis of common key genes and pathways of intracranial, abdominal, and thoracic aneurysms. BMC Cardiovasc Disord 21(1): 14.

43. Stafford N, Wilson C, Oceandy D, Neyses L, Cartwright EJ (2017) The plasma membrane calcium ATPases and their role as major new players in human disease. Physiol Rev 97(3): 1089-1125.

44. Piao W, Kasinath V, Saxena V, Lakhan R, Iyyathurai J, et al. (2021) LTβR Signaling Controls lymphatic migration of Immune Cells. Cells 10(4): 747.

45. Orłowska MB, Wyszyńska R, Pyrzyńska B, Maksymowicz M, Gołąb J, et al. (2019) Cholesterol restricts lymphotoxin β receptor-triggered NF-κB signaling. Cell Commun Signal 17(1): 171.

46. Hu D, Mohanta SK, Yin C, Peng L, Ma Z, et al. (2015) Artery tertiary lymphoid organs control aorta immunity and protect against atherosclerosis via vascular smooth muscle cell lymphotoxin β receptors. Immunity 42(6): 1100-1115.

47. Saito T, Hasegawa Y, Ishigaki Y, Yamada T, Gao J, et al. (2013) Importance of endothelial NF-kappaB signaling in vascular remodeling and aortic aneurysm formation. Cardiovasc Res 97(1): 106-114.

48. Hirano T (2021) IL-6 in inflammation, autoimmunity and cancer. Int Immun 33(3): 127-148.

49. Wang T, He X, Liu X, Liu Y, Zhang W, et al. (2017) Weighted gene co-expression network analysis identifies FKBP11 as a key regulator in acute aortic dissection through a NF-kB dependent pathway. Front Physiol 8: 1010.

50. Gerstmeier J, Weinigel C, Rummler S, Rådmark O, Werz O, et al. (2016) Time-resolved in situ assembly of the leukotriene-synthetic 5-lipoxygenase/5-lipoxygenase-activating protein complex in blood leukocytes. FASEB J 30(1): 276-285.

51. Gennaroa A, Araújoa AC, Buschc A, Jinc H, Wågsätere D, et al. (2018) Cysteinyl leukotriene receptor 1 antagonism prevents experimental abdominal aortic aneurysm. PNAS 115(8): 1907-1912.

52. Bhamidipati CM, Whatling CA, Mehta GS, Meher AK, Hajzus VA, et al. (2014) 5-lipoxygenase pathway in experimental abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 34(12): 2669-2678.

53. Lee JM, Park H, Noh ALSM, Kang JH, Chen L, et al. (2012) 5-Lipoxygenase mediates RANKL-induced osteoclast formation via the cysteinyl leukotriene receptor 1. J Immunol 189(11):5284-5292.

54. Sayantan J, Hu M, Shen M, Kassiri Z (2019) Extracellular matrix, regional heterogeneity of the aorta, and aortic aneurysm. Exp Mol Med 51(12): 1-15.

55. Camardo A, Carney S, Ramamurthi A (2020) Assessing the targeting and fate of cathepsin k antibody-modified nanoparticles in a rat abdominal aortic aneurysm model. Acta Biomaterialia 112: 225-233.

56. Busch S, Auth E, Scholl F, Huenecke S, Koehl U, et al. (2015) 5-lipoxygenase is a direct target of miR-19a-3p and miR-125b-5p. J Immunol 194(4): 1646-1653.

57. Araujo NNF, Wang HT, Germano JF, Farsky PS, Feldman A, et al. (2019) Dysregulation of microRNAs and target genes networks in human abdominal aortic aneurysm tissues. PLoS One 14(9): e0222782.

58. Chekalina N, Burmak Y, Petrov Y, Borisova Z, Manusha Y, et al. (2018) Quercetin reduces the transcriptional activity of NF-kB in stable coronary artery disease. Indian Heart J 70(5): 593-597.

59. Barnett SD, Buxton ILO (2017) The Role of S-Nitroso Glutathione Reductase (GSNOR) in human disease and therapy. Crit Rev Biochem Mol Biol 52(3): 340-354.

60. Wahab WMA, Moussa FI (2019) Neuroprotective effect of N-acetylcysteine against cisplatin-induced toxicity in rat brain by modulation of oxidative stress and inflammation. Drug Des Devel Ther 13: 1155-1162.

61. Lepley RA, Fitzpatrick FA (1998) 5-Lipoxygenase compartmentalization in granulocytic cells is modulated by an internal bipartite nuclear localizing sequence and nuclear factor kappa B complex formation. Arch Biochem Biophys 356(1): 71-76.

62. Rajendran NK, George BP, Chandran R, Tynga IV, Houreld N, et al. (2019) The influence of light on reactive oxygen species and NF- κB in disease progression. Antioxidants 8(12): 640.

63. Jabbarli R, Rauschenbach L, Dinger TF, Oppong MD, Rodemerk J, et al. (2020) In the wall lies the truth: A systematic review of diagnostic markers in intracranial aneurysms. Brain Pathol 30(3): 437-445.

64. Attiq A, Juriyati J, Husain K, Ahmad W (2018) Raging the war against inflammation with natural products. Front Pharmacol 9: 976.

65. Wang C, Wang T, Hu R, Dai J, Liu H, et al. (2020) Cyclooxygenase-2 facilitates new castle disease virus proliferation and is as a target for canthin-6-one antiviral activity. Front Microbiol 11: 987.

66. Aoki T, Frosen J, Fukuda M, Bando K, Shioi G, et al. (2017) Prostaglandin E_2-EP2-NF-κBsignaling in macrophages as a potential therapeutic target for intracranial aneurysms. Sci Signal 10(465): eaah6037.

67. Muhammad S, Chaudhry SR, Dobreva G, Lawton MT, Niemelä M (2021) Vascular macrophages as therapeutic targets to treat intracranial aneurysms. Front Immunol 12: 630381.

68. Rodemerk J, Junker A, Chen B, Pierscianek D, Dammann P, et al. (2020) Pathophysiology of intracranial aneurysms: cox-2 expression, iron deposition in aneurysm wall, and correlation with magnetic resonance imaging. Stroke 51(8): 2505-2513.

69. Cho W, Choe J (2020) Prostaglandin E2 stimulates COX-2 expression via mitogen-activated protein kinase p38 but not ERK in human follicular dendritic cell-like cells. BMC Immunol 21(1): 20.

70. Lenicov FR, Paletta AL, Prinz MG, Varese A, Pavillet CE, et al. (2018) Prostaglandin E2 antagonizes TGF-β actions during the differentiation of monocytes into dendritic cells. Front Immunol 22(9): 1441.

71. Kirkbya NS, Chanb MV, Zaissd AK, Vaze E, Jiaod J, et al. (2016) Systematic study of constitutive cyclooxygenase-2 expression: Role of NF-κB and NFAT transcriptional pathways. PNAS 113(2): 434-439.

72. Davis FM, Tsoi LC, Wasikowski R, Den Dekker A, Joshi A, et al. (2020) Epigenetic regulation of the PGE2 pathway modulates macrophage phenotype in normal and pathologic wound repair. JCI Insight 5(17): e138443.

73. Kim J, Hong SW, Kim S, Kim D, Hur DY, et al. (2017) yclooxygenase-2 expression is induced by celecoxib treatment in lung cancer cells and is transferred to neighbor cells via exosomes. Int J Oncol 52(2): 613-620.

74. Zaky AH, Elsers D, Bakry R, Abdelwanis M, Nabih O, et al. (2020) Prognostic value of accumulative expression of COX-2 and p53 in small and diffuse large B cell lymphoma. Pathol Oncol Res 26(2): 1183-1190.

75. Lai XL, Deng ZF, Zhu XG, Chen ZH (2019) APC gene suppresses intracranial aneurysm formation and rupture through inhibiting the NF-κB signaling pathway mediated inflammatory response. Biosci Rep 39(3): BSR20181909.

76. Hariharan A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M (2021) The role and therapeutic potential of NF-kappa-B pathway in severe COVID-19 patients. Inflammopharmacol 29(1): 91-100.

77. Mussbacher M, Salzmann M, Brostjan C, Hoesel B, Schoergenhofer C, et al. (2019) Cell type-specific roles of NF-κB linking inflammation and thrombosis. Front Immunol 10: 85.

78. Laurence DW, Homburg H, Yan F, Tang D, Fung KM, et al. (2021) A pilot study on biaxial mechanical, collagen microstructural, and morphological characterizations of a resected human intracranial aneurysm tissue. Sci Rep 11(1): 3525.

79. Du G, Geng D, Zhou K, Fan Y, Su R, et al. (2020) Identification of potential key pathways, genes and circulating markers in the development of intracranial aneurysm based on weighted gene co-expression network analysis. Artif Cells Nanomed Biotechnol 48(1): 999-1007.

80. Shi Y, Li S, Song Y, Liu P, Yang Z, et al. (2019) Nrf-2 signaling inhibits intracranial aneurysm formation and progression by modulating vascular smooth muscle cell phenotype and function. J Neuroinflammation 16(1): 185.

81. Kushamae M, Miyata H, Shirai M, Shimizu K, Oka M, et al. (2020) Involvement of neutrophils in machineries underlying the rupture of intracranial aneurysms in rats. Sci Rep 10(1): 20004.

82. Banks E, Joshy G, Korda RJ, Stavreski B, Soga K, et al. (2020) Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. BMC Med 17(1): 128.

83. Gupta S, Su H, Agrawal S, Gollapudi S (2018) Molecular changes associated with increased TNF-α-induced apoptotis in naïve (T_N) and central memory (T_{CM}) CD8+ T cells in aged humans. Immun Ageing 15: 2.

84. Li K, Cui M, Zhang K, Wang G, Zhai S (2020) LncRNA CRNDE affects the proliferation and apoptosis of vascular smooth muscle cells in abdominal aortic aneurysms by regulating the expression of Smad3 by Bcl-3. Cell Cycle 19(9): 1036-1047.

85. Ling GQ, Li XF, Lei XH, Zang ZY, Ma DY, et al. (2019) c-Jun N-terminal kinase inhibition attenuates early brain injury induced neuronal apoptosis via decreasing p53 phosphorylation and mitochondrial apoptotic pathway activation in subarachnoid hemorrhage rats. Molecular Medicine Reports 19(1): 327-337.

86. Guo S, Zhang R, Liu Q, Wan Q, Wang Y, et al. (2019) 2,3,7,8-Tetrachlorodibenzo-p-dioxin promotes injury-induced vascular neointima formation in mice. FACEB J 33(9): 10207-10217.

87. Kraczkowska W, Jagodziński PP (2019) The long non-coding RNA landscape of atherosclerotic plaques. Mol Diagn Ther 23: 735-749.

88. Pierce JB, Feinberg MW (2020) Long noncoding RNAs in atherosclerosis and vascular injury. pathobiology, biomarkers, and targets for therapy. Arterioscler Thromb Vasc Biol 40(9): 2002-2017.

89. Wasson CW, Abignano G, Hermes H, Malaab M, Ross RL, et al. (2020) Long non-coding RNA HOTAIR drives EZH2-dependent myofibroblast activation in systemic sclerosis through miRNA 34a-dependent activation of NOTCH. Ann Rheum Dis 79(4): 507-517.

90. Bakker MK, Spek RAA, Rheenen VW, Morel S, Bourcier R, et al. (2020) Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. Nat Genet 52(12): 1303-1313.

91. Manjula G, Pranavchand R, Kumuda I, Reddy BS, Reddy BM (2020) The SNP rs7865618 of 9p21.3 locus emerges as the most promising marker of coronary artery disease in the southern Indian population. Sci Rep 10: 21511.

92. Aarabi G, Zeller T, Heydecke G, Munz M, Schäfer A, et al. (2018) Roles of the Chr.9p21.3 *ANRIL* Locus in Regulating Inflammation and Implications for Anti-Inflammatory Drug Target Identification. Front Cardiovasc Med 5: 47.

93. Nakaoka H, Tajima A, Yoneyama T, Hosomichi K, Kasuya H, et al. (2014) Gene expression profiling reveals distinct molecular signatures associated with the rupture of intracranial aneurysm. Stroke 45(8): 2239-2245.

94. Jia G, Aroor AR, Jia C, Sowers JR (2019) Endothelial cell senescence in aging-related vascular dysfunction. Biochim Biophys Acta Mol Basis Dis 1865(7): 1802-1809.

95. Chikenji TS, Saito Y, Konari N, Nakano M, Mizue Y, et al. (2019) $p_{16}INK_4A$-expressing mesenchymal stromal cells restore the senescence-clearance-regeneration sequence that is impaired in chronic muscle inflammation. EBioMedicine 44: 86-97.

96. Holdt LM, Sass K, Gäbel G, Bergert H, Thiery J, et al. (2011) Expression of Chr_9p_21 genes $CDKN_2B$ ($p_{15}(INK_4b)$), $CDKN_2A$ ($p_{16}(INK_4a)$, $p_{14}(ARF)$) and MTAP in human atherosclerotic plaque. Atherosclerosis: 214(2): 264-270.

97. Micheli L, D'Andrea G, Ceccarelli M, Ferri A, R Scardigli R, et al. (2019) $p_{16}Ink_4a$ prevents the activation of aged quiescent dentate gyrus stem cells by physical exercise. Front Cell Neurosci 13: 10.

98. Nie FQ, Sun M, Yang JS, Xie M, Xu TP, et al. (2015) Long non-coding RNA ANRIL promotes non-small cell lung cancer cells proliferation and inhibits apoptosis by silencing KLF_2 and P_{21} expression. Mol Cancer Ther: 14(1): 268-277.

99. Huang MD, Chen WM, Qi FZ, Xia R, Sun M, et al. (2015) Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF_2. J Hematol Oncol 8: 50.

100. Luo JY, Li YH, Fang BB, Tian T, Liu F, et al. (2020) $NFKB_1$ gene rs28362491 ins/del variation is associated with higher susceptibility to myocardial infarction in a Chinese Han population. Sci Rep 10(1): 19518.

101. Li Q, Youn JY, Siu Kl, Priya M, Yixuan Z, et al. (2020) Knockout of dihydrofolate reductase in mice induces hypertension and abdominal aortic aneurysm via mitochondrial dysfunction. Redox Biol 24: 101185.

102. Yu L, Yin M, Yang X, Lu M, Tang F, et al. (2018) Calpain inhibitor I attenuates atherosclerosis and inflammation in atherosclerotic rats through eNOS/NO/NF-B pathway. Can J Physiol Pharmacol 96(1): 60-67.

103. Brien OJ, Hayder H, Zayed Y, Peng C (2018) Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol 9: (402).

104. Treiber T, Treiber N, Plessmann U, Harlander S, Daiß JL, et al. (2017) A compendium of RNA-binding proteins that regulate micro RNA biogenesis. Mol Cell 66(2): 270-284.

105. Kim JH, Kim JY, Park M, Kim S, Kim J, et al. (2019) NF-κB-dependent miR-31/155 biogenesis is essential for TNF-α-induced impairment of endothelial progenitor cell function. Exp Mol Med 52: 1298-1309.

106. He J, Zou Y, Liu X, Zhu J, Zhang J, et al. (2018) Association of common genetic variants in pre-microRNAs and neuroblastoma susceptibility: a two-center study in Chinese children. Mol Ther Nucleic Acids 11: 1-8.

107. Khan MS, Rahman B, Ul Haq T, Jalil F, Khan BM, et al. (2021) Deciphering the variants located in the $MIR_{196}A_2$, $MIR_{146}A$, and MIR_{423} with type-2 diabetes mellitus in Pakistani population. Genes (Basel) 12(5): 664.

108. Borghini A, Andreassi MG (2018) Genetic polymorphisms offer insight into the causal role of microRNA in coronary artery disease. Atherosclerosis 269: 63-70.

109. Bayraktar R, Bertilaccio MTS, Calin GA (2019) The interaction between two worlds: microRNAs and toll-like receptors. Front Immunol 10: 1053.

110. Venkatesh P, Phillippi J, Chukkapalli S, Rivera KM, Velsko I, et al. (2017) Aneurysm-Specific miR-221 and miR-146a participates in human thoracic and abdominal aortic aneurysms. Int J Mol Sci 18(4): 875.

111. Kang K, Bachu M, Park SH, Kang K, Bae S, et al. (2019) IFN-γ selectively suppresses a subset of TLR4-activated genes and enhancers to potentiate macrophage activation. Nat Commun 10(1): 3320.

112. Abdi J, Rashedi I, Keating A (2018) TLR pathway-miRNA interplay in mesenchymal stromal cells: regulatory roles and therapeutic directions. Stem Cells 36(11): 1655-1662.

113. Zitzer NC, Garzon R, Ranganathan P (2018) Toll-like receptor stimulation by microRNAs in acute graft-vs.-host disease. Front Immunol 9: 2561.

114. Courtois A, Nusgens B, Garbacki N, Hustinx R Gomez P, et al. (2015) Circulating microRNAs signature correlates with positive [^{18}F] fluorodeoxyglucose-positron emission tomography in patients with abdominal aortic aneurysm. J Vasc Surg 67(2): 585-595.

115. Li Y, Maegdefessel L (2017) Non-coding RNA contribution to thoracic and abdominal aortic aneurysm disease development and progression. Front Physiol 8: 429.

116. Zhang C, Wang H, Yang B (2020) miR-146a regulates inflammation and development in patients with abdominal aortic aneurysms by targeting $CARD_{10}$. Int Angiol 39(4): 314-322.

117. Bi S, Liu R, He L, Li J, Gu J (2021) Bioinformatics analysis of common key genes and pathways of intracranial, abdominal, and thoracic aneurysms. BMC Cardiovasc Disord 21(1): 14.

118. Lareyre F, Clement M, Moratal C, Loyer X, Jean BE, et al. (2019) Differential micro-RNA expression in diabetic patients with abdominal aortic aneurysm. Biochimie 162: 1-7.

119. Hu YW, Hu YR, Zhao JY, Li SF, Ma X, et al. (2014) An agomir of miR-144-3p accelerates plaque formation through impairing reverse cholesterol transport and promoting pro-inflammatory cytokine production. PLoS One 9(4): e94997.

120. Maegdefessel L, Spin JM, Raaz U, Eken SM, Toh R, et al. (2014) miR-24 limits aortic vascular inflammation and murine abdominal aneurysm development. Nat Commun 5: 5214.

121. Sun L, Zhao M, Zhang J, Lv M, Li Y, et al. (2017) MiR-29b downregulation induces phenotypic modulation of vascular smooth muscle cells: implication for intracranial aneurysm formation and progression to rupture. Cell Physiol Biochem 41(2): 510-518.

122. Wanhainen A, Mani K, Vorkapic E, De Basso R, Björck M, et al. (2018) Screening of circulating microRNA biomarkers for prevalence of abdominal aortic aneurysm and aneurysm growth. Atherosclerosis 256: 82-88.

123. Cerna V, Ostasov P, Pitule P, Molacek J, Treska V, et al. (2019) The expression profile of microRNAs in small and large abdominal aortic aneurysms. Cardiology Research and Practice 9: 1-8.

124. Plana E, Gálvez L, Medina P, Navarro S, Fornés-Ferrer V, et al. (2020) Identification of novel microRNA profiles dysregulated in plasma and tissue of abdominal aortic aneurysm patients. Int J Mol Sci 21(13): 4600.

125. Kim CW, Kumar S, Son DJ, Jang IH, Griendling KK, et al. (2014) Prevention of abdominal aortic aneurysm by anti-microRNA-712 or anti-microRNA-205 in angiotensin II-infused mice. Arterioscler Thromb Vasc Biol 34(7): 1412-1421.

126. Stather PW, Sylvius N, Sidlo DA, Dattani N, Verissimo A, et al. (2015) Identification of microRNAs associated with abdominal aortic aneurysms and peripheral arterial disease. Br J Surg 102(7): 755-766.

127. Busch A, Busch M, Scholz CJ, Kellersmann R, Otto C, et al. (2016) Aneurysm miRNA signature differs, depending on disease localization and morphology. Int J Mol Sci 17(1): 81.

128. Jin H, Jiang Y, Liu X, Meng X, Li Y (2020) Cell-free microRNA-21: biomarker for intracranial aneurysm rupture. Chin Neurosurg Jl 6: 15.

129. Ma X, Yao H, Yang Y, Jin L, Wang Y, et al. (2018) miR-195 suppresses abdominal aortic aneurysm through the TNF-α/NF-κB and VEGF/PI3K/Akt pathway. Int J Mol Med 41(4): 2350-2358.

130. Zhang S, Kan X, Li Y, Li P, Zhang C, et al. (2018) Deficiency of γδT cells protects against abdominal aortic aneurysms by regulating phosphoinositide 3-kinase/AKT signaling. J Vasc Surg 67(3): 899-908.

131. Keppler NKM, Parker VE, Darling TN, Martinez-Agosto JA (2016) Somatic overgrowth disorders of the PI3K/AKT/mTOR pathway & therapeutic strategies. Am J Med Genet C Semin Med Genet 172(4): 402-421.

132. Sun P, Wang L, Lu Y, Liu Y, Li L, et al. (2016) MicroRNA-195 targets VEGFR2 and has a tumor suppressive role in ACHN cells via PI3K/Akt and Raf/MEK/ERK signaling pathways. Int J Oncol 49(3): 1155-1163.

133. Mirzaie M, Fatehpur S, Guliyev Z, Schulz S, Reichert S (2021) The -94Ins/DelATTG promoter polymorphism in the transcription factor NF-Kb in patients with popliteal aneurysm. J Cardiol Vasc Med 7: 1-7.