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Commentary

NF-κB and Hypoxia

A Double-Edged Sword in Atherosclerosis

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Hypoxia, a decrease in oxygen tension within tissues, occurs in response to several pathophysiological disease states, including myocardial ischemia, atherosclerosis, and obstructive sleep apnea. HIF-1α, a basic helix-loop-helix transcription factor and a master regulator of cellular homeostatic responses to hypoxia, activates transcription of genes involved in energy metabolism, angiogenesis, apoptosis, and cell differentiation. HIF-1α is regulated post-transcriptionally by prolyl hydroxylases under normoxic conditions, an effect that allows for their recognition and ubiquitination by the von Hippel-Lindau E3 ubiquitin ligase and rapid degradation by the proteasome.[1–3] However, accumulating data indicate that HIF-1α may also be regulated in response to inflammatory stimuli in an NF-κB–dependent manner.[4,5] The interplay between hypoxia and inflammation, along with its pathological role in acute and chronic inflammatory disease states such as atherosclerosis, has emerged as a subject of significant scientific interest.[6]

Chronic Intermittent Hypoxia and Atherosclerosis

Obstructive sleep apnea (OSA), characterized by chronic intermittent hypoxia (CIH) as a result of repetitive episodes of complete or partial obstructions of the upper airway during sleep, is an independent risk factor for the development of cardiovascular disease. Furthermore, the prevalence of OSA has been estimated to be as high as 50% in persons with cardiometabolic disorders.[7] Atherosclerosis, a chronic inflammatory disease of the arterial wall, develops in a more aggressive manner in the context of OSA.[8,9] Experimentally, CIH initiates atherosclerosis in the presence of high-fat, diet-induced dyslipidemia in both wild-type C57BL/6J mice[10] and atherosclerotic-prone ApoE knockout (ApoE-KO) mice,[11] effects that established a causal link between CIH and atherosclerosis. More recent studies suggest that RANTES/CCL5 signaling, leukotriene B4 pathway activation, and several other inflammatory components contribute to CIH-induced atherosclerosis.[12–14] Despite these observations, the mechanisms by which outside-in hypoxic signaling accelerates the initiation and progression of atherosclerosis are poorly understood, in part because of the limitations of current animal models for CIH-induced atherosclerosis; such models typically involve exposure to CIH in animals with pre-existing atherosclerotic pathology, potentially obscuring the initiation phase of lesion development. Furthermore, because activation of NF-κB (particularly in the vascular endothelium) has been linked to increased atherosclerotic lesion formation, it has been hypothesized that the loss of NF-κB family members may reduce atherosclerosis, including atherosclerosis in response to CIH. In this issue, Fang et al[15] report development of two new mouse models of CIH-induced atherosclerosis; their study, surprisingly, revealed that loss of the NF-κB p50 subunit increased atherosclerosis in the presence of CIH.

In the first model, ApoE-KO mice were fed a normal chow diet and exposed to CIH. After 9 weeks of CIH exposure, no obvious lesions were observed in the thoracic and abdominal aorta, compared with sham-exposed ApoE-KO mice; a trend toward increased numbers of lesions in the aortic root did not reach significance. After 30 weeks of CIH exposure, however, atherosclerotic lesion areas increased in both the aortic root and the thoracic-abdominal aorta. Importantly, lesion areas of ApoE-KO mice given a high-fat diet were approximately threefold greater than in CIH-exposed ApoE-KO mice, suggesting that CIH is a much weaker physiological stimulus for atherosclerotic lesion forma-

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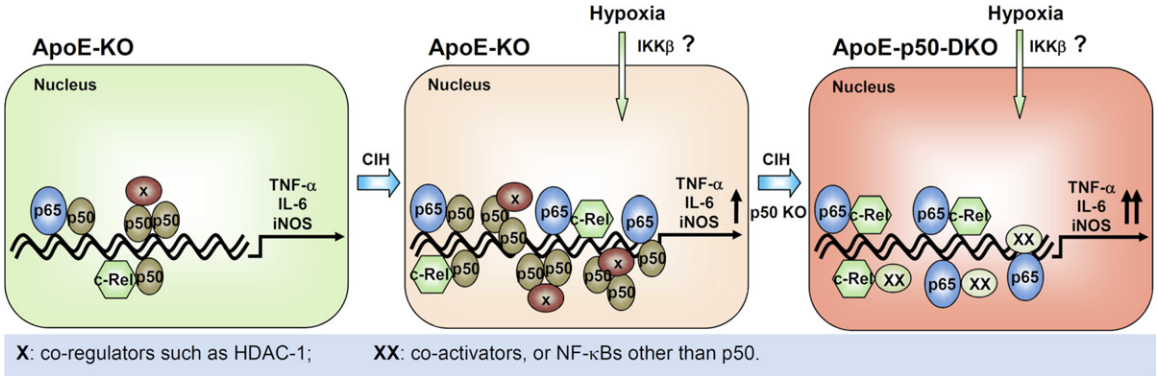

Figure 1. NF-κB p50 protects ApoE-KO mice from CIH-induced atherosclerosis. Under normoxic conditions in ApoE-KO mice (**left panel**), translocated NF-κB p65/p50 and c-Rel/p50 heterodimers bind to NF-κB-responsive targets and induce the expression of proinflammatory genes, such as those for TNF-α, IL-6, and iNOS. Whether hypoxia/HIF-1 signaling contributes to the phosphorylation of IKKβ and subsequent NF-κB activation was not examined in this study. In response to CIH in ApoE-KO mice (**middle panel**), NF-κB p50 is the dominant subunit and generates p50/p50 homodimers and p65/p50 and c-Rel/p50 heterodimers, thereby further increasing expression of TNF-α, IL-6, and iNOS. However, deletion of NF-κB p50 in CIH-exposed ApoE-KO mice (**right panel**) alters the ratio of NF-κB subunits in the nucleus, resulting in relatively high amounts of transactivating NF-κBs p65 and c-Rel and a complete lack of the transrepressive NF-κB p50, which in turn potentiate CIH-induced TNF-α, IL-6, and iNOS expression and accelerate atherosclerosis.

tion, compared with dyslipidemia. In the second model, compound ApoE and p50 double-knock-out mice (ApoE-p50-DKO) were fed a normal chow diet and exposed to CIH. Remarkably, after 9 weeks of CIH exposure, atherosclerotic lesion formation increased approximately 2.5-fold in ApoE-p50-DKO mice, compared with CIH-exposed ApoE-KO mice. Thus, ApoE-KO mice with systemic deficiency of p50 are more sensitive to CIH-induced atherogenesis, suggesting an atheroprotective role of the NF-κB p50 subunit in the presence of CIH.

Examination of the NF-κB signaling pathway revealed a reduction in IκBα expression in CIH-ApoE-KO mice, indicating activation of the canonical NF-κB pathway. Interestingly, supershift assays of NF-κB DNA-protein binding showed that the CIH-induced NF-κB complex in ApoE-KO mice is composed predominantly of p50/p50 homodimers, with minor contributions from c-Rel/p50 and likely also p65/p50 heterodimers. NF-κB DNA-binding was severely decreased by p50 gene deletion in ApoE-KO mice, particularly in response to CIH (Figure 1). Importantly, the expression of the proinflammatory NF-κB target genes *TNF*, *IL6*, and *NOS2* (encoding TNF-α, IL-6, and iNOS, respectively) was increased by CIH, and NF-κB p50 deletion further increased their expression, an effect that was associated with aortic accumulation of Mac3-positive macrophages.

Nonetheless, some caution is indicated in interpreting the accelerated atherosclerotic phenotype in ApoE-p50-DKO mice, given that these mice exhibited increased serum total cholesterol levels. Such increased serum total cholesterol levels can potentially contribute to lesion formation through excessive intralesional macrophage foam-cell formation, among other mechanisms. Although the mechanism by which p50 deficiency increases total cholesterol remains unclear (despite absence of changes in LDL, HDL, or triglyceride fractions), mRNA expression of hepatic LDL receptor, which participates in LDL-mediated cholesterol uptake and clearance, was significantly reduced. Further studies will be required to determine how p50 regulates LDL receptor expression and/or LDL formation and the relative contribution of a 1.7-fold increase in cholesterol in the CIH-exposed ApoE-p50-DKO mice. Nevertheless, the study by Fang et al[15] provides a mechanistic understanding of how outside-in hypoxia signaling promotes atherosclerosis, without the limitations of prior models confounded by pre-existing atherosclerosis. Although their study revealed a protective role of NF-κB p50 in CIH-induced atherosclerosis, the initiating events linking hypoxia to NF-κB–mediated inflammation remain incompletely understood.

NF-κB and Hypoxia

Emerging studies have revealed several mechanistic paradigms that link NF-κB and hypoxia signaling pathways. The NF-κB transcription factor family consists of five members: RelA, RelB, c-Rel, p50, and p52. RelA, RelB, and c-Rel contain a C-terminal transactivation domain, but no definable activation domains are found in p50 and p52. NF-κB p50 is processed from its precursor p105. The precursor p105 functions as an NF-κB inhibitor, blocking the activity of its dimeric NF-κB partners and retaining them in the cytoplasm. The NF-κB family members can form different homo- and heterodimers, with each dimer being involved in the regulation of a unique set of target genes. The p65/p50 heterodimer, which represents the most abundant NF-κB dimer, is activated in response to proinflammatory stimuli (such as TNF-α, IL-1β, and LPS) in almost all cell types through the canonical NF-κB signaling pathway. RelB/p52 heterodimers are activated by lymphotoxin, B-cell activating factor, or CD40 ligand via the noncanonical NF-κB pathway, which involves inducible proteolytic removal of the ankyrin-repeat domain of p100/RelB heterodimers. Several other heterodimers containing p50 have been described, including p50/c-Rel, p50/p50, and p50/RelB. For example, p50/c-Rel heterodimers are the primary component of constitutively active NF-κB observed in mature B cells. However, not all NF-κB dimers are transcriptionally active; in particular, p50/p50 homodimers have been found to transcriptionally repress target genes by preventing

transactivation domain-containing NF-κB dimers from binding to κB sites in unstimulated or resting cells.[16] Alternatively, p50 may interact with histone deacetylases or other coregulators that inhibit an activator of target genes.[17–19] Indeed, p50/p50 homodimers repress the expression of NF-κB target genes, such as those encoding TNF-α, IL-6, and IL-8.[20–22] For example, during prolonged exposure to LPS, the binding of p50 homodimers to the κB sites at the TNF-α promoter reduced transcriptional activation and blocked the production of TNF-α.[23]

Consistent with these reports, Fang et al[15] found that TNF-α, IL-6, and iNOS were induced in CIH-exposed ApoE-KO mice and that the induction was further potentiated in the absence of p50, suggesting that p50 plays a suppressive function for the gene expression of these proteins in response to CIH. These data also imply that the relative ratio of endogenous NF-κB subunits is critical for selective gene expression (Figure 1). Interestingly, although they found that the CIH-induced NF-κB complex is composed primarily of p50/p50 homodimers, small amounts of c-Rel/p50 and likely also p65/p50 heterodimers remain. Consequently, loss of transcriptionally repressive p50 may allow for increased heterodimerization and transcriptional activity of c-Rel/p50 or p65/p50 heterodimers on NF-κB–responsive promoters to induce TNF-α, IL-6, and iNOS expression in response to CIH.

Accumulating data from several studies indicate significant crosstalk between the HIF-1 and NF-κB signaling pathways. In response to hypoxia, the canonical NF-κB pathway is activated, in part, by inhibition of prolyl hydroxylases that negatively regulate IKKβ activity. Modest IKKβ activation by hypoxia leads to IκBα phosphorylation and degradation, followed by NF-κB p65 nuclear translocation, binding to κB elements, and induction of gene expression.[5,24] A further level of crosstalk between hypoxia and NF-κB has been reported, whereby HIF-1α can regulate NF-κB signaling through up-regulation of p65 and IKKα in neutrophils.[25] Conversely, NF-κB is able to bind the HIF-1α promoter and induce its expression *in vitro* and *in vivo* under hypoxic or normoxic conditions.[5] Thus, it would be interesting to investigate whether loss of NF-κB p50 alters HIF-1α promoter and expression in response to CIH in atherosclerotic-prone mice.

Is NF-κB p50 a Good Actor or Bad Actor in Inflammation?

The NF-κB p50 systemic knockout mice exhibit no developmental abnormalities at birth; adults, however, possess defects in immune responses involving B lymphocytes, development of LPS tolerance, skeletal muscle atrophy, and severe colitis after *Helicobacter hepaticus* infection.[23,26,27] NF-κB p50 also plays a protective role in neurovascular development, cell survival, aging in the central nervous system, and development of Huntington's disease.[28,29] In the study by Fang et al,[15] p50 deficiency potentiated CIH-induced atherosclerosis in ApoE-KO mice. Cell-type–specific effects of p50 deficiency in the context of CIH-induced atherosclerosis will have to be sorted out in future studies. For example, differentiated macrophages can be categorized into two broad types, M1 and M2, based on both expression and function of cytokines. Porta et al[30] identified p50 as a key regulator of M2-driven inflammatory reactions. In that study, p50 inhibited NF-κB–driven M1 polarization and IFN-β production; conversely, p50-deficient mice showed exacerbated M1-driven inflammation and defective capacity to mount allergy and helminth-driven M2-polarized inflammatory reactions. The p50-deficient macrophages also displayed impaired expression of M2-related genes for IL-10, TGF-β, CCL2, CCL17, CCL22, and type I arginase. Thus, p50 is a negative regulator of M1-associated gene expression (TNF-α, iNOS, and IFN-β), but it plays a nonredundant positive role in induction of M2-associated genes. In this light, the findings by Fang et al[15] of increased circulating or lesional expression of TNF-α, IL-6, and iNOS in CIH-exposed ApoE-p50-DKO mice are consistent with this premise and raise the possibility that the ratio of M1 to M2 macrophages may contribute to the phenotype.

Loss of p50, however, may be a double-edged sword in other relevant conditions associated with atherosclerosis. For example, p50-KO mice were protected from streptozotocin-induced diabetes, had less damage in response to focal cerebral ischemia, and had reduced ischemia-reperfusion injury revealed by smaller myocardial infarction size *in vivo*, an effect associated with less neutrophil infiltration despite increased ICAM-1 expression.[31] Furthermore, p50-KO mice develop less left ventricular dilation and have reduced early mortality after coronary artery ligation than wild-type mice.[32] Thus, NF-κB signaling appears to have divergent functions that can exhibit either protective or detrimental effects on cardiovascular tissues, depending on the cellular and pathophysiological context. Given that myocardial infarction and stroke are major complications of atherosclerosis, further studies are merited to establish the precise role of NF-κB p50 and to determine whether increasing p50 in a cell-specific manner may confer a beneficial effect in atherosclerosis and CIH without affecting tissue injury.

NF-κB and Atherosclerosis

Brand et al[33] detected activation of NF-κB in human vascular smooth muscle cells, macrophages, and endothelial cells in the fibrotic-thickened tunica intima/media and atheromatous areas of lesions, but not in vessels lacking atherosclerosis. Activated NF-κB was also detected in intimal cells in coronary arteries of pigs with a hypercholesterolemic diet[34] and in aortic endothelial cells in LDLR knockout mice after 2 weeks of a cholesterol-enriched diet.[35] Indeed, NF-κB downstream target genes, including those for VCAM-1 and ICAM-1, were up-regulated in response to hypercholesterolemia at sites predisposed to atherosclerotic lesion formation.[36] In addition to dyslipidemia, many atherogenic risk factors activate NF-κB, including bacterial and viral infection, hemodynamic shear-stress forces, angiotensin II, and advanced glycation end products.[35,37–39] A causal link

between endothelial NF-κB signaling pathway and atherosclerosis was experimentally validated *in vivo* by Gareus et al,[40] based on several mouse models with endothelial cell-specific NF-κB inhibition. These studies revealed that i) endothelial cell-specific NF-κB IKKγ ablation leads to a 30% reduction in atherosclerotic lesion size, ii) inducible IKKγ ablation reduced atherosclerosis by 33% in males and 47% in females, and iii) endothelial dominant-negative IκBα expression reduced atherosclerotic plaque area by 60%.

Although it is clear that endothelial NF-κB activation promotes the initiation and progression of atherosclerosis, the role of myeloid NF-κB signaling in atherosclerosis remains unclear. NF-κB plays an important role in cell survival. Kanters et al[41] showed that myeloid IKKβ deletion increased atherosclerosis in *LDLR*$^{-/-}$ mice. NF-κB pro-survival function in macrophages may limit lesion development in mouse models of atherosclerosis. Targeted deletion of p50 in hematopoietic cells led to reduced atherosclerotic lesion formation in *LDLR*$^{-/-}$ mice.[42] These lesions exhibited a more inflammatory phenotype, with relatively large numbers of T cells and B cells. Surprisingly, lesions in these mice exhibited a nearly complete absence of foam cells, likely because of reduced endocytosis of lipoproteins and decreased expression of scavenger receptor class A. Interestingly, overexpression of super-repressor of IκBα in macrophages decreased lipid ingestion by macrophage scavenger receptors and decreased foam-cell biogenesis. Fang et al[15] demonstrated that, in ApoE-p50-DKO mice, CIH did not affect HDL-mediated cholesterol reverse transport (there was no difference in hepatic ABCA1 and SR-B1 expression) or the expression of SREBP-2 (which is the master regulator of cholesterol synthesis), and did not increase cholesterol synthesis. Hepatic LDL receptor expression was reduced, however, and indeed the reduction of hepatic LDLR expression may be an important component of the observed phenotype, one that merits further investigation. Finally, these findings bear clinical relevance, because persons with OSA have a higher prevalence of dyslipidemia than those without OSA.[43]

Therapeutic Implications

NF-κB has been implicated in many pathological states, including autoimmune disease, cancer, cardiovascular disease, and other metabolic disorders. It may be quite attractive, therefore, to develop precisely engineered drugs to counter these pathologies caused by NF-κB activation without affecting the potential beneficial functions, particularly from p50. To date, several therapeutic strategies aimed at selectively blocking NF-κB activation in animal models have involved i) biological agents (eg, monoclonal antibodies) that reduce the activity of specific cytokines or their receptors, ii) small molecules that disrupt lymphocyte trafficking, iii) inhibitors of kinases (eg, IκB kinase), iv) proteasome inhibitors to stabilize IκBα, v) small peptides (eg, SN50) that target NF-κB nuclear translocation by inhibiting the nuclear import system, vi) small molecules that inhibit specific NF-κB DNA-protein binding to promoters, and vii) microRNAs that reduce NF-κB activity.[44,45] Several biological agents have been tested in clinical trials, including a humanized monoclonal antibody that blocks the activation of CCR2 by CCL2 and also an IL-1β receptor antagonist, anakinra (Kineret), which in 2001 was approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis. Treatment with IL-1β receptor antagonist also reversed insulin resistance and glucose intolerance in diabetes patients. Several agents that are able to inhibit NF-κB function are currently in clinical use as cancer chemotherapeutics. The efficacy and specificity of several rationally designed NF-κB inhibitors are being tested in a number of undergoing clinical trials. In the cardiovascular field, several widely used drugs have inhibitory effects on NF-κB activity or NF-κB target gene expression; these include aspirin, salsalate (salicylsalicylic acid), corticosteroids, and statins. Although neither inhibitors nor activators of specific NF-κB pathways are yet clinically available for use in cardiovascular disease, the study by Fang et al[15] provides important insights, including the notion that inhibition of NF-κB that preferentially affects p50/p50 homodimers may have deleterious effects in the context of CIH and atherosclerosis.[15] Given the prevalence of dyslipidemia, metabolic syndrome, and atherosclerosis in OSA subjects, augmenting the expression or function of NF-κB p50 may provide new targets in these high-risk individuals for cardiovascular disease. Finally, the recruitment of coregulators to the p50/p50 homodimeric NF-κB complex may have a particularly important selective advantage for the modulation of CIH-induced atherosclerosis. Understanding these events may inform the generation of druggable targets in persons with obstructive sleep apnea, atherosclerosis, or chronic ischemic disease states.

References

1. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ: The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature 1999, 399:271–275
2. Bruick RK, McKnight SL: A conserved family of prolyl-4-hydroxylases that modify HIF. Science 2001, 294:1337–1340
3. Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, von Kriegsheim A, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH, Pugh CW, Ratcliffe PJ: Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science 2001, 292:468–472
4. van Uden P, Kenneth NS, Rocha S: Regulation of hypoxia-inducible factor-1alpha by NF-kappaB. Biochem J 2008, 412:477–484
5. Rius J, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, Nizet V, Johnson RS, Haddad GG, Karin M: NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. Nature 2008, 453:807–811
6. Eltzschig HK, Carmeliet P: Hypoxia and inflammation. N Engl J Med 2011, 364:656–665
7. Lurie A: Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. Adv Cardiol 2011, 46:1–42
8. Drager LF, Polotsky VY, Lorenzi-Filho G: Obstructive sleep apnea: an emerging risk factor for atherosclerosis. Chest 2011, 140:534–542
9. Arnaud C, Dematteis M, Pepin JL, Baguet JP, Levy P: Obstructive sleep apnea, immuno-inflammation, and atherosclerosis. Semin Immunopathol 2009, 31:113–125

10. Savransky V, Nanayakkara A, Li J, Bevans S, Smith PL, Rodriguez A, Polotsky VY: Chronic intermittent hypoxia induces atherosclerosis. Am J Respir Crit Care Med 2007, 175:1290–1297
11. Jun J, Reinke C, Bedja D, Berkowitz D, Bevans-Fonti S, Li J, Barouch LA, Gabrielson K, Polotsky VY: Effect of intermittent hypoxia on atherosclerosis in apolipoprotein E-deficient mice. Atherosclerosis 2010, 209:381–386
12. Arnaud C, Poulain L, Levy P, Dematteis M: Inflammation contributes to the atherogenic role of intermittent hypoxia in apolipoprotein-E knock out mice. Atherosclerosis 2011, 219:425–431
13. Arnaud C, Beguin PC, Lantuejoul S, Pepin JL, Guillermet C, Pelli G, Burger F, Buatois V, Ribuot C, Baguet JP, Mach F, Levy P, Dematteis M: The inflammatory preatherosclerotic remodeling induced by intermittent hypoxia is attenuated by RANTES/CCL5 inhibition. Am J Respir Crit Care Med 2011, 184:724–731
14. Li RC, Haribabu B, Mathis SP, Kim J, Gozal D: Leukotriene B4 receptor-1 mediates intermittent hypoxia-induced atherogenesis. Am J Respir Crit Care Med 2011, 184:124–131
15. Fang G, Song D, Ye X, Mao SZ, Liu G, Liu SF: Chronic intermittent hypoxia exposure induces atherosclerosis in ApoE knockout mice: role of NF-kappaB p50. Am J Pathol 2012, 181:1530–1539
16. Grundström S, Anderson P, Scheipers P, Sundstedt A: Bcl-3 and NFkappaB p50-p50 homodimers act as transcriptional repressors in tolerant CD4+ T cells. J Biol Chem 2004, 279:8460–8468
17. Elsharkawy AM, Oakley F, Lin F, Packham G, Mann DA, Mann J: The NF-kappaB p50: p50:HDAC-1 repressor complex orchestrates transcriptional inhibition of multiple pro-inflammatory genes. J Hepatol 2010, 53:519–527
18. Ashburner BP, Westerheide SD, Baldwin AS Jr: The p65 (RelA) subunit of NF-kappaB interacts with the histone deacetylase (HDAC) corepressors HDAC1 and HDAC2 to negatively regulate gene expression. Mol Cell Biol 2001, 21:7065–7077
19. Kumar A, Lin Z, SenBanerjee S, Jain MK: Tumor necrosis factor alpha-mediated reduction of KLF2 is due to inhibition of MEF2 by NF-kappaB and histone deacetylases. Mol Cell Biol 2005, 25:5893–5903
20. Baer M, Dillner A, Schwartz RC, Sedon C, Nedospasov S, Johnson PF: Tumor necrosis factor alpha transcription in macrophages is attenuated by an autocrine factor that preferentially induces NF-kappaB p50. Mol Cell Biol 1998, 18:5678–5689
21. Tong X, Yin L, Washington R, Rosenberg DW, Giardina C: The p50-p50 NF-kappaB complex as a stimulus-specific repressor of gene activation. Mol Cell Biochem 2004, 265:171–183
22. Hirotani T, Lee PY, Kuwata H, Yamamoto M, Matsumoto M, Kawase I, Akira S, Takeda K: The nuclear IkappaB protein IkappaBNS selectively inhibits lipopolysaccharide-induced IL-6 production in macrophages of the colonic lamina propria. J Immunol 2005, 174:3650–3657
23. Bohuslav J, Kravchenko VV, Parry GC, Erlich JH, Gerondakis S, Mackman N, Ulevitch RJ: Regulation of an essential innate immune response by the p50 subunit of NF-kappaB. J Clin Invest 1998, 102:1645–1652
24. Cummins EP, Berra E, Comerford KM, Ginouves A, Fitzgerald KT, Seeballuck F, Godson C, Nielsen JE, Moynagh P, Pouyssegur J, Taylor CT: Prolyl hydroxylase-1 negatively regulates IkappaB kinase-beta, giving insight into hypoxia-induced NFkappaB activity. Proc Natl Acad Sci USA 2006, 103:18154–18159
25. Walmsley SR, Print C, Farahi N, Peyssonnaux C, Johnson RS, Cramer T, Sobolewski A, Condliffe AM, Cowburn AS, Johnson N, Chilvers ER: Hypoxia-induced neutrophil survival is mediated by HIF-1alpha-dependent NF-kappaB activity. J Exp Med 2005, 201:105–115
26. Sha WC, Liou HC, Tuomanen EI, Baltimore D: Targeted disruption of the p50 subunit of NF-kappa B leads to multifocal defects in immune responses. Cell 1995, 80:321–330
27. Tomczak MF, Erdman SE, Davidson A, Wang YY, Nambiar PR, Rogers AB, Rickman B, Luchetti D, Fox JG, Horwitz BH: Inhibition of Helicobacter hepaticus-induced colitis by IL-10 requires the p50/p105 subunit of NF-kappa B. J Immunol 2006, 177:7332–7339
28. Lu ZY, Yu SP, Wei JF, Wei L: Age-related neural degeneration in nuclear-factor kappaB p50 knockout mice. Neuroscience 2006, 139:965–978
29. Yu Z, Zhou D, Cheng G, Mattson MP: Neuroprotective role for the p50 subunit of NF-kappaB in an experimental model of Huntington's disease. J Mol Neurosci 2000, 15:31–44
30. Porta C, Rimoldi M, Raes G, Brys L, Ghezzi P, Di Liberto D, Dieli F, Ghisletti S, Natoli G, De Baetselier P, Mantovani A, Sica A: Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor kappaB. Proc Natl Acad Sci USA 2009, 106:14978–14983
31. Frantz S, Tillmanns J, Kuhlencordt PJ, Schmidt I, Adamek A, Dienesch C, Thum T, Gerondakis S, Ertl G, Bauersachs J: Tissue-specific effects of the nuclear factor kappaB subunit p50 on myocardial ischemia-reperfusion injury. Am J Pathol 2007, 171:507–512
32. Frantz S, Hu K, Bayer B, Gerondakis S, Strotmann J, Adamek A, Ertl G, Bauersachs J: Absence of NF-kappaB subunit p50 improves heart failure after myocardial infarction. FASEB J 2006, 20:1918–1920
33. Brand K, Page S, Rogler G, Bartsch A, Brandl R, Knuechel R, Page M, Kaltschmidt C, Baeuerle PA, Neumeier D: Activated transcription factor nuclear factor-kappa B is present in the atherosclerotic lesion. J Clin Invest 1996, 97:1715–1722
34. Wilson SH, Caplice NM, Simari RD, Holmes DR Jr, Carlson PJ, Lerman A: Activated nuclear factor-kappaB is present in the coronary vasculature in experimental hypercholesterolemia. Atherosclerosis 2000, 148:23–30
35. Hajra L, Evans AI, Chen M, Hyduk SJ, Collins T, Cybulsky MI: The NF-kappa B signal transduction pathway in aortic endothelial cells is primed for activation in regions predisposed to atherosclerotic lesion formation. Proc Natl Acad Sci USA 2000, 97:9052–9057
36. Iiyama K, Hajra L, Iiyama M, Li H, DiChiara M, Medoff BD, Cybulsky MI: Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesions and at sites predisposed to lesion formation. Circ Res 1999, 85:199–207
37. Hernández-Presa M, Bustos C, Ortego M, Tuñon J, Renedo G, Ruiz-Ortega M, Egido J: Angiotensin-converting enzyme inhibition prevents arterial nuclear factor-kappa B activation, monocyte chemoattractant protein-1 expression, and macrophage infiltration in a rabbit model of early accelerated atherosclerosis. Circulation 1997, 95:1532–1541
38. Rodriguez-Ayala E, Anderstam B, Suliman ME, Seeberger A, Heimbürger O, Lindholm B, Stenvinkel P: Enhanced RAGE-mediated NFkappaB stimulation in inflamed hemodialysis patients. Atherosclerosis 2005, 180:333–340
39. Shah PK: Link between infection and atherosclerosis: who are the culprits: viruses, bacteria, both, or neither? Circulation 2001, 103:5–6
40. Gareus R, Kotsaki E, Xanthoulea S, van der Made I, Gijbels MJ, Kardakaris R, Polykratis A, Kollias G, de Winther MP, Pasparakis M: Endothelial cell-specific NF-kappaB inhibition protects mice from atherosclerosis. Cell Metab 2008, 8:372–383
41. Kanters E, Pasparakis M, Gijbels MJ, Vergouwe MN, Partouns-Hendriks I, Fijneman RJ, Clausen BE, Förster I, Kockx MM, Rajewsky K, Kraal G, Hofker MH, de Winther MP: Inhibition of NF-kappaB activation in macrophages increases atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2003, 112:1176–1185
42. Kanters E, Gijbels MJ, van der Made I, Vergouwe MN, Heeringa P, Kraal G, Hofker MH, de Winther MP: Hematopoietic NF-kappaB1 deficiency results in small atherosclerotic lesions with an inflammatory phenotype. Blood 2004, 103:934–940
43. Drager LF, Jun J, Polotsky VY: Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis [Erratum appeared in Curr Opin Endocrinol Diabetes Obes 2010, 17:394]. Curr Opin Endocrinol Diabetes Obes 2010, 17:161–165
44. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, Hunninghake GM, Vera MP; MICU Registry, Blackwell TS, Baron RM, Feinberg MW: MicroRNA-181b regulates NF-kappaB-mediated vascular inflammation. J Clin Invest 2012, 122:1973–1990
45. Fang Y, Shi C, Manduchi E, Civelek M, Davies PF: MicroRNA-10a regulation of proinflammatory phenotype in athero-susceptible endothelium in vivo and in vitro. Proc Natl Acad Sci USA 2010, 107:13450–13455