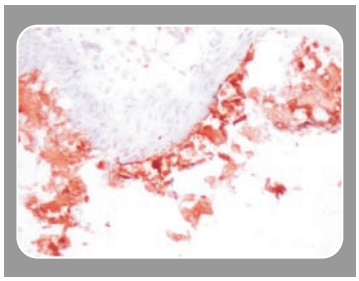
abrupt obstruction of the vessel lumen by a thrombus formed on the contact of a ruptured or eroded atherosclerotic plaque. The available data strongly suggest that immuno-inflammatory–related mechanisms are the major determinants of plaque complications. Therefore, most of the important advances in the comprehension of the mechanisms of atherosclerosis have come from studies aimed at elucidating the critical components involved in the modulation of the immuno-inflammatory balance within the plaque. However, despite the increasing knowledge regarding the role of inflammation in atherogenesis, the precise intracellular transduction pathways involved in this process remain largely unexplored.

Recent studies have pointed to the transcription factor nuclear factor κB (NF-κB) as potentially one of the most important proinflammatory pathways in atherogenesis. Various risk factors for atherosclerosis, including hypercholesterolemia, diabetes and its associated advanced glycation end products, hypertension, elevated plasma homocysteine levels, and increased oxidative stress, which is common to all the preceding conditions, are important activators of NF-κB. Activated NF-κB has been identified in smooth muscle cells, macrophages, and endothelial cells of human atherosclerotic lesions,[1] and enhanced activation of this transcription factor has been shown to occur very early following a high-fat, cholate-free diet in low-density lipoprotein receptor (LDLR)–deficient mice.[2] However, apart from significant positive correlations between activated NF-κB and proatherogenic activity, the direct role of NF-κB in the development and composition of atherosclerotic plaques had not yet been assessed.

In a recent study, Kanters et al, using LDLR-deficient mice with a macrophage-restricted deletion of IκB kinase 2 (IKK2) leading to specific inhibition of NF-κB activation in macrophages, reported the unexpected finding of increased atherosclerotic lesion formation and inflammation.[3] This result was associated with a significant reduction in the anti-inflammatory and anti-atherogenic cytokine interleukin-10 (IL-10), suggesting that a certain level of NF-κB activation was required for the control of the inflammatory reaction and the protection against unabated inflammatory and proatherogenic responses. This is in agreement with studies showing a central role for NF-κB in the induction of "protective" anti-apoptotic and anti-inflammatory genes, critical to the resolution of the inflammatory process.[4]



However, according to the study by Kanters and colleagues in this issue of *Blood* (page 934), the detrimental effect of NF-κB inhibition in atherogenesis depends on how NF-κB activity is inhibited. In this study, Kanters et al examined the effects of hematopoietic NF-κB1 (p50) deficiency in the development of atherosclerotic lesions in LDLR knockout mice. Instead of promoting the formation of larger inflammatory lesions, as was the case with IKK2 deficiency, a significant decrease in lesion size in mice with NF-κB1 deficiency, despite enhanced accumulation of T and B lymphocytes within the lesions, was observed. This could be explained, at least in part, by the observation that, in contrast to IKK2 deficiency, NF-κB1 deficiency did not lead to an alteration of the inflammatory balance in favor of a proatherogenic phenotype. Despite increased tumor necrosis factor (TNF) expression by NF-κB1$^{-/-}$ macrophages, other major proatherogenic molecules such as monocyte chemoattractant protein-1 (MCP-1) were down-regulated, whereas critical antiatherogenic factors such as IL-10 were significantly up-regulated. Decreased MCP-1 production and increased IL-10 expression may have contributed to limitation of plaque size despite enhanced accumulation of T cells. Another plausible mechanism leading to inhibition of lesion development in NF-κB1–deficient animals could be attributed to a potential defect in the uptake of oxidized low-density lipoprotein (oxLDL) by macrophages, as characteristic foam cells were absent in NF-κB1$^{-/-}$ lesions and both scavenger receptor class A (SR-A) expression and uptake of oxLDL were significantly reduced in NF-κB1$^{-/-}$ macrophages upon ex vivo stimulation with lipopolysaccharide (LPS). Whether this in vitro effect, observed following LPS stimulation, is relevant to the in vivo situation remains to be determined.

NF-κB appears to be at the crossroads of the inflammatory response in atherosclerosis, fine-tuning the response of the vessel wall to injury. Kanters et al should be commended for these provocative studies on the role of NF-κB, one of the most important proinflammatory transcription factors, in atherosclerosis.

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Memory depending on an intimate relationship

Accumulating evidence suggests a critical role for interleukin-15 (IL-15) in the development and maintenance of CD8 memory T cells. Nevertheless, there are some unsolved issues as to how IL-15 acts on target cells. Based on in vitro studies, it was postulated that nonlymphoid cells secrete IL-15, and T/natural killer (NK) cells expressing all 3 IL-15 receptor (IL-15R) components (α, β, and γ chain [γC]) bind it and proliferate.

However, Lodolce et al[1] challenged this paradigm. Using adoptive transfer experiments involving IL-15Rα$^{-/-}$ and wild-type (wt) mice, they demonstrated that although the expression of IL-15Rα by radiation-resistant "environmental" cells is crucial, the expression of IL-15Rα by T cells is dispensable for the survival of CD8 T cells. But how do T cells respond to IL-15 in vivo without IL-15Rα?

In parallel, Dubois et al[2] demonstrated that activated monocytes bear membrane-associated IL-15 bound by IL-15Rα and present IL-15 in *trans* to neighboring T cells. This IL-15 transpresentation model presented a reasonable solution to the paradox presented by Lodolce et al.[1] Taken together, the suggested scenario would be that IL-15 is first captured by environmental cells expressing IL-15Rα, and then it is transpresented to CD8 memory T cells or NK cells to support their proliferation.

In this issue, Schluns and colleagues (page 988) further advance the model by defining the specific cell types that are capable of presenting IL-15 in *trans* to CD8 memory T cells. Using bone marrow (BM) chimeras generated from IL-15Rα$^{-/-}$ and wt mice, they first confirmed the observation made by Burkett et al[3] that memory CD8 cells proliferate in wt mice even if the cells lack the autologous expression of IL-15Rα, but their proliferation critically depends on IL-15Rα expression by bone marrow–derived cells.

The most intriguing observation of their study is that CD8 memory T cells proliferated in the spleen of chimeras expressing IL-15Rα only on BM-derived nonlymphoid cells, but not in chimeras expressing IL-15Rα on parenchymal cells. Interestingly, memory CD8 T cells that reside in the lungs did not show such preference in their cell-type dependency on IL-15Rα expression, as lung memory CD8 T cells proliferated, albeit slightly less robustly, in chimeras expressing IL-15Rα on either BM-derived or parenchymal cells.

This observation suggests that a cell-specific molecule may be required in addition to IL-15Rα for the IL-15 transpresentation to function. In addition, memory CD8 T cells from different tissues may have different characteristics, which may account for the tissue-specific occurrence of various immunologic events, including the development of autoimmune diseases. Last, though it may sound paradoxical, we should not be so hasty to ignore the relevance of autologous IL-15Rα expression on T cells, as the effect of IL-15 on the long-term survival of memory CD8 T cells is not fully understood.

Gett et al[4] reported that the expression levels of IL-15Rα, determined by the strength of the initial antigen stimulation, define the fitness status of CD8 T cells and affect their long-term survival in response to IL-15. Nonetheless, the IL-15 transpresentation paradigm seems to shed a new light on our understanding of the involvement of IL-15 in the maintenance of CD8 memory T cells.

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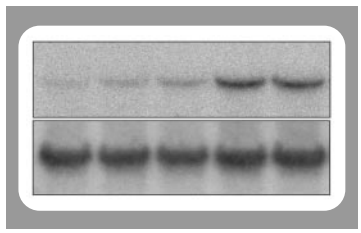
HIF: a paradigm of biologic versatility

HIF is a hypoxia-inducible transcription factor with a remarkably broad physiologic repertoire. It is of special interest to hematologists because research on HIF began with an in-depth study of the regulation of the erythropoietin gene. The identification of a critical response element within a 3′ enhancer, necessary and sufficient for hypoxic induction of erythropoietin expression, led Wang and Semenza to the identification of HIF.[1] This heterodimeric transcription factor was shown to bind to homologous response elements in a number of biologically important genes, including those involved in angiogenesis, glycolysis, apoptosis, iron homeostasis, and nitric oxide metabolism. The activation of HIF by hypoxia depends on stabilization of its α subunit under low oxygen tensions. Above a threshold level of



oxygen, the protein is degraded by means of hydroxylation of 2 proline residues in the oxygen-dependent degradation domain of HIFα. This posttranslational modification enables HIF-α to bind to von Hippel Lindau protein, an interaction that is necessary for subsequent degradation in the proteasome. This elegant mechanism for oxygen sensing and signal transduction is well understood at the molecular level. However, as the HIF story has unfolded it has become apparent that this transcription factor is activated by a number of other biologic stimuli besides hypoxia. These include insulin, insulin-like growth factors 1 and 2, interleukin-1β, tumor necrosis factor α, and prostaglandin E2. The physiologic significance of most of these alternate inducers of HIF is unclear. In this issue of *Blood*, Blouin and colleagues (page 1124) present strong evidence for an additional inducer of HIF: lipopolysaccharide (LPS). They demonstrate that LPS can be as robust an inducer of HIF as hypoxia. Moreover, it appears to be cell-specific, with a particularly strong effect in macrophages. It is already known that HIF plays a crucial role in macrophage biology, mediating the enhancement of anaerobic glycolysis that is critical for cellular function. In addition, HIF is required for macrophage motility and engulfment of microorganisms. The stimulation of HIF by LPS, as may occur during the cell's digestion of bacteria, could well provide an additional boost to HIF activation and enhancement of macrophage function. As mentioned above, the primary mechanism by which hypoxia induces HIF