10.1 Introduction

Inflammation is a basic pathological mechanism that underlies a variety of diseases. The inflammatory reaction involves the complex interactions between inflammatory cells (neutrophils, lymphocytes and monocytes/macrophages) and vascular cells (endothelial [EC] and smooth muscle cells [SMC]). The role of vascular cells during the inflammatory process is critical. Multiple cytokines and growth factors are present at sites of inflammation, and each of these can potentially influence the nature of the inflammatory response [1]. EC and SMC must integrate the signals generated by these multiple factors to effectively regulate the immunoinflammatory response through the expression of adhesion molecules, cytokines, chemokines, matrix metalloproteinases (MMPs) and growth factors. Research in vascular biology has progressed remarkably in the last decade, resulting in a better understanding of the vascular cell responses to inflammatory stimuli, as well as in the identification of the major intracellular inflammatory signaling pathways, NF-κB, AP-1 and JAK/STAT. Much recent works show that vascular inflammation can be limited by anti-inflammatory counter regulatory mechanisms that maintain the integrity and homeostasis of the vascular wall. This might be of particular importance in inflammatory diseases such as atherosclerosis, aneurysm, septic shock or ischemia/reperfusion. Critically situated at the boundary between blood and tissues, the endothelium is a focus for inflammatory processes. EC receive signals from humoral factors, inflammatory mediators, and physical forces from both the circulation and the tissue. A number of potential triggers capable of inducing
proinflammatory and prothrombotic cellular responses have been identified; these include modified lipoproteins, proinflammatory cytokines, chemokines, vasoactive peptides (angiotensin II, endothelin), neuropeptides (substance P), hyperglycemia and advanced glycosylated end products (AGE), smoking, oxidative stress [2]. SMC also are targets of these triggers. The purpose of the present review is to describe recent advances in the understanding of the mechanisms of vascular inflammation.

10.2 Inflammation-Associated Signaling Pathways

10.2.1 NF-κB

The NF-κB pathway is one of the main signaling pathways activated in response to proinflammatory cytokines, including TNF-α, IL-1 and IL-18, as well as following activation of the Toll like receptors (TLR) by the pattern-recognition of pathogen-associated molecular patterns (PAMPs) (Fig. 10.1). Activation of this pathway plays a central role in vascular inflammation through the regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes such as cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS). NF-κB is a dimeric transcription factor formed by the hetero or homodimerization of proteins of the Rel family, including p50 and p65 (reviewed in [3]). In its inactive form NF-κB is bound to inhibitor of κB (I-κBα/β) in the cytoplasm. Prolinflammatory cytokines and pathogens act through distinct signaling pathways that converge on the activation of an IκB kinase (IKK) complex containing two kinases IKK1/IKKα and IKK2/IKKβ and the regulatory protein NEMO (NF-κB essential modifier, also named IKKγ); IKK activation initiates IκBα/β phosphorylation at specific amino-terminal serine residues. Phosphorylated IκB is then ubiquitinated, leading to its degradation by the 26S proteasome. This releases NF-κB dimers from the cytoplasmic NF-κB–IκB complex, allowing them to translocate to the nucleus. Once in the nucleus, NF-κB binds to κB enhancer elements on specific genes promoting transcription. Target genes of NF-κB include IκBα, the synthesis of which ensures that NF-κB is transiently activated. This negative feedback regulation gives rise to oscillations in NF-κB translocation.

NF-κB is a redox-sensitive transcription factor, and the intracellular redox status of the cell is extremely important in the regulation of NF-κB activity (reviewed in [4]). Anti-oxidants, such as aspirin, N-acetyl-cysteine (NAC) and flavonoids can therefore inhibit the activation of NF-κB. A number of natural constitutive or inducible pathways inhibiting NF-κB activity also exist. For example, A1 and A20, two products of cytopoprotective genes, are induced in response to inflammatory stimuli to protect EC from exaggerated activation [5]. The inducible form of the heme oxygenase (HO-1) is another example of endogenous anti-inflammatory pathway induced in response to inflammatory stimuli. HO-1 can be upregulated in EC by TNF and IL-1, and HO-1 possesses potent anti-apoptotic and anti-inflammatory