Atherosclerosis involves upregulation of the canonical nuclear factor-kappa B (NF-κB) signaling pathway in several vascular cell types throughout evolution of the disease.

The canonical NF-κB pathway
NF-κB comprises a family of heterodimeric transcription factors that reside in the cytoplasm of every cell and upon activation translocate to the nucleus. The canonical pathway is activated by a wide variety of agents including inflammatory stimuli, pathogens, free radicals, stress, and nicotine smoke. These disparate signaling pathways ultimately lead to phosphorylation of the IKK complex. This complex is composed of a regulatory subunit (IKKγ, also known as IKKε or NEMO) and two similar subunits (IKKα and IKKβ). Typically, the IKK complex is activated by phosphorylation of IKKγ, which in turn phosphorylates IKKα. Phosphorylated IKKα is degraded by the proteasome pathway and the resulting IKKβ (p50/p50 dimer) forms an example of IKK2 to regulate the expression of almost 400 different genes (some indicated below).

NF-κB and the onset of atherosclerosis
Atherosclerosis develops at large vessel branch points, where turbulent blood flow activates shear stress sensors of endothelial cells. One such sensor is thought to be platelet endothelial cell adhesion molecule (PECAM1) in complex with VE-cadherin, β3 integrin, which then engages with extracellular matrix proteins containing the RGD binding site. A second round of PI3K activation and PIP3 production ensues, which ultimately leads to phosphorylation of the IKK complex through an unclear RAC pathway.

Macrophages/foam cells and other inflammatory cells accumulating within the atherosclerotic plaque produce a variety of NF-κB-dependent proinflammatory cytokines that enhance plaque formation (tumor necrosis factor α (TNFα), IL-1, IL-6, IL-12, interferon-γ (IFNγ)). Of these interleukin 1 (IL-1) and IL-6 are key cytokines, both activating NF-κB and increasing macrophage and foam cell foaminess. Other NF-κB-encoded genes that may influence atherosclerosis are chemokines (CXCL1, CCL13, and plakoglobin) that attract inflammatory cells to atherosclerotic lesions, matrix metalloproteinase-9, which may facilitate migration of inflammatory and smooth muscle cells within the plaque, and tissue factor and plasminogen activator inhibitor 1 (PAI-1), which convey a procongesting tone to the plaque.

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