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Regulation of iNOS Expression in Inflammation and as a Target of Anti-inflammatory Drugs

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Nitric oxide (NO) is a gaseous signaling molecule that regulates various physiological and pathophysiological processes in the human body, including vascular tone, neurotransmission, and antimicrobial and inflammatory responses. In inflammation, NO is produced through iNOS pathway, which is induced in inflammatory and tissue cells in response to microbial products and pro-inflammatory cytokines.

At cellular and molecular level, NO has direct and indirect effects. An example of the direct effects is its action on the activity of a variety of enzymes including the stimulatory effect on guanylate cyclase which forms cGMP; and cGMP is an intracellular mediator of many physiological effects of NO. In an inflammatory focus, when NO is produced in higher amounts, the indirect effects through NO-derived radicals become more important. Nitrosylation and nitration reactions mediate many of the indirect effects of NO. Peroxynitrite is a molecule formed in a reaction of NO and superoxide. Peroxynitrite is a powerful nitrating and oxidizing agent which is responsible for many of the harmful effects of NO in inflammation.

In relation to infections, NO is a part of the defense mechanisms aimed to target invading pathogens. In the inflammatory process itself, NO has regulatory, pro-inflammatory and destructive effects. In many chronic inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease, increased iNOS expression and enhanced NO production have been shown to have detrimental effects. Accordingly, selective iNOS inhibitors have proved to be anti-inflammatory in many experimentally-induced chronic inflammatory diseases.

Nuclear factor kB (NF-kB) and signal transducer and activator of transcription-1 (STAT-1) are important transcription factors for both human and murine iNOS. Those pathways – and iNOS expression – can be regulated / inhibited by antioxidants and other inhibitors of NF-kB, and by inhibitors of JAK-STAT pathways. In addition, anti-inflammatory steroids have been reported to inhibit NF-kB pathway. The pathways are not unique for iNOS, and their inhibitors down-regulate also the production of many other inflammatory factors.

In addition to transcriptional regulation, iNOS expression is regulated also at post-transcriptional level. Interestingly, unstimulated cells may show significant basal activity of iNOS promoter constructs and continuous iNOS transcription while iNOS mRNA and protein expression or NO synthesis is not detected. Therefore, it is likely that unstimulated cells produce highly unstable iNOS mRNA which is stabilized in inflammatory conditions. Based on sequence analysis, the 3'-untranslated region (3'-UTR) in both human and murine iNOS mRNA contains adenosine-uridine –rich elements (AREs) that are related to stabilization / destabilization of transiently expressed inflammatory and other genes. Four ARE binding proteins – HuR, AUF-1, TTP and KSRP – have been reported to regulate the stability of iNOS mRNA. In addition, c-Jun N-terminal kinase (JNK) and protein kinase C-delta (PKC-delta) pathways have been shown to mediate signals to stabilize iNOS mRNA. Destabilization of mRNA of iNOS and other transiently expressed inflammatory genes may be therapeutically important; so far factors like dexamethasone, cGMP, forskolin – cAMP, beta-adrenergic agonists, and inhibitors of p38, JNK and PKC-delta pathways have been reported to regulate the stability of iNOS mRNA and subsequent iNOS expression and NO production in inflammatory conditions.

After iNOS protein is produced, it may be directed to enhanced / reduced degradation. The calpain and proteasome pathways are the major proteolytic pathways recognized in the degradation of iNOS protein. For example, transforming growth factor-beta (TGF-beta) and peroxisome proliferator-activated receptor-alpha (PPAR-alpha) agonists have been shown to inhibit NO production by enhancing iNOS protein degradation in chondrocytes and in macrophages.

Based on many cellular and animal models, compounds that inhibit the activity or expression of iNOS have anti-inflammatory properties, and are likely to be useful in the treatment of inflammatory diseases which are complicated with excessive NO production through iNOS pathway. The basic research on the mechanisms how iNOS expression is regulated transcriptionally and post-transciprionally provides knowledge which can be utilized in the development of more selectively targeted medicines for inflammatory diseases.