PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Anti-inflammatory effects of NF-?B

ArticleInfo		
ArticleID	:	284
ArticleDOI	:	10.1186/ar-2002-74852
ArticleCitationID	:	74852
ArticleSequenceNumber	:	37
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2002–1–17 Received : 2002–1–17 OnlineDate : 2002–1–17
ArticleCopyright	:	Biomed Central Ltd2002
ArticleGrants	:	
ArticleContext	:	130754411

Cheryl Smythe,[Aff1]

Aff1 Faculty of Medicine, Imperial College, London, UK

Keywords

Anti-inflammatory, apoptosis, exudate, leukocyte, NF-?B, PDTC, pleurisy

Context

Inflammation is a self-resolving process during which both pro- and anti-inflammatory mediators are temporally expressed. The transcription factor NF-?B is known to positively regulate the expression of proinflammatory mediators such as cytokines, growth factors and adhesion molecules and is therefore considered to be an interesting target for therapeutic intervention. However, some evidence suggests a role for NF-?B in the resolution of the inflammatory response. Therefore using two animal models, this study investigates the role of leukocyte NF-?B throughout the inflammatory response.

Significant findings

NF-?B activation in leukocytes from rat carrageenin pleurisy was found to be biphasic. cRel-p50 NF-?B complexes were predominant at 6h, with increased inducible nitric oxide synthase expression. In contrast, at 48h NF-?B complexes comprised of p50-p50 homodimers were associated with increased cyclooxygenase-2 expression. The NF-?B inhibitor PDTC significantly reduced the exudate volume and the number of extravasated leukocytes when administered simultaneously with the carrageenin challenge (prophylactically). However, if administered 24h after challenge (therapeutically), exudate volume and leukocyte number increased, while the level of TGF-? and the number of apoptotic leukocytes decreased. Temporal gene expression analysis demonstrated that levels of lymphotoxin ?, TNF-a and the anti-apoptotic protein Bcl2 were elevated 6h after challenge, while TGF-&946;1 and the proapoptotic Bcl2 homolog Bax were expressed at 48h. Expression of lymphotoxin ? and TNF-a was inhibited at 6h if the NF-?B inhibitor was administered prophylactically. However if administered therapeutically, expression of TGF-?1 and Bax was reduced, and processing of p105 to p50 was inhibited.

Comments

NF-?B biology is complex. The transcription factor is composed of either homo- or heterodimers from the rel family that are regulated by inhibitory molecules, which are in turn regulated by multiple kinase cascades. However, understanding these complexities has allowed us to shed light on the subtleties of NF-?B signalling, which is sometimes proinflammatory and other times anti-inflammatory. This study demonstrates this dual role of NF-?B in an in vivo model of inflammation. Depending on the time of intervention, NF-?B inhibition can either inhibit inflammation or prolong the inflammatory response by preventing its resolution. In order to establish whether this is a general phenomenon, this study now needs to be repeated in a more complex inflammatory model. Development of inhibitors that are specific for individual components of the rel family might allow the inhibition of NF-?B-mediated proinflammatory effects without inhibiting the resolution of inflammation. Such inhibitors would be invaluable in the treatment of inflammatory conditions such as rheumatoid arthritis.

Methods

Carrageenin-induced pleurisy, mouse carrageenin air pouch, electrophoretic mobility-shift assay, ELISA, western blotting, annexin V apoptosis and RNase protection assays

Additional information

References

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