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Annexin A1 (AnxA1) is a glucocorticoid-regulated protein endowed with anti-inflammatory and proresolving properties. Intact AnxA1 is a 37-kDa protein that may be cleaved in vivo at the N-terminal region by neutrophil proteases including elastase and proteinase-3, generating the 33-kDa isoform that is largely inactive. In this study, we investigated the dynamics of AnxA1 expression and the effects of synthetic (sivelestat [SIV]; Eglin) and natural (secretory leukocyte protease inhibitor [SLPI]; Elafin) protease inhibitors on the resolution of LPS-induced inflammation. During the settings of LPS inflammation AnxA1 cleavage associated closely with the peak of neutrophil and elastase expression and activity. SLPI expression increased during resolving phase of the pleurisy. Therapeutic treatment of LPS-challenge mice with recombinant human SLPI or Elafin accelerated resolution, an effect associated with increased numbers of apoptotic neutrophils in the pleural exudates, inhibition of elastase, and modulation of the survival-controlling proteins NF-κB and Mcl-1. Similar effects were observed with SIV, which dose-dependently inhibited neutrophil elastase and shortened resolution intervals. Mechanistically, SIV-induced resolution was caspase-dependent, associated to increased levels of intact AnxA1 and decreased expression of NF-κB and Mcl-1. The proresolving effect of antiproteases was also observed in a model of monosodium urate crystals-induced inflammation. SIV skewed macrophages toward resolving phenotypes and enhanced efferocytosis of apoptotic neutrophils. A neutralizing antiserum against AnxA1 and a nonselective antagonist of AnxA1 receptor abolished the accelerated resolution promoted by SIV. Collectively, these results show that elastase inhibition not only inhibits inflammation but actually promotes resolution, and this response is mediated by protection of endogenous intact AnxA1 with ensuing augmentation of neutrophil apoptosis.