Proteinase 3 and neutrophil elastase enhance inflammation in mice by inactivating antiinflammatory progranulin.

Abstract: Neutrophil granulocytes form the body's first line of antibacterial defense, but they also contribute to tissue injury and noninfectious, chronic inflammation. Proteinase 3 (PR3) and neutrophil elastase (NE) are 2 abundant neutrophil serine proteases implicated in antimicrobial defense with overlapping and potentially redundant substrate specificity. Here, we unraveled a cooperative role for PR3 and NE in neutrophil activation and noninfectious inflammation in vivo, which we believe to be novel. Mice lacking both PR3 and NE demonstrated strongly diminished immune complex-mediated (IC-mediated) neutrophil infiltration in vivo as well as reduced activation of isolated neutrophils by ICs in vitro. In contrast, in mice lacking just NE, neutrophil recruitment to ICs was only marginally impaired. The defects in mice lacking both PR3 and NE were directly linked to the accumulation of antiinflammatory progranulin (PGRN). Both PR3 and NE cleaved PGRN in vitro and during neutrophil activation and inflammation in vivo. Local administration of recombinant PGRN potently inhibited neutrophilic inflammation in vivo, demonstrating that PGRN represents a crucial inflammation-suppressing mediator. We conclude that PR3 and NE enhance neutrophil-dependent inflammation by eliminating the local antiinflammatory activity of PGRN.
Our results support the use of serine protease inhibitors as antiinflammatory agents.

Zeitschriftentitel / Abkürzung:
J Clin Invest

Jahr: 2008
Band: 118
Heft / Issue: 7
Seiten: 2438-47
Sprache: eng

Pubmed:

Print-ISSN: 0021-9738

TUM Einrichtung:
r Dermatologie und Allergologie

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Klinik und Poliklinik für Dermatologie und Allergologie > 2008

entries: