Proteolytic regulation of the urokinase receptor/CD87 on monocytic cells by neutrophil elastase and cathepsin G.

The urokinase receptor (CD87) participates to the pericellular proteolytic potential of migrating cells and to the recruitment of leukocytes during inflammation. It consists of three structurally homologous domains, with the C-terminal domain D3 attached to cell membranes through a GPI anchor. CD87 is susceptible to an endoproteolytic processing removing the N-terminal domain D1 and generating truncated D2D3 membrane species, thus modulating CD87-associated functions. Full-length or truncated CD87 can be also released from cells via juxtamembrane cleavage by phospholipases and/or by yet unidentified proteinases. Using a recombinant CD87 and the CD87-positive monocytic U937 cell line and isolated blood monocytes, we show by protein immunoblotting and flow immunocytometry that the human neutrophil serine-proteinases elastase and cathepsin G cleave CD87 within the D1-D2 linker sequence, while in addition cathepsin G is highly efficient in cleaving the C terminus of D3. The combination of cathepsin G and elastase provided by degranulated neutrophils results in enzymatic cooperation leading to the release from monocytic cells of a truncated D2D3 species resembling that previously described in pathological body fluids. Using mass spectrometry analysis, the proteolytic fragmentation of synthetic peptides mapping the D1-D2 linker and D3 C-terminal
domains identifies potential cleavage sites for each enzyme and suggests the existence of a mechanism regulating the CD87(D1-D2)-associated chemotactic activity. Finally, isolated or combined elastase and cathepsin G drastically reduce the capacity of cells to bind urokinase. Secretable leukocyte serine-proteinases are thus endowed with high potential for the regulation of CD87 expression and function on inflammatory cells.