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.