Group X secreted phospholipase A_2 is matured intracellularly by furin and proprotein convertase 5

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Group X (GX) secreted phospholipase A_2 ($sPLA_2$) is the most potent among $sPLA_2$s in hydrolysing cell membrane phosphatidylcholine, and is involved in a variety of (patho)physiological processes, including reproduction, atherosclerosis, asthma and cancer. GX $sPLA_2$ is produced as a proenzyme (pro-GX) and contains a short propeptide ending with a dibasic motif, suggesting cleavage by proprotein convertases (PCs). Although the removal of this propeptide is clearly required for enzymatic activity, the cellular location and the protease(s) involved in proenzyme activation are unknown. In this study we analysed the maturation of GX by PCs in HEK293 cells.

Using recombinant mouse and human pro-GX we found that of the five PCs expressed in HEK293 cells, only furin, PC5 and PC7 cause a complete removal of the propeptide *in vitro*. In order to determine which PCs are involved in the maturation of pro-GX in mammalian cells, HEK293 cells stably expressing the full-length mouse and human pro-GX were used. The conversion of precursor $sPLA_2$s was enhanced by overexpression of PCs, and was blocked by various PC inhibitors and siRNA against PCs. The results obtained show that furin and PC5, but not PC7, can mature pro-GX in HEK293 cells and that removal of the pro-peptide occurs already during secretion of the $sPLA_2$ from the cell.

Our results demonstrate that the group X $sPLA_2$ proenzyme is matured intracellularly by furin and PC5, suggesting a redundancy of proteases involved in the cleavage of pro-GX $sPLA_2$ in HEK293 cells and most likely also *in vivo*.