An internal signal sequence directs intramembrane proteolysis of a cellular immunoglobulin-domain protein

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Precursor proteolysis is a crucial mechanism for regulating protein structure and function. Signal peptidase (SP) is an enzyme with a well-defined role in cleaving N-terminal signal sequences but no demonstrated function in the proteolysis of cellular precursor proteins. We provide evidence that SP mediates intraprotein cleavage of IgSF1, a large cellular immunoglobulin (Ig)-domain protein that is processed into two separate Ig-domain proteins. In addition, our results suggest the involvement of signal peptide peptidase (SPP), an intramembrane protease, which acts on substrates that have been previously cleaved by signal peptidase (SP). We show that IgSF1 is processed through sequential proteolysis by SP and SPP. Cleavage is directed by an internal signal sequence and generates two separate Ig-domain proteins from a polytopic precursor. Our findings suggest that SP and SPP function are not restricted to N-terminal signal sequence cleavage but also contribute to the processing of cellular transmembrane proteins.
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