

Domain and Functional Analysis of a Novel Platelet-Endothelial Cell Surface Protein;SCUBE1

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摘要

Abstract

SCUBE1 (signal peptide-CUB-EGF domain-containing protein 1) is a novel, secreted, cell surface glycoprotein expressed during early embryogenesis and found in platelet and endothelial cells. This protein is composed of an N-terminal signal peptide sequence followed by nine tandemly arranged epidermal growth factor (EGF)-like repeats, a spacer region, three cysteine-rich repeat motifs, and one CUB domain at the C terminus. However, little is known about its domain and biological function. Here, we generated a comprehensive panel of domain deletion constructs and a new genetic mouse model with targeted disruption of Scube1 (Scube1(Delta cub/Delta cub)) to investigate the domain function and biological significance. A number of cell-based assays were utilized to define the critical role of the spacer region for membrane association and establish that the EGF-like repeats 7-9 are sufficient for the formation of SCUBE1-mediated homophilic adhesions in a calcium-dependent fashion. Biochemical and molecular analyses showed that the C-terminal cysteine-rich motifs and CUB domain could directly bind and antagonize the bone morphogenetic protein activity. Furthermore, genetic ablation of this C-terminal region resulted in brain malformation in the Scube1(Delta cub/Delta cub) embryos. Together, our results support the dual roles of SCUBE1 on brain morphogenesis and cell-cell adhesions through its distinct domain function.