

Expanding the Role of THU

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Protein secretion is a fundamental biological process essential for intercellular communication. In conventional secretion, the SRP-SEC61 system acts in cargo translocation. However, it remains unclear how cargoes lacking a signal peptide enter secretory vesicles in unconventional protein secretion (UcPS), and how diverse UcPS cargoes are specifically controlled in different settings has not been determined. Here we identify the TMED family proteins as cargo translocators in UcPS. TMEDs individually and cooperatively regulate translocation of different sets of UcPS cargoes into secretory vesicles and facilitate cargo release. The ER-Golgi intermediate compartment (ERGIC)/Golgi acts as the station of translocation due to its special lipid composition, where sphingomyelin stimulates translocation but cholesterol antagonizes the effect. TMED10 forms a channel with two open states, with a high current state correlating with translocation activity. Together, these findings implicate TMEDs as a new class of protein channels for differential translocation and release of multitude UcPS cargoes.