Computational modeling of C-terminal tails to predict the calcium-dependent secretion of ER resident proteins

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Contact Information:

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All queries, feedback or suggestions are also very welcome.

Research Paper Sections:

The sections of the research paper input text parsed in this audit.

Section No.	Headings	Sentences
Section: 1	Abstract	9
Section: 2	Introduction	18
N/A	--- --- --- --- --- --- ---	0
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The Sentence Audit Of The Research Paper

Title

Computational modeling of C-terminal tails to predict the calcium-dependent secretion of ER resident proteins

S1 [001] **Abstract**

S1 [002] The lumen of the endoplasmic reticulum (ER) has resident proteins that are critical to perform the various tasks of the ER such as protein maturation and lipid metabolism.

> The lumen ...
> ... of the endoplasmic reticulum ...
> ... (ER) ...
> ... has resident proteins ...
> ... that are critical ...
> ... to perform the various tasks ...
> ... of the ER ...
> ... such as protein maturation ...
> ... and lipid metabolism.

S1 [003] These ER resident proteins typically have a carboxy-terminal ER retention sequence (ERS).

> These ER resident proteins typically have a carboxy-terminal ER retention sequence ...
> ... (ERS).

S1 [004] The canonical ERS is Lys-Asp-Glu-Leu (KDEL) and when an ER resident protein moves from the ER to the Golgi, KDEL receptors (KDELRs) in the Golgi recognize the ERS and return the protein to the ER lumen.

> The canonical ERS is Lys-Asp-Glu-Leu ...
> ... (KDEL) ...
> ... and ...
> ... when an ER resident protein moves ...
> ... from the ER ...
> ... to the Golgi, ...
> ... KDEL receptors ...
> ... (KDELRs) ...
> ... in the Golgi recognize the ERS ...
> ... and return the protein ...
> ... to the ER lumen.

S1 [005] Depletion of ER calcium leads to the mass departure of ER resident proteins in a process termed exodosis, which is also regulated by KDELRs.

> Depletion ...
> ... of ER calcium leads ...
> ... to the mass departure ...
> ... of ER resident proteins ...
> ... in a process termed exodosis, ...
> ... which is also regulated ...
> ... by KDELRs.

S1 [006]   Here, by combining computational prediction with machine learning-based models and experimental validation, we identify carboxy tail sequences of ER resident proteins divergent from the canonical "KDEL" ERS.

> Here, ...
>
> ... by combining computational prediction ...
>
> ... with machine learning-based models ...
>
> ... and experimental validation, ...
>
> ... we identify carboxy tail sequences ...
>
> ... of ER resident proteins divergent ...
>
> ... from the canonical "KDEL" ...
>
> ... ERS.

S1 [007]   Using molecular modeling and simulations, we demonstrated that two representative non-canonical ERS can stably bind to the KDELR.

> Using molecular modeling ...
>
> ... and simulations, ...
>
> ... we demonstrated ...
>
> ... that two representative non-canonical ERS can stably bind ...
>
> ... to the KDELR.

S1 [008]   Collectively, we developed a method to predict whether a carboxy-terminal sequence acts as a putative ERS that would undergo secretion in response to ER calcium depletion and interact with the KDELRs.

> Collectively, ...
>
> ... we developed a method ...
>
> ... to predict ...
>
> ... whether a carboxy-terminal sequence acts ...
>
> ... as a putative ERS ...
>
> ... that would undergo secretion ...
>
> ... in response ...
>
> ... to ER calcium depletion ...
>
> ... and interact ...
>
> ... with the KDELRs.

S1 [009]   Identification of proteins that undergo exodosis will further our understanding of changes in ER proteostasis under physiological and pathological conditions where ER calcium is depleted.

> Identification ...
>
> ... of proteins ...
>
> ... that undergo exodosis will further our understanding ...
>
> ... of changes ...
>
> ... in ER proteostasis ...
>
> ... under physiological ...
>
> ... and pathological conditions ...
>
> ... where ER calcium is depleted.

S2 [010]   Introduction

S2 [011] The classical secretory pathway involves the movement of proteins from the endoplasmic reticulum (ER) to the Golgi and then to the cell surface.

> The classical secretory pathway involves the movement ...
>
> ... of proteins ...
>
> ... from the endoplasmic reticulum ...
>
> ... (ER) ...
>
> ... to the Golgi ...
>
> ... and then ...
>
> ... to the cell surface.

S2 [012] Resident proteins of the ER counteract this flow by using short peptide sequences.

> Resident proteins ...
>
> ... of the ER counteract this flow ...
>
> ... by using short peptide sequences.

S2 [013] For soluble proteins, a carboxy-terminal (C-terminal) ER retention sequence (ERS) interacts with KDEL receptors in the Golgi membrane to return proteins back to the ER lumen in a COPI-mediated manner (Munro and Pelham, 1987, Lewis and Pelham, 1992a, Orci et al., 1997).

> For soluble proteins, ...
>
> ... a carboxy-terminal ...
>
> ... (C-terminal) ...
>
> ... ER retention sequence ...
>
> ... (ERS) ...
>
> ... interacts ...
>
> ... with KDEL receptors ...
>
> ... in the Golgi membrane ...
>
> ... to return proteins back ...
>
> ... to the ER lumen ...
>
> ... in a COPI-mediated manner ...
>
> ... (Munro ...
>
> ... and Pelham, 1987, ...
>
> ... Lewis ...
>
> ... and Pelham, 1992a, ...
>
> ... Orci et al., 1997).

S2 [014] Mammals express three KDEL receptor isoforms, KDELR1, KDELR2, and KDELR3, all of which function as part of a Golgi-to-ER retrieval pathway to maintain the ER proteome (Lewis and Pelham, 1990, Lewis and Pelham, 1992b, Hsu et al., 1992, Collins et al., 2004, Raykhel et al., 2007).

> Mammals express three KDEL receptor isoforms, ...
>
> ... KDELR1, ...
>
> ... KDELR2, ...
>
> ... and KDELR3, ...
>
> ... all of ...
>
> ... which function ...
>
> ... as part ...

... of a Golgi-to-ER retrieval pathway ...

... to maintain the ER proteome ...

... (Lewis ...

... and Pelham, 1990, ...

... Lewis ...

... and Pelham, 1992b, ...

... Hsu et al., 1992, ...

... Collins et al., 2004, ...

... Raykhel et al., 2007).

S2 [015]   Maintaining ERS-containing proteins within the ER lumen is necessary for these proteins to carry out the diverse functions of the ER including protein trafficking and modification and lipid and carbohydrate metabolism.

Maintaining ERS-containing proteins ...

... within the ER lumen is necessary ...

... for these proteins ...

... to carry out the diverse functions ...

... of the ER including protein trafficking ...

... and modification ...

... and lipid ...

... and carbohydrate metabolism.

S2 [016]   Loss of these proteins from the ER lumen may compromise ER function and lead to gain of function elsewhere inside or outside of the cell.

Loss ...

... of these proteins ...

... from the ER lumen ...

... may compromise ER function ...

... and lead ...

... to gain ...

... of function elsewhere ...

... inside ...

... or outside ...

... of the cell.

S2 [017]   In mammals, the KDEL (lysine-aspartate-glutamate-leucine) motif is considered the canonical ERS.

In mammals, ...

... the KDEL ...

... (lysine-aspartate-glutamate-leucine) ...

... motif is considered the canonical ERS.

S2 [018]   The first observations of a luminal ER retention sequence noted that three ER resident proteins (BiP/Grp78, Grp94, protein disulfide isomerase) shared a C-terminal KDEL sequence and that deletion of this sequence resulted in secretion of the protein (Munro and Pelham, 1987).

The first observations ...

... of a luminal ER retention sequence noted ...

... that three ER resident proteins ...

... (BiP/Grp78, ...

End of Sample Audit