SUMO on CRMPs - wrestling for pain?

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The collapsin response mediator proteins (CRMPs) are an intensely studied protein family, with functions in several neurobiological processes, including axonal guidance and synaptic function; however, the detailed molecular mechanisms of CRMP action are to a large extent unknown. CRMP2 was originally cloned as a protein relevant for neurodevelopment in \textit{C. elegans}.\textsuperscript{1} It is the best-characterized member of the CRMP family, with several reported binding partners and post-translational modifications (PTMs). Increasing evidence suggests close interplay between PTMs and protein-protein interactions in CRMPs.

The Khanna laboratory has shown that CRMP2 plays a role in nociception, and its functions appear to be mediated through voltage-gated sodium (Na\textsubscript{V}) as well as calcium (Ca\textsubscript{V}) channels. The current paper\textsuperscript{2} is an addendum to a larger study published recently,\textsuperscript{3} and these studies focus on CRMP conservation and structure and the relationships between CRMP2 SUMOylation and the trafficking of the Na\textsubscript{V}1.7 channel to the plasma membrane. The authors identified Lys374 as a SUMOylation target in CRMP2, and SUMOylation is required for the correct localization of Na\textsubscript{V}1.7. From structural studies, it is clear that the SUMOylated residue is not accessible for modification in the homotetrameric structure.\textsuperscript{2,4} Hence, breakdown of the homotetramers into monomers, or possibly dimers, must take place for this PTM to be possible. This is a feasible scenario, as CRMPs form both homo- and heterotetramers, and the different oligomeric interfaces within the CRMP tetramer show different levels of conservation.\textsuperscript{5} Interestingly, very recent work\textsuperscript{6} has shown that phospho-mimicking mutations in the CRMP2 C-terminal region break the tetramer down into homodimers—in these homodimers, the SUMOylation site is, indeed, accessible (Fig. 1). These homodimers contain the oligomeric interface we predicted to be forming CRMP2 dimers in a CRMP1-CRMP2 heterotetramer.\textsuperscript{5}

Priming by Cdk5 phosphorylation at the CRMP2 C-terminal tail is required for SUMOylation.\textsuperscript{3} In addition to its folded tetrameric core, CRMP2 has a long positively charged tail, which has not been detected by crystallography and is predicted to be disordered.\textsuperscript{4} This tail is the major site for CRMP2 phosphorylation. It, thus, seems that PTMs on the C-terminal segment of CRMP2 can have surprisingly drastic structural effects on the entire CRMP2 homotetramer, exposing functional sites buried within the tetrameric assembly. This opens up new possibilities of designing molecules regulating CRMP2 oligomerization with the aim of affecting its neuronal functions. The scenario stresses the importance of intrinsically disordered regions in proteins and highlights the role of molecular flexibility even in the case of apparently rigidly folded protein domains and complexes.

A common feature of SUMOylation is that a relatively small fraction of SUMO modification can cause large effects on target protein function. In CRMP2, SUMOylation of a single CRMP2 monomer will prevent the formation of tetramers.
and interfere with their functions, effectively amplifying the SUMOylation signal. Similar mechanisms could be also relevant in other molecular cascades regulated by SUMOylation.

Nociception is dependent on \( \text{Na}_V \) channels at the synaptic-terminals of pain-sensing neurons, and different channel subtypes are involved in different variants of pain. The inhibition of these channels leads to the loss of pain sensation, but selectivity and side effects remain problematic. Furthermore, mutations in \( \text{Na}_V1.7 \), the channel shown to rely on CRMP2-mediated pathways in the current study, are linked to hereditary chronic pain syndromes. It is, thus, clear that molecules involved in the signal transduction, transport, and activation cascades of \( \text{Na}_V \) channels are attractive targets for pharmacological intervention with analgesics. The current studies\(^2,3\) are nicely supported by recent high-resolution studies on voltage-gated channels, including \( \text{Na}_V7 \) and \( \text{Ca}_V8 \)—a sign of the high timeliness of basic CRMP2 research.

As CRMP2 is cytosolic, its effects should be mediated through direct or indirect interactions with the ion channel cytoplasmic loops. However, at the moment, it is not fully clear, whether CRMP2 would directly bind to \( \text{Na}_V1.7 \) or other channels, or if its effects actually are more indirect (Fig. 1). The regulation of oligomeric state through different PTMs appears, indeed, to be a central mechanism in CRMP family protein function. While future work will inevitably clarify these open questions, the proven involvement of CRMPs in nociception and the regulation of ion channels highlights their biomedical importance and promotes the CRMP family as promising neurologic drug targets.

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