Ion selectivity of the mechanosensitive channel MscS is determined by charged residues within the cytoplasmic vestibulum

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The mechanosensitive (MS) channel of small conductance (MscS) has been characterized at both functional and structural levels and plays a major role in protection of bacterial cells against hypoosmotic shock. However, outstanding questions need to be addressed in order to understand better the structure and function relationship in MscS in particular its physiological role in bacteria and specifically what controls ionic selectivity and regulates the conductance and gating characteristics of the channel.

In this study we investigated the role that the cytoplasmic vestibular domain plays in MscS channel function by recording MscS single channel activity in liposome patches containing reconstituted wild-type and mutant MscS channels. Our results indicate that ion selectivity of MscS and its homologues differs from the ion selectivity of voltage-gated K^+, Na^+, Ca^{2+} or Cl^- channels since charged residues around the seven vestibular portals and their electrostatic interactions with permeating cations determine selectivity and regulate conductance and gating of these channels. By testing permeation of major monovalent and divalent cations in the wild-type and two vestibular MscS mutants we were able to demonstrate that the MscS selectivity mechanism resembled the selectivity of anion-selective channels, which is linked to a hydrated size of the co-permeating cation. Furthermore, we found that the cytoplasmic vestibulum should not only determine the ion selectivity of the MscS-like channels but should also control their rectifying and gating properties. This suggests that the MscS selectivity mechanism might have during the evolution been adapted to anion-selective channels in multicellular organisms.

Moreover, our findings indicate that MscS may also act as a gateway for external Ca^{2+} ions, whose interaction with acidic residues within the cytoplasmic vestibulum helps to restrict excessive rise of intracellular calcium, which has been implicated in a number of bacterial cell functions, including heat shock, pathogenicity, chemotaxis, differentiation and the cell cycle. Consequently, in addition to their role as safety valves rescuing bacteria from deleterious effects of hypoosmotic shocks a physiological role of the MscS class of channels seems to be in regulation of intracellular calcium concentration in bacterial cells.

Supported by the School of Pharmacy and Pharmaceutical Sciences and Cardiff University Endowment Fund, Erasmus Programme and National Medical and Health Research Council of Australia.