

## **THE MEMBRANE SKELETON: MECHANOPROTECTOR AND MEDIATOR OF MECHANOSENSITIVE SURFACE AREA**

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Membrane “mechanoprotection” is the collection of features that ensure plasma membrane tensions remain not only sublytic, but too low to interfere with the functional activity of membrane proteins. Early expectations about mechanosensitive channels were that membrane skeleton stress would provide mechano-gating energy to channels. In diverse ion channels [1], we have shown that plasma membrane stretch can alter channel behavior, but importantly, disrupted membrane skeleton makes it *easier* not harder for mechanical stimuli to perturb the channels. This is strong evidence that “working” membrane skeleton is mechanoprotective of channels during plasma membrane stress, that is that membrane skeleton acts as a load-bearing element in a way that spares the in-parallel bilayer surround of channels from full loads. What arrangements of spectrin, actin and associated proteins serve to confer mechanoprotection on the bilayer? Is mechanoprotection temporarily abrogated during membrane turnover? About these fundamental questions on the working mechanics of membrane skeleton very little is known.

Surface area regulation (SAR) is the collection of processes driving loss/addition of surface bilayer so as to control plasma membrane area. SAR, we think, is mechanosensitive: we postulate that the “SA set-point” is a local membrane tension set-point [2].

In neurons, we impose swell/shrink perturbations to study the dynamics of cortical F-actin and spectrin during mechanosensitive SAR. The shrink step promotes rapid retrieval of excess surface area. Retrieval at discrete sites is via membrane invaginations (initially  $\sim 1\mu\text{m}$  diameter) but only at points on the substratum-adherent plasma membrane. All indications are that the invaginating membrane is drawn inward under tension. Is retrieved membrane naked or cloaked with mechanoprotective membrane skeleton? Whilst invaginations will form in the absence of F-actin, they are in control cells, well-endowed at the earliest fixation point ( $<2$  min post-invagination) with an F-actin/spectrin membrane skeleton. Is this membrane skeleton present from the outset or do the elements rapidly relocate to the invaginating membrane? This is an open question but we know that in  $<2$  min invaginations can exhibit dramatic build-ups of motile F-actin. We do not yet know if the spectrin scaffold is needed for

initiating the invagination of bilayer or for the subsequent actomyosin activity that accompanies the reprocessing of invaginated membrane.

Thus, for animal cells, whether plasma membrane is non-adherent or adherent and whether it has a static or changing area, bilayer relies on membrane skeleton for mechanical resiliency. Channels' stretch-responses "report" that naked bilayer leaves integral membrane proteins overly vulnerable to membrane loads. SAR studies during abrupt volume jumps suggest that so long as relocating plasma membrane is still topologically "surface membrane", membrane skeleton accompanies the bilayer. To directly tests whether the membrane skeleton's mechanoprotective functions remain in force during the membrane relocations of mechanosensitive SAR will, however, be difficult.

## REFERENCES

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2. Morris, C.E. and Homann, U. Cell surface area regulation and membrane tension. **J. Membr. Biol.** 179 (2001) 79-102.