



## 50 YEARS AGO

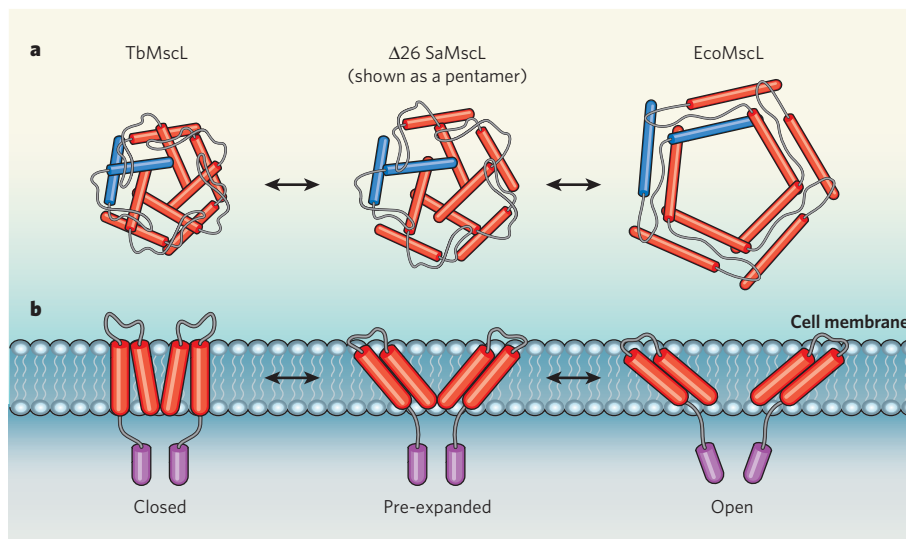
*The Human Response to an Expanding Universe.* By Harlow Shapley — [The author of this book] is a world-renowned figure in the fields of astronomy and cosmography... Dr. Shapley begins by attempting an obituary of the anthropocentric view that man is the centre of the cosmos, and continues by interpreting the consequences to man (or rather to certain aspects of rational thinking) of the latest scientific discoveries in the cosmos...

Dr. Shapley's displacement of human life from its once supreme position does not make him a pessimist, for he argues cogently that there must be at least a hundred million planets capable of supporting some form of life. Dr. Shapley concludes his book with what he calls "a Martian look" into the future. He dismisses the prospect of the Earth's collision with a star, or of wandering from its orbit and getting too near or too far away from the Sun. Nor does he envisage a biological calamity wiping out the whole human race. The real danger is man himself, who is busy perfecting the tools for performing an operation which is unlikely to be performed by natural forces. From *Nature* 5 September 1959

## 100 YEARS AGO

In February last Dr. N. Annandale obtained on the Orissa coast of India a number of small more or less nearly globular organisms in the tide-wash. When placed in water their shape changed from globular to conical, and indicated that they were evidently pelagic sea-anemones, although devoid of tentacles. The mouth is conspicuous, forming a relatively long, narrow slit expanded at one end, and the whole organism presents a milky appearance... As these actinians, which are apparently adult, although no gonads are visible, evidently indicate a new generic and specific type, Dr. Annandale has described them under the name *Anactinia pelagica*. From *Nature* 2 September 1909

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**Figure 1 | Opening of the MscL channel.** The MscL channel opens in cell membranes to release osmotic pressure in the cell. The crystal structure of the MscL from *Mycobacterium tuberculosis*<sup>8</sup> (TbMscL) revealed the closed state of the channel, whereas the open state was seen in the spectroscopically derived structure<sup>10</sup> of EcoMscL (the MscL from *Escherichia coli*). Rees and colleagues<sup>6</sup> now report the crystal structure of an intermediate, 'pre-expanded' state of a truncated MscL from *Staphylococcus aureus* ( $\Delta 26$  SaMscL). **a**, In these extracellular views looking down at the MscL structure, the movements of the helices that line the pore as the channel opens (or closes) are visible. The cross-section of the channel expands from left to right, but the pore remains closed in the pre-expanded state. The  $\Delta 26$  SaMscL channel is actually a tetramer, but is shown here as a pentamer for comparison with the open and closed states. An individual monomer is highlighted in blue. **b**, Side views reveal that the helices lining the inside of the pore tilt towards the plane of the membrane as the channel moves from the closed to the pre-expanded state, and that the whole channel structure becomes flatter. The helices maintain this orientation as the cross-section of the channel expands to reach the open state.

have a better handle on the conformational rearrangements in the channels that underlie their opening.

MscL is nonselective for the ions and small molecules it transports and is activated at membrane tensions close to the breaking point of the membrane bilayer. It is thus usually thought of as a bacterium's last line of defence against hypo-osmotic shock. Over the past decade, genetic, structural and biophysical data have provided a fairly detailed picture of the channel's basic architecture<sup>8</sup> and functional behaviour<sup>9</sup>, and have defined the types of structural rearrangement that could support the formation of very large pores characteristic of MscL<sup>10,11</sup>. Rees's group previously reported the MscL crystal structure from *Mycobacterium tuberculosis*<sup>8</sup> (TbMscL), which is generally agreed to represent the closed conformation of the channel. The new structure<sup>6</sup> looks like an intermediate conformation, somewhere between the open and closed states.

It has been proposed<sup>12,13</sup> that a domain of MscL known as the cytoplasmic bundle acts as a sieve that limits the passage of large molecules through the pore. By removing the last 26 amino-acid residues of this cytoplasmic domain from SaMscL, Rees and colleagues<sup>6</sup> were able to drive the (typically stable) closed conformation of the channel to an expanded, partially open state. This state is characterized by a significant tilt of the TM1 helices —

transmembrane helices that line the pore of the channel — towards the plane of the membrane. The conformational change shortens the length of the water-permeation pathway and makes the whole channel flatter than it is in the closed state (Fig. 1). The authors also found that the activity of, and the current through, their truncated channels in functional measurements is greater than that of wild-type channels, supporting the idea that the structural changes observed in the crystal structure also occur in functional channels.

Rees and colleagues' crystal structure<sup>6</sup> provides an explicit conformational pathway from the closed to the open state of SaMscL: the first physical transition generates a 'pre-expanded' state in which the cross-sectional area ( $A$ ) of the channel is slightly larger than in the closed state (Fig. 1). This is likely to be the most tension-dependent state of the mechanism, as the probability that the channel will open should be proportional to  $-\gamma\Delta A$ , where  $\gamma$  is the lateral tension in the membrane<sup>9</sup>. The pre-expanded state maintains a narrow pore, still flanked by the inner TM1 helices, and is therefore predicted to be non-conductive. The present structure<sup>6</sup> is thus in excellent agreement with earlier models of the pre-expanded state<sup>9,11,14</sup>.

Although Rees and colleagues' structure does not have a pore wide enough to conduct, the fact that the transmembrane helices are tilted away from the normal of the membrane, together with the expansion of the