begins to act like a horn. Sealing the ear canal as illustrated in Figure 1.1 provides a small confined volume of air that eardrum vibrations can work against to produce sound pressure right down to low frequencies. Sealing the ear canal is an essential part of the OAE recording technique. It is achieved in humans by inserting the OAE measurement probe into the ear canal using a soft plastic tip to ensure a good seal. The probe either contains or is coupled to the recording microphone and acoustic stimulator. An additional practical benefit of sealing

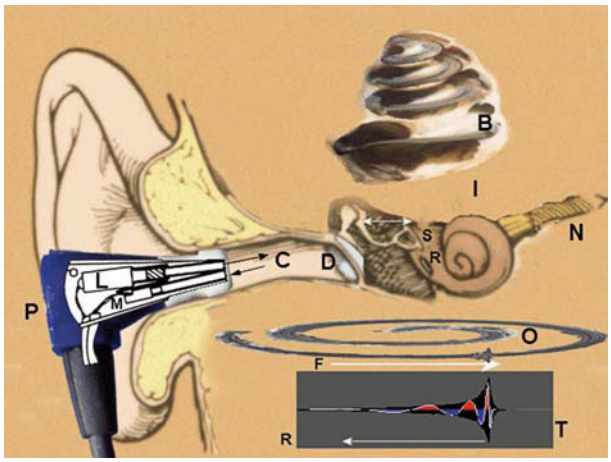

FIGURE 1.1. In otoacoustic emission recording, a probe P containing a microphone M records the sound pressure in the closed ear canal C. Ear canal sound pressure can arise from sounds created by the probe loudspeaker L (the stimulus) or from vibration of the eardrum D driven by the cochlea I through the ossicular chain, which links the stapes S to the ear drum D. In stimulated otoacoustic emission recording, sound from the probe causes oscillatory motion of the stapes, a corresponding displacement of cochlear fluid, and complementary motion of the round window R. The basilar membrane of the cochlear partition receives energy from this cochlear fluid motion, causing a wave to travel along the basilar membrane BM in the forward direction F. The traveling wave shape T is shown schematically for a single pure-tone stimulus, and this wave delivers excitation to the sensory cells within the spiral organ of Corti (shown excised from an electron micrograph image as O). In the single-tone-stimulation case, there is a distinct place where the maximum vibration of the BM occurs just basal to a region where the energy is absorbed and the wave is halted. Typically, from somewhere around the peak some wave energy is retransmitted back to the base of the cochlea, probably as a reverse traveling wave in direction R. The stimulation process then works in reverse. The stapes and round window are moved in a complementary manner by cochlear fluid vibration causing a vibration of the ossicles and finally of the eardrum, leading to the creation of new sound pressure in the ear canal at the same frequency as the stimulus. For two tones or any other complex sound there is an additional way for energy to escape back to the ear canal if intermodulation distortion is created. (Thanks to Andy Forge, Ade Pye, and Martin Robinette for permission to use these images.)

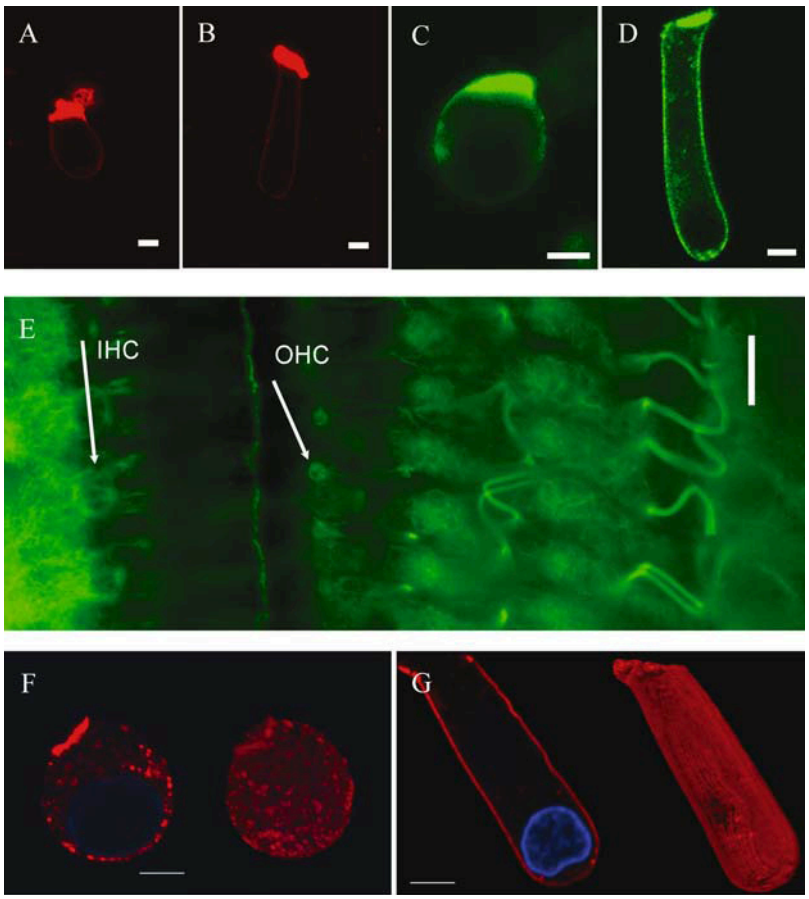

FIGURE 5.2. Molecular composition of the cytoskeleton and PM in OHCs. (**A, B**) F-actin in the lateral wall and cuticular plate of isolated gerbil OHCs at P6 (**A**) and mature (**B**, P18). (**C, D**) Spectrin in the lateral wall and cuticular plate of isolated gerbil OHCs at P6 (**C**) and P18 (**D**). Spectrin label during development extends basally from the cuticular plate during development. Scale bars represent 5 μm for **A–D**. (**E**) Tubulin in the cytoskeleton of organ of Corti cells in a whole mount of gerbil tissue. Whole mount was labeled with an antibody to β_I tubulin. Note how microtubules in the IHC originate at a ring at the level of the cuticular plate, while microtubules in the OHC originate at the basal body. The scale bars represent 10 μm. (**F, G**) Prestin in the lateral wall and under the cuticular plate in isolated OHCs from developing (**F**, P9) and mature (**G**, P21) gerbil. Each panel shows a cross section (left) and a collapsed three-dimensional representation (right) of an isolated OHC labeled with an antibody to prestin (red in the on-line version) and the nuclear stain DAPI. Prestin incorporation in the PM during development is in patches (**F**). Prestin completely occupies the basal PM (**G**), including the nuclear compartment. The scale bars in **F** and **G** represent 5 μm.

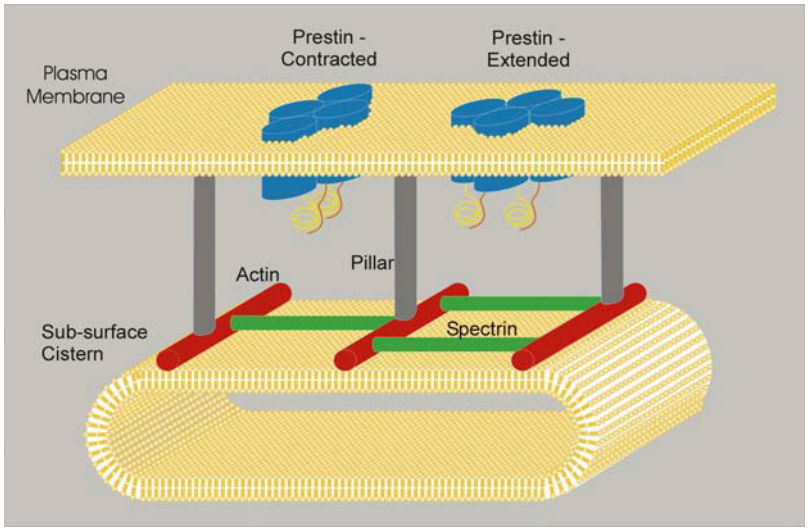

FIGURE 5.3. Diagram of the structure of the OHC lateral wall. The diagram includes tetramers of prestin in possible contracted and extended configurations. The carboxy terminus of prestin is rendered in a light shade, while the amino terminus is in a darker shade. A color version of this figure is available on-line.

lipid and cholesterol composition suggests that a significant contribution of PM lipid content to OHC electromotility is possible (Holley 1996). In fact, the PM is frequently considered to be the primary contributor to OHC axial stiffness (Holley and Ashmore 1988b; Tolomeo et al., 1996; He et al., 2003b), which is critical for transmission of motor force to the organ of Corti (see later). Comparison of the stiffness moduli of the intact lateral wall and isolated cortical lattice indicates that the PM is a major contributor to the total axial stiffness of the intact OHC (Tolomeo et al. 1996). Others have, however, contended that the cortical lattice is the primary contributor to OHC axial stiffness (Adachi and Iwasa 1997; Oghalai et al. 1998).

The density of membrane particles in the OHC lateral wall PM approaches 6000/μm^2 in freeze–fracture observations (Forge 1991; Kalinec et al. 1992), an extraordinary number, comparable to the density of nicotinic acetylcholine receptors at the rat neuromuscular junction (9000/μm^2; Grohovaz et al. 1982). The membrane particles in the OHC are distributed over a much greater area, of course, than at the neuromuscular junction, thus the overall number of particles is very large, several millions in the longest guinea pig OHCs. The particles have been equated in number with the motor protein prestin (discussed later) (Kalinec et al. 1992). However, the particles, which are 10–11 nm in diameter, are too large to be composed of a single protein moiety. However, while the OHC PM must also contain many common membrane proteins such as ion channels, these cannot account for more than a few thousand particles per cell, thus the motor protein is still the preferred candidate. A specialized glucose transporter,

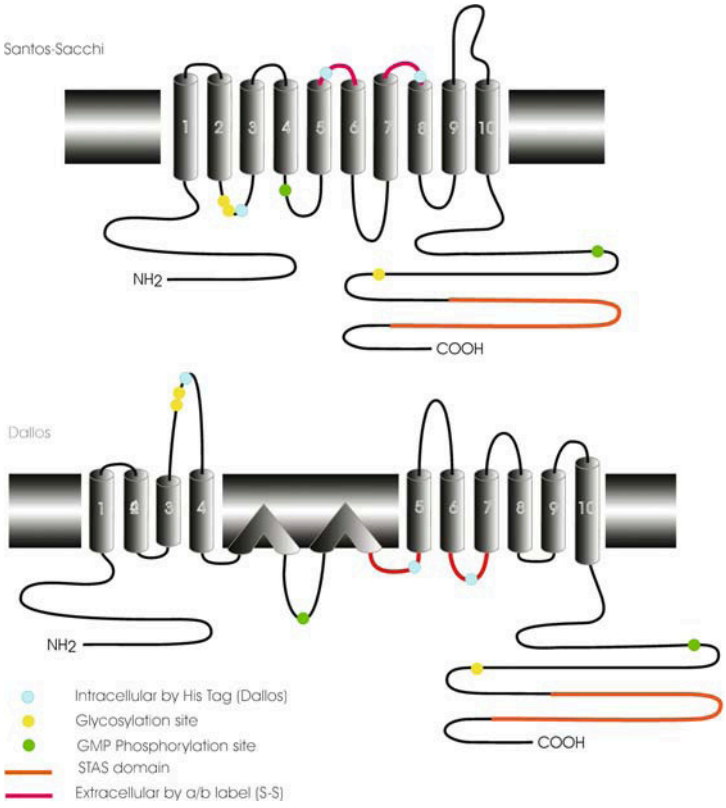

FIGURE 5.5. Proposed prestin 10 membrane spanning region topologies from Santos-Sacchi (above) and Dallos (below). The lengths of membrane spanning regions and intra- and extracellular loops are approximately to scale, based on published information and sequence analysis using TMPred and Kyle–Doolittle. The Santos-Sacchi structure is from Navaratnam et al. (2005); the Dallos structure is inferred from Deak et al. (2005). The numbering of the membrane spanning regions in the Dallos structure has been changed to accord with common practice.

was interesting, however, that the antibodies prepared against those segments only weakly labeled native prestin in OHCs (their Fig. 1). The region between loops 5 and 6 was independently observed to be extracellular by Adler et al. (2003).

The Brownell group has very recently drawn attention to two membrane spanning regions close to the amino terminus, which they inferred from an analysis called evolutionary trace, using a large number of published prestin-like and prestin-unlike sequences from the SLC26 family (Rajagopalan et al. 2006). Site directed mutagenesis in these regions demonstrated the importance of some residues in formation of NLC. Interestingly, the two membrane-spanning regions identified in this study only partly correspond to regions identified by the two other groups.

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