# Driving the Early Auditory Network the Old-Fashioned Way

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**Spontaneous neuronal activity during the development of the auditory sensory system is important in establishing mature connectivity. Wang et al. show that glia-like cells drive spontaneous spiking in neighboring cochlear inner hair cells via a process that involves osmotic cell shrinkage and the secretion of potassium ions.**

The formation of the mature brain requires not only genetic programs but also electrical activity (Spitzer, 2006). In developing sensory systems, early spontaneous activity (neuronal spiking) that occurs independent of sensory input is critical for establishing mature projections and connections (Blankenship and Feller, 2010). In many systems, including the auditory system, spontaneous activity is observed within a sensory processing circuit before the sensory organ is present. In this issue of *Cell*, Wang et al. (2015) show that a pathway widely used for epithelial fluid secretion has been adapted in the developing auditory system by inner supporting cells to drive bursts of activity in inner hair cells (Figure 1). The work illustrates the importance of shape change of inner support cells and provides insight into a mechanism that synchronizes activity within clusters of spiking cells.

Pioneering work from the Bergles lab (Tritsch et al., 2007) was the first to show that the cochlear system is the site of initiation of spontaneous activity during the prehearing stage of auditory system development. The Kölliker organ, which transiently appears during this developmental period in the cochlea, is responsible for generating calcium burst spiking in the inner hair cells that in turn leads to activation of spiral ganglion neurons and subsequent propagation into central auditory nuclei such as the medial nuclei of the trapezoid body and the central nucleus of the inferior colliculus (Tritsch et al., 2010). After the auditory system develops further and hearing is established, the spontaneous oscillations and the Kölliker organ disappear.

The mechanism by which spontaneous cochlear activity is generated has been a longstanding question. It is known that during the prehearing stage calcium spike activity of the cochlear inner hair cells is activated by spontaneous ATP release from the glia-like inner support cells in the Kölliker organ (Tritsch et al., 2007). Release of ATP starts a complex series of events that ultimately result in bursts of calcium spikes in clusters of inner hair cells. Glutamate is released by the inner hair cells to trigger patterned bursts of action potentials in primary auditory neurons that in turn activate central auditory networks (Tritsch et al., 2010). Although the release of ATP is the initial trigger, there are several observations in the Kölliker organ that have been difficult to understand in the context of inner hair cell activation. For example, a calcium wave propagates through the inner supporting cells in the Kölliker organ and is associated with a shape change that is detected optically as a change in light scattering (Tritsch et al., 2007). Most importantly, the mechanism by which ATP elicits calcium spike bursts in clusters of inner hair cells has remained unresolved.

The critical observation in the new study by Wang et al. is that the calcium-activated chloride channel TMEM16a

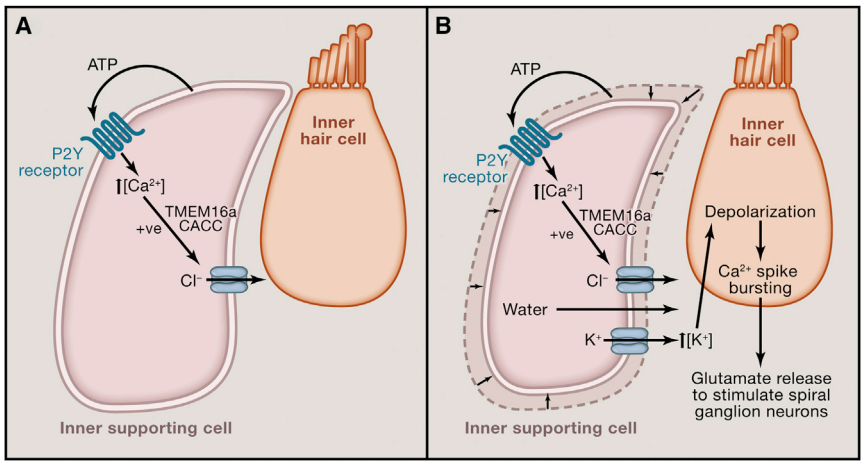


**Figure 1. Stimulation of Spontaneous Calcium Spike Bursting in Inner Hair Cells**
(A and B) Depicted is the stimulation of inner hair cells (IHCs) by glia-like inner supporting cells (ISCs) of the Kölliker organ in the cochlea. (A) Spontaneous release of ATP from ISC acts in an autocrine manner on P2Y receptors to increase intracellular [$Ca^{2+}$] that in turn gates open TMEM16a the calcium activated calcium channels (CACC) that are highly expressed in ISCs. (B) The efflux of $Cl^-$ from ISCs via open TMEM16a channels shrink ISCs by crenation (cell shrinkage by osmosis) and trigger K+ efflux through K leak channels. High external [$K^+$] depolarizes clusters of IHCs causing $Ca^{2+}$ spike bursting and the release of glutamate to stimulate spiral ganglion neurons that activate central auditory nuclei.

(Schroeder et al., 2008) is highly expressed in inner supporting cells and the calcium transient activated by ATP generates a substantial chloride efflux current in these cells. Surprisingly, the burst firing of inner hair cells is not due to the direct activation of purinergic receptors on hair cells but is instead due to the ATP-triggered calcium signals and chloride efflux in the glial-like supporting cells. Burst firing in hair cells is lost when expression of TMEM16a channels is reduced or eliminated in the inner supporting cells. The clue to the mechanism came from the similarities with observations between fluid secretion from epithelial cells and the shape change of the inner supporting cells. ATP triggers crenation, the term for osmosis-induced cell shrinkage, in inner supporting cells due to the efflux of water associated with the substantial chloride efflux observed after TMEM16a activation. In exocrine epithelia of various organs the efflux of chloride via TMEM16a (Huang et al., 2012) causes the concurrent efflux of K+ and water to maintain ionic and osmotic gradients (Frizzell and Hanrahan, 2012). Wang et al. show that the efflux of $K^+$ from inner supporting cells is sufficient to increase extracellular to approximately 12 mM (Wang et al., 2015). This change in external [$K^+$] is both required and sufficient for inner supporting cells to trigger calcium spike bursting in inner hair cells.

In the central nervous system, astrocytes are the glial cells that keep extracellular [$K^+$] within a very narrow range around 3 mM (Kofuji and Newman, 2004). Increases of several mM are generated by neuronal activity and seizures are characterized by external [$K^+$] up to 13-15 mM. $K^+$ efflux could occur from astrocytes due to spatial buffering by glial networks when $K^+$ diffuses through astrocytes from regions of high to low extracellular [$K^+$] (Kofuji and Newman, 2004). Astrocytes also have a GABA-activated $Cl^-$ current, first proposed by Bormann and Kettenmann (Bormann and Kettenmann, 1988) to generate $K^+$ efflux to depolarize neurons. The discovery of the mechanism underlying $K^+$ efflux from inner supporting cells and the profound impact on hair cell calcium bursting will certainly lead to investigations on the impact of $Cl^-$ and associated $K^+$ effluxes from astrocytes in regulating neuronal circuit excitability in the developing central nervous system.

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# A Metabolic Switch for Th17 Pathogenicity


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**T helper 17 (Th17) cells are critical for host defense but can also drive autoimmunity. This divergent behavior is explored by Gaublomme et al. and Wang et al., who identify inflammation-associated genes by measuring gene expression in nearly 1,000 individual Th17 cells and show that *CD5L* affects the expression of pro-inflammatory genes by altering lipid synthesis.**


T helper (Th) cells are workhorses of adaptive immunity, which as their name implies, help other immune cells respond appropriately to pathogens. The Th paradigm began with two lineages: Th1 cells that respond to intracellular pathogens and Th2 cells that respond to extracellular parasites. A third lineage, Th17 cells, was identified more recently (Harrington et al., 2006; Stockinger and Veldhoen, 2007; Toh and Miossec, 2007). As various groups began to map the mechanisms that specified their development, the heterogeneity of Th17 cells began to be appreciated (Ghoreschi et al., 2010). While originally the role of Th17 cells in autoimmunity was emphasized, it has become clear that non-pathogenic Th17 cells in the gut are controlled by the microbiome and are critical for intestinal barrier function (Littman and Rudensky, 2010). However, the molecular mechanisms underlying these divergent behaviors remain relatively poorly understood.