Tumor necrosis factor-β enhances microvascular tone and reduces blood flow in the cochlea via enhanced sphingosine-1-phosphate signaling.

We sought to demonstrate that tumor necrosis factor (TNF)-β, via sphingosine-1-phosphate signaling, has the potential to alter cochlear blood flow and thus, cause ischemic hearing loss. We performed intravital fluorescence microscopy to measure blood flow and capillary diameter in anesthetized guinea pigs. To measure capillary diameter ex vivo, capillary beds from the gerbil spiral ligament were isolated from the cochlear lateral wall and maintained in an organ bath. Isolated gerbil spiral modiolar arteries, maintained and transfected in organ culture, were used to measure calcium sensitivity (calcium-tone relationship). In a clinical study, a total of 12 adult patients presenting with typical symptoms of sudden hearing loss who were not responsive or only partially responsive to prednisolone treatment were identified and selected for etanercept treatment. Etanercept (25 mg s.c.) was self-administered twice a week for 12 weeks. TNF-β induced a proconstrictive state throughout the cochlear microvasculature, which reduced capillary diameter and cochlear blood flow in vivo. In vitro isolated preparations of the spiral modiolar artery and spiral ligament capillaries confirmed these observations. Antagonizing sphingosine-1-phosphate receptor 2 subtype signaling (by 1 μmol/L JTE013) attenuated the effects of
TNF-? in all models. TNF-? activated sphingosine kinase 1 (Sk1) and induced its translocation to the smooth muscle cell membrane. Expression of a dominant-negative Sk1 mutant (Sk1(G82D)) eliminated both baseline spiral modiolar artery calcium sensitivity and TNF-? effects, whereas a nonphosphorylatable Sk1 mutant (Sk1(S225A)) blocked the effects of TNF-? only. A small group of etanercept-treated, hearing loss patients recovered according to a 1-phase exponential decay (half-life=1.56 ± 0.20 weeks), which matched the kinetics predicted for a vascular origin. TNF-? indeed reduces cochlear blood flow via activation of vascular sphingosine-1-phosphate signaling. This integrates hearing loss into the family of ischemic microvascular pathologies, with implications for risk stratification, diagnosis, and treatment.