

Effects of an anti - PD-1 immune checkpoint inhibitor on hearing in a murine model

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The mechanism of action of immune checkpoint inhibitors (ICIs) is based on inhibiting molecules like CTLA4, PD-1 and PD-L1 thus activating the immune system against the tumor. This activation often leads to side effects called immune-related adverse events (irAEs). Although the immune response plays an important role in the pathomechanism of hearing losses, only sporadic cases of sudden bilateral hearing loss are reported following ICI administration. Thorough preclinical studies on the effect of ICIs on the audiovestibular system have not been performed yet. Our aim was to investigate the effect of PD-1 inhibition on hearing function and cochlear morphology in mice.

C57BL/6J mice were treated for 4 weeks (intraperitoneally, 200 µg/mouse, 3 times/week) either with InVivoMAb rat IgG2a isotype control monoclonal antibody (n = 10) or InVivoMAb anti-mouse PD-1 monoclonal antibody (n = 10). At the end of the treatment period hearing thresholds were measured with auditory brainstem response audiometry (ABR). Cochleae were histologically processed: outer and inner hair cells, spiral ganglion neurons and macrophages were examined with Alexa Fluor 594 phalloidin, hematoxylin-eosin, and Iba1 staining, respectively.

Hearing function and the number and morphology of spiral ganglion neurons showed no difference between the two groups. Examining the number of hair cells with two-way ANOVA, inner and outer hair cells were unaltered in the apical-middle cochlear turns. However, a significant ($p = 0.04$) reduction of age-related hair cell degeneration was observed in the basal cochlear turn of the ICI treated group at frequencies higher than 32 kHz. In the same region, the number of Iba1-positive macrophages showed a 1.56-fold increase in the ICI treated group. We conclude that the anti – PD-1 monoclonal antibody treatment had no effect on hearing function and cochlear morphology in the most relevant frequency range (4-32 kHz). Our results do not prove that ICI treatment can lead to IrAEs in the inner ear. However, the increased macrophage activity in the basal region (32-70 kHz) and the concomitant protection against age-related hair cell degeneration suggests that a slight increase in the cochlear immune activity might have otoprotective effects.

Keywords: sensorineural hearing loss, immune checkpoint inhibitor, hair cells, spiral ganglion, macrophage