ImmunoTools *special* Award 2021

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Impact of immune cell infiltration on vestibular schwannoma volume and growth

Vestibular schwannoma (VS) is the most common benign tumor of the cerebellopontine angle and originates from Schwann cells surrounding neurons in the peripheral nervous system. Since the vestibulocochlear nerve in particular is affected, which is responsible for hearing and balance, patients diagnosed of having VS often suffer from unilateral hearing loss, tinnitus, nerve palsy or dizziness.

The size of VS varies widely. Regardless of the patient's age, some VS grow very rapidly within a few months and other stagnate in growth over several years. While large tumors are usually operated or irradiated immediately, the growth of smaller tumors is monitored regularly by Magnetic Resonance Imaging (MRI) (scan and wait). Due to the unpredictability of the growth rate of this benign tumor, it is often difficult to determine the optimal time for therapy.

Therefore, the aim of our project is to identify an influencing factor on the development of tumor size. The study comprises of approximately 180 participants, making it one of the largest studies in VS research. The data set consists of all adult VS patients treated at the neurosurgical department of the university hospital Halle (Saale) with existing preoperative data (MRI images) on the development of tumor size over a minimum period of 6 months and subsequent surgical VS removal. Patients with irradiated tumors, recurrence or hereditary neurofibromatosis were excluded.

First, a comprehensive database was established with various clinical information, for example, patient age, sex, and KOOS grade of VS. In addition, tumor size was determined by volumetry using preoperative MRI images and growth rate, in patients with multiple preoperative MRI images.

RNA was isolated from the tumor samples. Real-time quantitative PCR was performed to analyze tumor growth factors.

The determination of the proliferation marker Ki-67 did not show any correlation to tumor volume or tumor growth rate. This result suggests that the increase in size is not exclusively due to Schwann cell proliferation. Based on this finding, we hypothesized that a larger tumor volume could be related to the infiltration of immune cells. Therefore, quantitative determination of the macrophage markers CD68 and CD163 was performed. The determination of CD68 showed a significantly positive correlation with the KOOS grade, tumor volume and growth rate of VS. CD163 showed a positive correlation with CD68. These results strongly indicate an influence of macrophages on tumor volume.

For further investigation, the quantitative results need to be supplemented by an immunohistochemical examination of the tumor tissue. Multiplex immunohistochemistry is planned to analyze immune cell infiltration in VS, which may provide more detailed information on the distribution of lymphocytes, macrophages and other immune cells. The subject of our studies is not only the immune cells themselves, but also receptors expressed on activated immune cells, such as CD69 and CD25, which are found after activation of T lymphocytes, B lymphocytes and NK cells. Due to these findings, it might be possible to deduce conclusions about the size differences of VS based on immune cell infiltration.

The use of ImmunoTools antibodies would provide very important insight into the distribution of immune cells in VS. Obtaining accurate information on the growth prognosis of VS associated with immune cell infiltration, as well as the determination of these immune cells, offers opportunities for therapeutic targets to decrease the growth rate.

In summary, this project offers the possibility to better delineate the adequate time for therapy of VS and to understand the tumor biology, thus saving the patient from severe symptoms or even from surgery, which is not primarily necessary.