WT1 Expression in Adult Granular Cell Tumor of the Vocal Cord and Tongue

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To the Editors,

The head and neck are classical sites for granular cell tumor (GCT) development. A neurogenic origin is now widely accepted for this tumor type [1–3]. We have recently had the opportunity to study two GCTs for the WT1 (Wilms-tumor-1) protein/gene product, known to be expressed in peripheral neurofibromas and schwannomas [4]. Both tumors occurred in women (51- and 44-years old) with smoking habits: at present for the patient with vocal cord GCT (5 cigarettes/day) and 15 years previously (for 10 years) for the patient with tongue GCT. On immunohistochemistry cytoplasmic S100- and CD68-proteins were expressed in tumor cells in a diffuse intracytoplasmic pattern, although granular (Fig. 1). Bcl-2 showed a similar cytoplasmic expression pattern with membrane accentuation. Both tumors expressed also WT1 in a cytoplasmic and/or perimembranous/membranous pattern. In several cells of the vocal cord GCT, WT1-protein showed a perinuclear, focal accumulation. Ki67 was expressed in rare tumor cell nuclei in both tumors. The results of this study suggest that the WT1-protein is expressed in the majority of tumor cells of the GCTs we have studied. Identification of WT1 expression in these examples is supportive of the neural derivation of GCTs. The expression pattern was not only cytoplasmic as reported for neurofibromas and

schwannomas [4] but also perimembranous/membranous. Similarly to the findings in testicular tunica albuginea GCT, we have not seen nuclear staining [5]. Interestingly some cells showed intracytoplasmic heterogeneity in the expression of the WT1 transcription factor, with a peculiar perinuclear, focal, eccentric accumulation in several cells. The lack of complete overlap with the diffuse, rather homogeneous, cytoplasmic S100- or CD68-protein expression patterns suggests a heterogeneity, possibly in origin and/or composition, of the known cytoplasmic components of GCT cells namely the lysosome granules and the replicated basal lamina material, already suggested by the difficult electron microscopy diagnosis [3, 6]. A nuclear-cytoplasmic shuttling is reported for WT1, which is found in cytoplasmic polysomes [7] and shown to interfere also with translation. Moreover, the extensive expression pattern of the WT1 gene product we have observed in the two examples of benign tumors, is consistent with the role of candidate-oncogene stated by Hartkamp and Roberts [8]. Interestingly, Bcl-2, direct target of WT1, is shown to increase in rhabdoid tumor cell lines with WT1 overexpression [9]. Bcl-2 is also considered to coincide with WT1 in sporadic Wilms tumors [10]. In agreement with these observations in malignant tumors and, with previous reports of laryngeal and lingual GCTs as well, are our results showing expression of Bcl-2 in both tumors [11, 12]. The lack of microscopic intratumor apoptosis or necrosis/necroptosis along with the presence of several nuclei positive for Ki67, rather suggest an interference for WT1 with proliferation than with apoptosis in these benign tumors.

In conclusion, the WT1-protein is expressed in vocal cord and tongue GCT consistent with the neurogenic origin hypothesis. Further explorations are required in order to fully understand the intracytoplasmic heterogeneity of

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Fig. 1 The granular cell tumors (GCT) (vocal cord **a–e**; tongue **f–j**) consisted in a subepithelial proliferation of large cells with abundant eosinophilic cytoplasm, compact for the vocal cord GCT and dissociating the muscle layers for the tongue GCT (**a**, **f** *asterisk* mucosa). The tumor cells expressed diffusely the S100- and CD68-proteins, with a homogenous intracytoplasmic granular pattern (**b**, **b inset** and **c**, **c inset**, respectively; *asterisk* for vocal fold mucosa and, **g** and **h** respectively for the tongue GCT). The WT1-protein was expressed by the majority of the tumor cells (**d**, **d inset** and, **i**, **i** *white arrows* for positive tumor cells). The expression patterns were cytoplasmic (with perinuclear focal accumulation in some cells) or perimembrane/membrane (**d** *black-arrow*/cytoplasmic staining, *white-arrow*/perimembranous/membranous staining). Bcl-2 was expressed diffusely, with perinuclear accentuation (**e** *arrows*, *asterisk* mucosa; **j** *arrows*). Original magnification $\times 2.5$ (**b inset**, **c inset**, **d inset**, **f inset**), $\times 10$ (**a**, **f**), $\times 40$ (**b**, **c**, **d**, **e**, **g**, **h**, **i**, **j**)

WT1 expression, different from the homogenously granular pattern of S100- and CD68-protein expression.

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