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SOX10 downregulation in tumor cells affects extracellular vesicle production and function in the tumor microenvironment

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The transcription factor SRY-Box Transcription Factor 10 (SOX10) is highly expressed in the majority of melanoma and a subtype of glioblastoma. During first-line therapy, SOX10 expression is reduced in many patients. This loss of SOX10 commonly appears to be associated with increased therapy resistance. In my thesis work, I modeled therapy-dependent SOX10 suppression in vitro by treating melanoma and glioblastoma cell lines with the BRAF inhibitor Vemurafenib and Temozolomide, respectively. The downregulation of SOX10 expression was rescued by the inhibition of transforming growth factor-beta signaling. Genetic knockdown of SOX10 in the HT144 and A375 melanoma, and LN229 glioblastoma cell lines resulted in reduced cell proliferation, expression of β-galactosidase by a fraction of the cells, and the upregulation of cytokine expression. Furthermore, SOX10 suppression increased exosome production by melanoma and glioblastoma cell lines and in a syngeneic glioblastoma mouse model. Cell culture media conditioned by melanoma HT144-SOX10-knockdown cells were applied to PBMC-derived macrophages to explore the function of SOX10-knockdown exosomes on myeloid cells. Conditioned media and isolated exosome fractions from SOX10-knockdown cells induced the increased secretion of cytokines and upregulated expression of pro-inflammatory and immunosuppressive genes by the macrophages. In contrast, depletion of extracellular vesicles from the conditioned media reduced the expression of pro-inflammatory genes in comparison to conditioned media of control cells. Furthermore, conditioned media of macrophages treated with SOX10-knockdown exosomes promoted cell migration of melanoma cells. Pharmacologic Inhibition of Toll-like receptor 8 with the Inhibitor CU-CPT8M suppressed the induction of the pro-inflammatory phenotype of macrophages by SOX10 knockdown exosomes. In conclusion, the presented data support the hypothesis that standard melanoma and glioblastoma therapies lead to transforming growth factor-beta-dependent downregulation of SOX10 and the increased production of tumor-cell exosomes, which induce a pro-inflammatory phenotype in macrophages, mediated by Toll-like receptor 8. These data suggest that tumor-exosomes might be essential in therapy-induced progression of melanoma and glioblastoma and provide a basis for the exploration of the underlying mechanisms and the identification of interference points for targeted therapies.