Impaired aldehyde dehydrogenase 1 subfamily member 2A-dependent retinoic acid signaling is related with a mesenchymal-like phenotype and an unfavorable prognosis of head and neck squamous cell carcinoma.

An inverse correlation between expression of the aldehyde dehydrogenase 1 subfamily A2 (ALDH1A2) and gene promoter methylation has been identified as a common feature of oropharyngeal squamous cell carcinoma (OPSCC). Moreover, low ALDH1A2 expression was associated with an unfavorable prognosis of OPSCC patients, however the causal link between reduced ALDH1A2 function and treatment failure has not been addressed so far. Serial sections from tissue microarrays of patients with primary OPSCC (n = 101) were stained by immunohistochemistry for key regulators of retinoic acid (RA) signaling, including ALDH1A2. Survival with respect to these regulators was investigated by univariate Kaplan-Meier analysis and multivariate Cox regression proportional hazard models. The impact of ALDH1A2-RAR signaling on tumor-relevant processes was addressed in established tumor cell lines and in an orthotopic mouse xenograft model. Immunohistochemical analysis showed an improved prognosis of ALDH1A2(high) OPSCC only in the presence of CRABP2, an intracellular RA transporter. Moreover, an ALDH1A2(high)CRABP2(high)
staining pattern served as an independent predictor for progression-free (HR: 0.395, p = 0.007) and overall survival (HR: 0.303, p = 0.002), suggesting a critical impact of RA metabolism and signaling on clinical outcome. Functionally, ALDH1A2 expression and activity in tumor cell lines were related to RA levels. While administration of retinoids inhibited clonogenic growth and proliferation, the pharmacological inhibition of ALDH1A2-RAR signaling resulted in loss of cell-cell adhesion and a mesenchymal-like phenotype. Xenograft tumors derived from FaDu cells with stable silencing of ALDH1A2 and primary tumors from OPSCC patients with low ALDH1A2 expression exhibited a mesenchymal-like phenotype characterized by vimentin expression. This study has unraveled a critical role of ALDH1A2-RAR signaling in the pathogenesis of head and neck cancer and our data implicate that patients with ALDH1A2(low) tumors might benefit from adjuvant treatment with retinoids.