Katharina Seidensaal

Dr. med.

Function and regulation of the tumor suppressor aldehyde dehydrogenase 1A2 in the pathogenesis of head and neck squamous cell carcinoma

Hals-Nasen-Ohrenheilkunde

PD Dr. rer. nat. Jochen Hess

Previously, our group showed that enhanced levels of ALDH1A2 are associated with improved overall and progression free survival. Furthermore, epigenetic silencing was suggested as one mode of regulation of ALDH1A2 expression and high ALDH1A2 levels correlated to a positive HPV status. However, the molecular mechanisms behind this association were not addressed, so far.
In conclusion, this work shows the great importance of the retinoic acid signaling pathway in HNSCC as several components of this pathway have been identified as biomarkers for enhanced patient survival. ALDH1A2 is regarded as the key component of RA signaling, but the favorable clinical outcome of ALDH1A2high tumors critically depends on the presence of the transporter CRABP2, which was not detected in 42% of cases. High expression and nuclear localization of RARβ were associated with improved survival confirming its role as the crucial retinoic acid receptor in the pathogenesis of OPSCC. Furthermore, FABP5 was associated with enhanced survival due to unrevealed mechanisms and signaling by FABP5-PPARβ/δ as a negative predictor of outcome and source for treatment failure was not observed, as well as there was no inverse relationship of FABP5 and CRABP2.
In this work, it is proposed that the levels of ALDH1A2 and presence of CRABP2 can stratify patients for RA therapy and identify those at risk for treatment failure. Indeed, cell culture experiments provided evidence that ALDH1A2 expressing FaDu cells are more resistant to RA therapy, while the ALDH1A2 low cell line Cal27 is not. Synthetic retinoids were superior to RA, as they are independent of the ALDH1A2 status and as effective as RA in the ALDH1A2 low cell line Cal27. Especially, adapalene is very promising as it has been shown to be independent of CRABP2 by others and taking additionally the findings of this work into account this substance might circumvent both proteins and reduce the risk of treatment failure. Based on these findings, it is worth speculating that identification of patients, who profit from restoration of RA-signaling, in line with the concept of personalized oncology, might in future be feasible by the assessment of RA signaling components.