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Title: Anti-tumorigenic effect of age-/diabetes-related advanced glycation end-products in lung carcinoma

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Body: Background: Clinicopathological studies indicated that lung carcinoma progression is impaired by advanced age and diabetes, which are either characterized by accumulation of advanced glycation end-products (AGEs). AGEs result from the non-enzymatic reaction of sugars with proteins in the body and in foods. Therefore, our study aimed at the effect of AGEs on the non-small cell lung carcinoma (NSCLC) progression. Methods: AGEs were quantified by detecting the AGE fluorescence in plasma samples of NSCLC patients prior to surgery. Experimentally, the tumor effect of circulating AGEs was studied by using NSCLC spheroids and plasma samples increasingly modified with AGEs, and NSCLC-bearing mice of whom elevated AGE level were induced by AGE-enriched food. Results: High plasma AGE levels were characterized by a later reoccurrence of the tumor after curative surgery and a higher long-term survival rate compared to patients with low levels (25% vs. 47% 5-year-survival, P = 0.011). In this regard, in vitro studies showed a lower spheroid growth of NSCLC cells in the presence of AGE-modified plasma than non-modified plasma. By in vitro application of plasma samples from NSCLC patients or mice with different AGE levels, we also found an inverse correlation between the NSCLC spheroid growth and the plasma AGE level. Moreover, the in vivo tumorigenicity assay demonstrated that mice with higher levels of circulating AGEs developed smaller tumors than mice with normal AGE levels. Conclusion: The plasma AGE level has prognostic relevance for NSCLC patients, in which the tumor growth-inhibiting effect of circulating AGEs might play a critical role.