



Ruprecht-Karls-Universität Heidelberg
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Dissertations-Kurzfassung

Titel der Dissertation: Hyaluronidasen in disease processes

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Enhanced hyaluronidase activity in the serum, urinary and kidney has been reported in STZ-induced rats. Increased plasma HA levels and hyaluronidase activity have also been found in patients with diabetes. In my MD thesis, I have therefore investigated the role of Hyal1 in STZ-induced hyperglycemia in animal models. The blood glucose levels were increased while the blood insulin levels were decreased after injection of STZ into mice. However, the blood glucose and insulin levels were unaffected by knockout of Hyal1 in mice treated with STZ. Previous studies showed that elevated level of glucose can increase the accumulation of HA. Accordingly, I found that the total HA levels in the liver were significantly higher in the Hyal1 KO mice than the WT mice. STZ treatment decreased the total HA levels in the serum but not in the other tissue extracts analyzed in both the WT and KO mice. STZ treatment resulted in a significant upregulation of Hyal1 transcription in the WT mice compared to the control group. Accumulation of EMC components is an early sign of diabetic nephropathy, and HA has been reported to be elevated in the renal interstitium and islet during experimental diabetes. STZ treatment induced the local accumulation of HA in the liver, in the cortex of the kidney especially around the glomerulus, and in the pancreatic islets in both groups, but had no effects on HA levels in the lung. KIAA1199, a novel hyaluronan (HA) binding protein, has been found to play a key role in the depolymerization of HA, which is independent of the two hyaluronidasen Hyal1 and Hyal2 and the cell surface receptor CD44. Upregulation of KIAA1199 has been detected and correlated with poor clinical outcome in several types of human cancers. Moreover, KIAA1199 has been shown to play an important role in tumor progression. Here I first analyzed the expression and prognostic role of KIAA1199 in human soft-tissue sarcoma by mining the public datasets. I found that compared with control tissues, high levels of KIAA1199 was detected in two types of human sarcoma. Second, high levels of KIAA1199 were associated with poor disease-free survival in patients with sarcoma. These findings suggest that KIAA1199 expression might be useful for predicting the outcome sarcoma patients. Exposure to type II collagen, DDR1 overexpression increased the gene and protein expression of KIAA1199 in HT-1080 cells. Next, I analyzed the role of KIAA1199 in the degradation of HA by using siRNA-mediated KIAA1199 knockdown. In the presence of both DDR1 overexpression and exogenous collagen treatment, the total HA levels below 100 kDa in the conditioned medium of the KIAA1199 knockdown group were significantly higher than the the NT siRNA group, suggesting that KIAA1199 contributes to the degradation of HA.