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Autoantibodies against Tumor-Associated Antigens in the Early Detection of Gastric Cancer

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Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related death worldwide. In most countries relative 5-year survival rates for gastric cancer are low, e.g. 33% for patients diagnosed with gastric cancer in Germany in 2009 and 2010. Only in Japan and South Korea, where population-based screenings by photofluorography or endoscopy are established, relative 5-year survival rates approach 70%. This demonstrates the importance of early detection of gastric cancer and the need to find new screening modalities that are also suited for a use outside of high-risk regions in Eastern Asia. Autoantibodies against tumor-associated antigens have been found in serum of patients with various types of cancers and may serve as biomarkers for early detection of gastric cancer as well. However, studies that systematically assess the diagnostic value of a large number of autoantibodies in gastric cancer patients and controls are sparse.

This dissertation aimed to provide further insight into autoantibodies in the early detection of gastric cancer by a) conducting a systematic literature review and b) by performing own autoantibody measurements in serum samples from multiple well-defined population-based and patient cohorts.

First, a systematic literature review was conducted to summarize existing knowledge on autoantibodies and their diagnostic value in gastric cancer. Two databases (MEDLINE, Web of Science®) were systematically searched to identify studies which performed serological testing for autoantibodies in gastric cancer patients and controls. Data on study characteristics and results were extracted independently by two investigators. Overall, 39 articles reporting the detection of 34 different autoantibodies met the inclusion criteria for the review. The most common antibody detection method was enzyme-linked immunosorbent assay and the most frequently assessed

autoantibody was anti-TP53, which was tested in 13 studies. Most antibodies were assessed in only one study and only few authors evaluated the diagnostic value of combinations of multiple autoantibodies. For single autoantibodies, specificity was generally very high (median: 99.15%), but sensitivity was mostly rather low (median: 12.35%). For some autoantibody combinations, however, substantially higher sensitivity at reasonably high levels of specificity could be achieved.

Next, own autoantibody measurements using two different measurement technologies were performed in cooperation with the Division of Molecular Diagnostics of Oncogenic Infections, DKFZ, Heidelberg, Germany and the Linē Lab, Latvian Biomedical Research and Study Center, Riga, Latvia. With the aid of phage-displayed antigen microarrays, autoantibodies against 169 phage clones were measured in serum samples from 156 gastric cancer patients and 158 healthy controls. For single autoantibodies sensitivities for gastric cancer detection at 98% specificity ranged from 0% to 9%. A previously described classification algorithm achieved 17% sensitivity at 90% specificity which is considerably worse than the previously reported diagnostic performance for this algorithm.

Bead-based multiplex serology was used to simultaneously measure autoantibody responses against 64 candidate TAAs in serum samples from 329 gastric cancer patients, 321 healthy controls and 518 participants with other diseases of the digestive tract. For the 64 tested autoantibodies sensitivities ranged from 0 to 12% at 98% specificity and for all autoantibodies measured by both multiplex serology and phage-displayed antigen microarrays, sensitivities at 98% specificity were higher in the multiplex serology measurements. A combination of autoantibodies against five TAAs (MAGEA4 + CTAG1 + TP53 + ERBB2_C + SDCCAG8) was able to detect 32% of the gastric cancer patients at a specificity of 87% in the validation set. Sensitivities for early and late stage gastric cancers were similar, while chronic atrophic gastritis, a precursor lesion of gastric cancer, was not detectable. However, the 5-autoantibody marker panel also detected 30% of the colorectal cancer patients, 26% of the esophageal cancer patients and 22% of the pancreatic cancer patients. Thus, autoantibodies seem not to be specific for gastric cancer.

Finally, the diagnostic value of combined testing for serum pepsinogens and autoantibodies was evaluated in a subset of the study population (147 gastric cancer cases, 137 controls). Sensitivity

and specificity of a combination of the 5-autoantibody marker panel and the pepsinogen I to pepsinogen II ratio were 43% and 84%, respectively, compared to 33% and 90%, respectively for the autoantibody test alone.

In conclusion, the tested autoantibodies and combinations alone did not reach sufficient sensitivity for gastric cancer screening. Nevertheless, some autoantibodies, such as anti-MAGEA4, anti-CTAG1 or anti-TP53 and their combinations could possibly contribute to the development of cancer early detection tests (not necessarily restricted to gastric cancer) when being combined with other markers. Research on the identification of suitable combination partners, in addition to improvements in measurement technologies and strategies for data analysis, deserves further attention. Also the value of autoantibodies for prognosis and monitoring of responses to immunotherapy should be further explored to exploit the full potential of autoantibodies.