Immunotherapy of Breast Cancer

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Immunooncology and its translation into the clinic represents a bridge between basic research and clinical practice in cancer medicine. It benefits from an increased knowledge obtained from i) genome-scale studies regarding the molecular pathways involved in tumorigenesis, ii) analyses of immune-relevant molecules, and iii) immunomonitoring of the tumor microenvironment (TME) and peripheral blood in order to characterize the importance of the innate and adaptive immune responses for tumor rejection. Despite the encouraging recent success of different immunotherapeutic strategies, neither the complex genetics of individual susceptibility to cancer nor the enormous complexity of the somatic changes in tumors nor the alterations in the composition of the TME and immune cell repertoire observed could be discarded. These parameters might affect the antitumoral immune response and efficacy of immunotherapies and therefore demand particular attention for the design of personalized (immuno-)therapies.

Breast cancer (BC) represents the most common cancer in women worldwide. Although conventional treatment approaches of this disease, such as surgery, radiotherapy, chemotherapy, and endocrine therapy, have become more efficient for patients with locally advanced or metastatic BC over the last decades, these treatment modalities still have broad limitations regarding the frequency of response and the development of intrinsic and acquired resistance. Based on the implementation of high-throughput technologies a better understanding of the molecular and immunologic phenotype of BC led to the identification and characterization of distinct subtypes of this heterogeneous disease. What is more, this resulted in the development of more individualized, targeted therapies, including immunotherapies, which also eradicate or minimize resistance with higher specificity and lower toxicity. However, so far the clinical efficacy of immunotherapies in BC is not as high as expected. It is assumed that an increased knowledge of the dynamic interaction between tumors and the immune system is a key issue for the design of improved immunotherapies in this disease.

The current issue of *BREAST CARE* with focus on ‘Immunotherapy of Breast Cancer’ highlights the state of the art and the major topics of tumor immunology/immunooncology in BC by the use of molecular and immunological profiling, which also repre-

sent the basis for individualized immunotherapies [1–4]. These include the underlying mechanisms of BC cells to evade immune surveillance, the role of the TME, and mutational signatures resulting in the identification of neoantigens, which is important for BC pathogenesis and progression, the response rate of patients to different immunotherapeutics, and the development of novel immunotherapies. The strategies of immune escape are diverse, and this could be due to intrinsic and acquired resistance to CD8⁺ cytotoxic T lymphocytes (CTL) and/or natural killer cells mediated by impaired expression or structural alterations of HLA class I antigens, components of the antigen-processing machinery, as well as the interferon signal transduction pathways. The great challenge is to translate the potential benefits of greater scientific knowledge into more efficient immunotherapies. Furthermore, the composition of immune cell infiltration of BC lesions has clinical relevance. The frequency and localization of tumor-infiltrating lymphocytes (TIL) in the TME is not only correlated with a better prognosis but also with a good response to chemotherapy in some BC subtypes, in particular in triple-negative and human epidermal growth factor receptor 2-positive BC. The presence of TIL in the TME reflects a pre-existing antitumor immunity, and different immune subsets have been shown to participate in the innate and/or adaptive immunity of BC.

During the clinical manifestation of the tumor, waste products of the tumor (e.g. lactate), lower pH, as well as the expression of immune checkpoints and regulatory T cells could exhaust T cells so that they cannot kill tumor cells consequently, leading to the development of peripheral tolerance. Therefore, cancer vaccines targeting shared antigens, most of which are non-mutated self-antigens and shared in patients with different malignant diseases, represent good candidates for immunotherapy. By means of in vitro co-cultivation of T cells with tumor cells, a strong T cell response measured by cytotoxicity as well as cytokine release against some of these shared antigens was shown. However, cancer vaccines as well as adoptive T cell transfer targeting these shared antigens could not provide satisfactory clinical benefits. This might be explained by immune escape mechanisms of the tumor but also by the elimination of T cells with high-affinity receptors for self-antigens during

thymic selection (central tolerance), resulting in the development of only very few intrinsic effector cells targeting the shared antigens. Furthermore, next-generation sequencing identified a large number of neoantigens, which are individually mutated antigens generated during tumor proliferation and metastasis formation. These neoantigens have been recently shown to be targets for immune cells to activate antitumor immunity. In BC, a broad spectrum of neoantigens has been identified, and neoantigen-specific T cell responses have been observed using co-cultivation of T cells with BC cells. Therefore, personalized cancer vaccines targeting these neoantigens are currently being developed both by different researchers and by various biotech companies, which then might lead to an improved antitumoral efficacy.

Releasing the brake used by e.g. CTLA-4 and PD-1/PDL-1 to inhibit proper immune responses in tumor patients is a promising approach to reactivate pre-existing intrinsic effector T cells. A modest single-agent activity of PD1/PD-L1 antibodies in BC patients has generated hope that BC might be treatable with immunotherapies. Currently, the development of novel inhibitors directed against other checkpoint molecules is in progress. Furthermore, the immune cytolytic activity in spontaneous BC, the burden of nonsynonymous tumor mutations, and the predicted load of neoepitopes are modest in BC when compared to patients with melanoma and non-small cell lung cancer. It is suggested that combination therapies using different immune checkpoint inhibi-

tors, immune agents with non-redundant mechanisms of action, neoantigens, and anti-angiogenic drugs may be a promising strategy to improve the cure of BC in the near future and have high priority. However, it is noteworthy that combination therapies often cause higher toxicities, and so far the combinations, sequence, and duration of treatment require detailed study designs. For most BC subtypes exhibiting a relatively modest T cell infiltration, major challenges include the reversion of the immune suppression in the TME as well as failed or suboptimal T cell priming. Agents that trigger de novo T cell responses or T cell migration into the tumor may be critical for the successful development of cancer immunotherapy and immune prevention in BC. Thus, the challenges in the coming years in order to enhance the efficacy are the establishment of personalized immunotherapies based on an increased understanding of the immune biology, identification of patient-specific immune suppressive mechanisms, targeting of neoantigens, but also non-mutated BC-associated antigens, and reverting the immune suppressive phenotype and/or TME, which might provide novel perspectives for the treatment of BC in the future.

Disclosure Statement

No conflicts of interest.

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