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Rationale for immunological approaches to breast cancer therapy

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ABSTRACT

Despite great advances in early detection, as well as surgical resection of breast tumours, breast cancer remains the deadliest cancer for women worldwide. Moreover, its incidence is without pair, accounting for twice as many new cancer cases as the second most prevalent cancer, colorectal carcinoma. There is therefore a strong need for new therapeutic approaches to breast cancers. Immunotherapies are novel treatment modalities which aim to use immune mediators to attack cancerous cells. Recent clinical results show that these may not only mediate tumour regressions but also cures in some cases. In this review, we discuss the relevance of the immune system in the development of new carcinomas, as well as its importance in mediating cancer regression. We also dissect the known different approaches to harness the immune system to attack breast tumours. Namely, therapies using the passive transfer of either tumour-specific antibodies or cytotoxic cells have been researched and in some cases are already standard of care. Additionally, therapeutic vaccines and immune checkpoint blockade have recently demonstrated great therapeutic efficacy and have generated great excitement for the development of new treatments. Immunotherapies have the potential to generate tumour specific responses, as well as long-lasting remissions, which is why studying those approaches is crucial for the future of cancer medicine.

1. Introduction

Breast cancer is the most common cancer to affect women worldwide. Although population monitoring, early detection and new specific treatments have led to a decrease in the mortality rate, breast cancer remains the main cause of cancer-related deaths in women (Fig. 1). Moreover, recent controversy on the need for routine mammography has shown the limits of the early screening potential to decrease mortality [1]. Thus, it is more important than ever to focus on developing new treatments for breast cancer patients. Surgery, chemotherapy and radiotherapy are potentially curative methods that have been used for decades, with success in some cases. However, they are unsuccessful in controlling advanced metastatic breast cancer, as well as some aggressive subtypes of cancers. Fortunately, recent advances in basic research opened new possibilities to attack tumours via the harnessing of the immune system's powerful defence mechanisms. These new methods are exposed and discussed in this review.

2. Classification of breast cancers

Different varieties of carcinomas are usually pooled under the "breast cancer" terminology. However, breast cancers can be organised in different subtypes, a classification that is determinant for the standard recommended treatment, as well as for the patient's prognosis. Since 2013, breast cancers are molecularly characterized into 4 different subgroups [3]: Luminal A and B, HER2 positive, and triple negative (Fig. 2).

Tumours classified as luminal A arise in the lumen of the milk duct of the mammary glands. They are characterized by expression of both the oestrogen and progesterone receptors (ER and PR). Luminal A tumours usually have the best prognosis, and respond well to treatment with the ER antagonist tamoxifen [4] and aromatase inhibitors such as anastrozole [5]. Luminal B tumours also derive from luminal epithelial cells but are more aggressive and do not respond as well as the luminal A tumours to endocrine treatment [6]. For this reason, additional cytotoxic therapy is usually recommended [3]. They are ER positive but PR negative and can be either human epidermal growth factor receptor 2 (HER2) positive or negative. HER2+ tumours can be treated with the anti-HER2 monoclonal antibody trastuzumab in addition to chemotherapy, which improves the survival rate by 30% compared to

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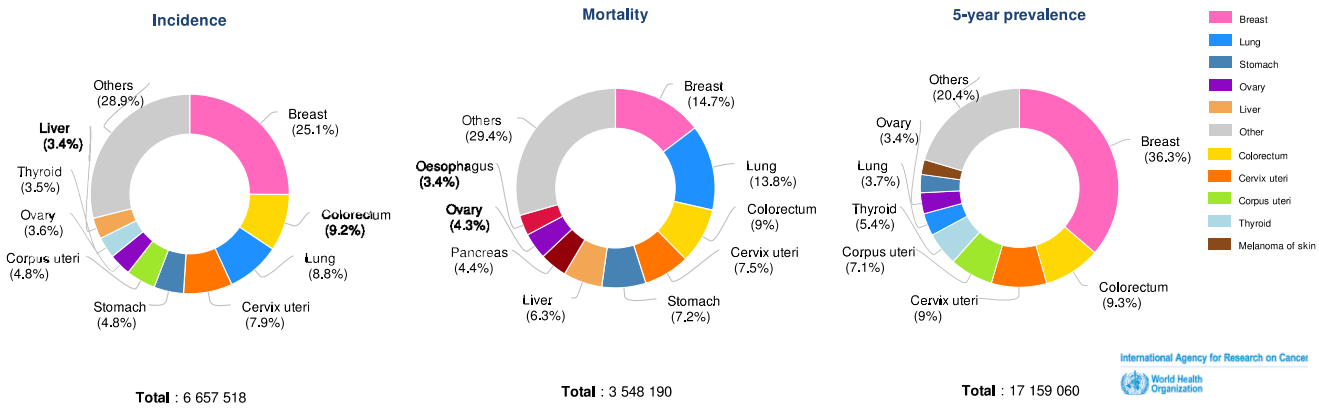

Fig. 1. Incidence, mortality and 5-year prevalence of different types of cancer in women in the world in 2012 [2].

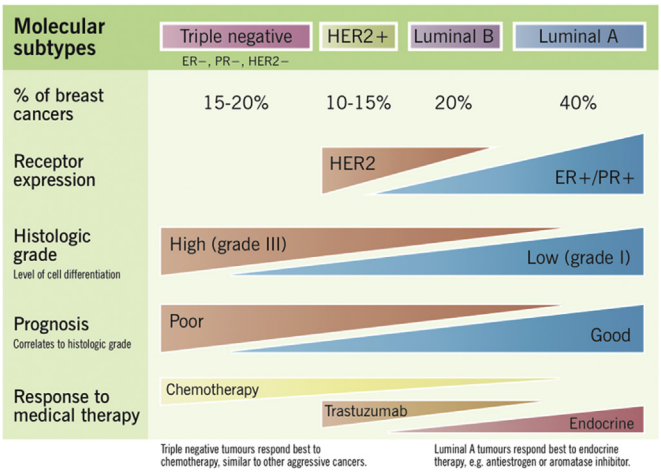

Fig. 2. Adapted from http://www.pathophys.org/breast-cancer/breastcancer-copy/.

chemotherapy alone [7,8]. Finally the triple negative breast cancers (TNBC) do not express any of the aforementioned markers. They are hence not eligible for any of the available targeted therapies and have to be treated with chemotherapy alone. As a consequence, TNBC is the breast cancer subtype that displays the worst prognosis. Moreover, the TNBC group is quite heterogeneous and is comprised of tumours that can be further classified into different categories according to their molecular profile [9].

From all the TNBC subtypes, the "immune-enriched" subtype has the best prognosis, which fits the hypothesis that a good infiltration of the tumour by the immune system helps to fight tumour progression [10–12]. However, some immune cells are associated with poor prognosis. Indeed it has been reported that high expression of genes associated with the M2-like macrophage phenotype correlates with worse outcome [12]. These and other observations suggest the importance of the immune system in the outcome of breast cancer. It is now widely accepted that to develop, cancers need to escape antitumoral immune responses as well as create a tumour-promoting inflammation by attracting pro-tumoral immune cells [13]. We will now discuss the effects of the immune system on breast cancer occurrence and development.

3. Immunosurveillance

It is now known that the immune system influences the outcome of cancer. However, it took a while before scientists could demonstrate the importance of the immune system to prevent the growth of tumours. For instance, to address this question, in 1974, Stutman and colleagues studied the ability of athymic nude mice to resist tumour development induced by the subcutaneous injection of the carcinogen 3-methylcholanthrene (MCA). Surprisingly, the athymic mice developed tumours at a similar rate compared to the control immunocompetent cohort. Thus, the researchers concluded that immunosurveillance did not occur in this context of tumour development [14]. However, as it was later discovered, athymic nude mice do retain some adaptive immune cells such as αβ and γδ T cells, and most innate immune cells as well [15,16], which might compensate for the absence of T cells coming from the thymus in this tumour model.

In the following decades, the possibility to genetically modify whole organisms allowed the creation of a mouse strain lacking the recombination-activating gene-2 ($RAG2^{-/-}$). Mice of this genotype have no functional B and T cells, as the genetic rearrangement of the BCR and TCR cannot occur. In 2001, Shankaran et al. observed that $RAG2^{-/-}$ mice developed tumours earlier and with greater frequency than control mice upon local treatment with MCA. These results showed that the complete absence of an adaptive immune system hindered the natural protection against tumour growth, thus demonstrating the existence of immunosurveillance [17]. Since then, studies in humans have pointed towards similar conclusions. Indeed, immunosuppression after an organ transplantation has been shown to increase the likelihood to develop both virally- and non-virally- induced cancers [18,19]. Additionally, genetic immunodeficiencies are also accompanied by an increase in cancer incidence [20]. Finally, studies have shown the importance of immune cells in cancer protection in immunocompetent cancer patient. Indeed the infiltration of high numbers of $CD8^+$ T cells in solid tumours has been correlated with better prognosis for many types of cancer, showing the protective potential of these cytotoxic cells [21]. More specifically in breast cancer, the presence of tumour-infiltrating lymphocytes (TILs) in the stroma of tumours was correlated with better response to chemotherapy [22] and better overall survival [23] in two early publications. These were quickly followed by many studies reaching similar conclusions on the prognostic power of TILs infiltration in breast cancer [24,25]. Efforts are well underway to harmonize the immunohistological methods to characterize breast cancer TILs in a way that facilitates comparisons and scientific communication between heterogeneous research centers and pathology laboratories worldwide [26].

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