Biochimica et Biophysica Acta 1843 (2014) 2334–2340

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Can calcium signaling be harnessed for cancer immunotherapy?☆,☆☆

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ARTICLE INFO

Article history:
Received 26 December 2013
Accepted 29 January 2014
Available online 11 February 2014

Keywords:
Immunology
Oncology
Active immunotherapy
Passive immunotherapy
Calcium signaling

ABSTRACT

Experimental evidence shows the importance of the immune system in controlling tumor appearance and growth. Immunotherapy is defined as the treatment of a disease by inducing, enhancing or suppressing an immune response. In the context of cancer treatment, it involves breaking tolerance to a cancer-specific self-antigen and/or enhancing the existing anti-tumor immune response, be it specific or not. Part of the complexity in developing such treatment is that cancers are selected to escape adaptive or innate immune responses. These escape mechanisms are numerous and they may cumulate in one cancer. Moreover, different cancers of a same type may present different combinations of escape mechanisms. The limited success of immunotherapeutics in the clinic as stand-alone products may in part be explained by the fact that most of them only activate one facet of the immune response. It is important to identify novel methods to broaden the efficacy of immunotherapeutics. Calcium signaling is central to numerous cellular processes, leading to immune responses, cancer growth and apoptosis induced by cancer treatments. Calcium signaling in cancer therapy and control will be integrated to current cancer immunotherapy approaches. This article is part of a Special Issue entitled: Calcium Signaling in Health and Disease. Guest Editors: Geert Bultynck, Jacques Haiech, Claus W. Heizmann, Joachim Krebs, and Marc Moreau.

1. Introduction

Cancer is one of the most devastating pathologies in terms of epidemiology and outcome. In the world, 14 million new cases occurred in 2012 with 8 million deaths. Interestingly, there is less variation in mortality than in incidence between more developed and less developed countries (http://globocan.iarc.fr). This demonstrates that prevention in the western world plays a significant role in identifying cancer patients but having a larger choice of treatment modalities has a limited impact on this disease. The social costs of cancer are enormous (200 billion USD in the US in 2008) and the World Health Organization projects an increase in cancer related deaths from 7.6 million in 2008 to 13.1 million in 2030 worldwide (http://www.who.int/topics/cancer). Although treatment options are numerous, they all share limited success and toxicity. An underexploited tool in this arsenal is the use of the immune system to fight the patient's own cancer. This paradigm is known as immunotherapy and an important body of preclinical data shows that all arms of the human immune system are involved [1]. Ample approaches have been or are being evaluated in clinical settings and in many cases, they have generated disappointing results [2]. Many reasons can explain these results and the accumulating information from immunotherapy-based clinical trials demonstrates that this approach will best perform when used in combination with additional anti-cancer treatments [3]. These may either be standard of care or novel anti-cancer treatments. From this standpoint, calcium signaling is clearly over-looked in cancer therapy in general and particularly in the context of an immune intervention targeting cancers. Calcium is central in many biological processes including the elaboration and the control of an immune response [4]. Modification of calcium signaling to enhance tumor-targeting immunity could be done at the level of the innate arm of the immune stimulation. Besides being possibly sufficient to control cancer growth, it is required for proper antigen presentation to the immune system and development of the specific response [5]. Calcium signaling also plays an important role in the elaboration of an adaptive, antigen-specific, immune response which is thought crucial in the control of cancer. The latter intervention could act by enhancing or by preventing the resorption of the effector response directed against the cancer or the environment upon which it strives. It may also act by relieving the cancer-induced immunosuppression.

Enhancing the efficacy of immunotherapy may give this technology the potential of controlling and/or eliminating tumors on a stand-alone basis but also to have additive effects on cancer growth when used with standard of care therapies [6]. This concept comes from their non-overlapping modes of action. The former generally involve inhibiting cell division yielding an intrinsic cell death signal while immunotherapy acts by extrinsic cytotoxic mechanisms driven by immune mediators. More recently, synergy between the two treatment modalities has been proposed [7]. Indeed, in addition to their specific, non-redundant effects, cell death pathways induced by some chemotherapeutic drugs, radiotherapy or photodynamic therapy are immunostimulatory and

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☆☆ The author declares no conflict of interest.

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http://dx.doi.org/10.1016/j.bbamcr.2014.01.034

could thereby enhance the efficacy of an immune intervention. Finally, the generation of an anamnestic anti-tumor response may impact on tumor reoccurrence and metastasis. Calcium is involved in all these steps and controlling its metabolism punctually and/or locally could significantly help in the anti-tumor control [8].

2. History

In its broadest definition, immunotherapy is the treatment of a disease by inducing, enhancing or dampening an immune response. Immunotherapy may therefore be applied to any condition in which an immune component is involved and ranges from inflammation and autoimmunity, in which the goal is to diminish an exacerbated immune response, to chronic infections and cancer where the immune response must be boosted. The concept that the immune response has a role in controlling cancer has existed for many years but has only been convincingly demonstrated recently [1]. This was done by first inducing tumors with a carcinogen in either immunodeficient or immunocompetent mice. Each tumor was then split in half with one half being grafted in an immunodeficient animal and the other in an immunocompetent animal (Fig. 1).

It was observed that cancers taken from immunodeficient animals grew when transplanted in similarly immunodeficient animals but that they were rejected when transplanted in immunocompetent animals. Conversely, cancers arising in immunocompetent animals had the capacity to grow in either type of grafted mouse. These results show that spontaneously arising tumors are immunogenic, that the immune system is capable of eliminating them and more importantly, that the immune system exerts a selective pressure on the cancer and selects out cells that have the capacity to evade this immune response. The role of immune-surveillance in controlling cancer initiation and progression has also been indisputably demonstrated by the increase frequency of various types of cancers in immunodeficient mouse strains (reviewed in [1]). In a more clinically relevant setting, the demonstration that the intra-tumoral cytotoxic T cell infiltrate (CD8+) is correlated with a favorable outcome of the patient treatment and that it can be used as a predictive marker shows that the immune response existing in a patient undeniably plays a role in controlling the cancer's evolution even in the context of standard of care therapies [9].

The concept that the immune system may be used in the treatment of cancer originates from serendipitous observations made in the late 18th century which associated cancer regression and infections. The first immunotherapeutic intervention per se was developed by William Coley, in 1893 in which a mixture of killed *Streptococcus pyogenes* and *Neisseria marcescens* was used to treat several types of cancers [10]. This product was commercialized for 70 years before being classified as a "new drug" by the FDA in 1963. This limited its use to clinical trials that yielded unclear results and production was stopped.

Since this period, important technological advances, a better understanding of immune mechanisms and their interaction with cancer has led to the preclinical and clinical evaluations of numerous compounds and approaches to harness the patient's immune response to their cancer. While this field is rapidly evolving, to date, only a handful of products are commercialized and are the backbone of only 3% of cancer therapies. This is expected to go up to 60% in the next 10 years and represents a potential market of 35 billion USD (http://www.reuters.com/article/2013/05/22/us-cancer-immunotherapy-idUSBRE94L0CF20130522). The oldest approved cancer immunotherapeutic product still in use is the tuberculosis vaccine Bacille Calmet–Guérin (BCG) which was approved in 1976 to treat early, non-invasive bladder cancer [11]. It is believed to act by binding to urothelial carcinoma cells, causing a modification in the cytokine and chemokine milieu which will attract phagocytes. These latter cells produce Th1-type cytokines which will orient the immune response toward a more cytotoxic response [12].

3. Definitions

Immunotherapeutic interventions applied to cancer are generally classified as either active or passive (Fig. 2).

The former may be non-specific and involves a general stimulation of the immune system achieved with molecules such as cytokines. In this instance, tumor control may be exerted by innate immune mechanisms and/or the pre-existing antigen-specific immune response, independent of the knowledge of the antigen. At the other end of the spectrum of active immunotherapy, an immune response directed to an antigen expressed specifically or mainly on cancer cells may be achieved by therapeutic vaccination. The common denominator of this type of treatment is the exposure of the host's immune system to a given cancer antigen in a context such that it will stimulate a specific response [13]. An alternative active approach is termed adoptive T cell transfer (ATCT) (reviewed in [14]). It consists in amplifying ex vivo patient's tumor infiltrating lymphocytes (TILs), or cells from the blood, in conditions that will enrich for cells that express a T cell receptor (TCR) recognizing a tumor antigen presented in the context of syngeneic major histocompatibility complex (MHC). This procedure has been further modified by engineering ex vivo amplified effector T cells with retroviruses or lentiviruses to make them express a receptor specific for an antigen [15].

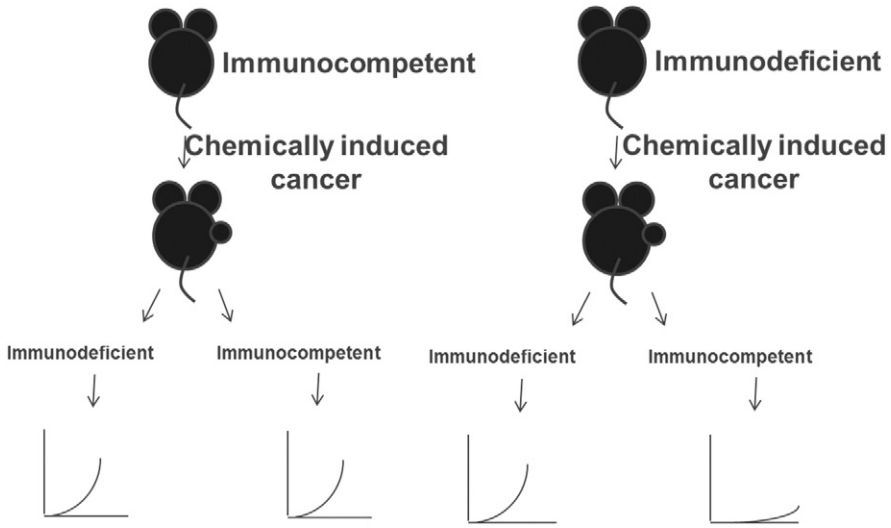

Fig. 1. Cancer immunoediting experiment. See text for details. Graphs below describe tumor volume (Y axis) vs time (X axis).