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Review

Recent advances in the field of anti-cancer immunotherapy

Henrique Neves, Hang Fai Kwok *

Faculty of Health Sciences, University of Macau, Avenida de Universidade, Taipa, Macau

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ABSTRACT

Background: The main goal of anti-cancer therapy is to specifically inhibit the malignant activity of cancer cells, while leaving healthy cells unaffected. As such, for every proposed therapy, it is important to keep in mind the therapeutic index — the ratio of the toxic dose over the therapeutic dose. The use of immunotherapy has allowed a means to both specifically block protein–protein interaction and deliver cytotoxic events to a tumor-specific antigen.

Review scope: It is the objective of this review to give an overview on current immunotherapy treatment for cancers using monoclonal antibodies. We demonstrate three exciting targets for immunotherapy, TNF-α Converting Enzyme (TACE), Cathepsin S and Urokinase Plasmogen Activator and go over the advances made with one of the most used monoclonal antibodies in cancer therapy, Rituximab; as well as Herceptin, which is used for breast cancer therapy. Furthermore, we touch on other venues of immunotherapy, such as adaptive cell transfer, the use of nucleic acids and the use of dendritic cells. Finally, we summarize some ongoing studies that spell tentative advancements for anti-cancer immunotherapy.

General significance: Immunotherapy is at the forefront of anti-cancer therapies, allying both a high degree of specificity to general high effectiveness and fewer side-effects.

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1. Introduction

The 21st century has ushered in an era of great scientific progress and discoveries, resulting in a surge of interest by the general public in

* Corresponding author. Tel.: +853 8822 4991.
E-mail address: hfkwok@umac.mo (H.F. Kwok).

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all manner of research. Modern science looks to improve lives, focusing not only in the eradication of disease, but also in extending the average lifespan of humans. Unfortunately, as people live longer, new problems arise. As age increases, an individual is more likely to develop complications, namely degenerative diseases, such as cancer.

In cancer biology, tumors are described as complex tissues comprised of heterogeneous neoplastic cells interwoven with tumor-associated stroma. The characterization of proteins associated with tumors presents opportunities for targeted therapeutic intervention. This approach is called "targeted therapy". However, the heterogeneity of tumors dictates that, in order to achieve successful clinical treatment, it is necessary to employ a combination of targeted therapies. The most specific targeted therapies currently in use are monoclonal antibodies.

In the last decade, the use of antibody therapy in the field of oncology has shown very promising results [1]. Due to their high specificity, antibodies represent a promising method for interfering with a single target molecule, with high selectivity. Back in 1980, the first patient with relapsed lymphoma was treated using a therapeutic antibody approach. While the antibody was shown to be clinically ineffective, the therapy was deemed innocuous and was well-tolerated [2,3]. These safety and tolerated rationales built up the groundwork that led to the use of therapeutic antibodies in the treatment of cancer.

During the past few years, attention has turned to using antibodies to target different tumor-associated antigens. These include surface glycoproteins associated with clusters of differentiation, CTLA-A, or pathways regulated by growth factors [4]. Furthermore, while the use of monoclonal antibodies monotherapy has had a tremendous impact on cancer treatment, namely in non-Hodgkin's lymphoma, their efficiency has been further improved through the combination of chemotherapy along with monoclonal antibodies [5].

However, many of the studies presented ambiguous or insufficient criteria for clinical objective response. Results from such studies may improperly imply effectiveness when compared to historical controls. This emphasizes the need for thoughtful changes in the application of cancer treatment approaches, such as a combination of multi-targeting antibody-based therapy [6–8].

2. Monoclonal antibody immunotherapy

One of the most promising and exciting fields in modern anti-cancer therapy involves the use of monoclonal antibodies which, once administered to the patient, will selectively and efficiently, target a particular protein involved, in some way, with the proliferation of tumor cells. A large number of monoclonal antibody therapies have already been approved and are currently in use, as described in Table 1.

In the cases described below – TACE/ADAM17, Cathepsin S and Urokinase Plasminogen Activator – the proteins show an abnormally high expression in cancer cells. This makes them the perfect targets for inhibition through the use of monoclonal antibodies.

Furthermore, we also take a look at Rituximab, one of the principal antibodies used in anti-cancer therapy, as well as Herceptin, the only antibody therapy approved by the FDA that targets the human epidermal growth receptor 2 protein.

2.1. TNF-α Converting Enzyme (TACE)

Many growth factors and cytokines require proteolytic release from the cell surface for their activation [11]. TNF-α converting enzyme (TACE), also known as A Disintegrin and Metalloprotease 17 (ADAM17); is a transmembrane metalloprotease responsible for solubilizing many pathologically significant membrane substrates and is an appealing therapeutic target for the treatment of several diseases [11]. In terms of structure, mature ADAM-family ectodomains contain a globular metalloprotease catalytic domain, a disulfide-dependent disintegrin-cysteine rich (Dis-Cys) domain and, in some cases, an epidermal growth factor (EGF)-like domain [11].

Initially, TACE was described as an enzyme, whose function was attributed to solubilizing membrane-associated pro-TNF-α [12] — a process named "ectodomain shedding". Since then, TACE has been described as capable of cleaving epidermal growth factor receptor (EGFR) ligands [13,14], extracellular Notch1 [15], adhesion molecules [16] and cell-surface receptors [17]. Ever since proteolytic cleavage has been proven to be indispensable for the activation of many of these substrates, TACE has been studied as a target in the treatment of cancer [18] and rheumatoid arthritis [19]. Furthermore, dysregulation of ectodomain shedding has been linked to autoimmune and cardiovascular diseases, neurodegeneration, infection and inflammation [20].

Several studies have demonstrated that TACE is over-expressed in various tumor cells, such as those from ovarian cancer, breast cancer, pancreatic ductal adenocarcinoma, colorectal carcinoma, gastric cancer stem cells, gastrointestinal stromal tumors (GIST), non-small cell lung carcinoma and head and neck cancer [21]. This protein has also been associated in governing endothelial cell migration and pathological angiogenesis, which are equally relevant to tumor growth [21]. Chemotherapy may activate TACE, leading to growth factor shedding, which contributes to resistance in colorectal cancer models, as well as contributing to resistance to trastuzumab in breast cancer [21].

There is a very high homology (96%) between the human and mouse TACE ectodomains, which makes the antibody selection and production process even more important. Adding to that, there is the need to adhere to the therapeutic requirements for human antibodies and the desire to avoid metzicin active site immunoreactivity. For these reasons, antibody phage-display presents an attractive technology for producing a specific TACE inhibitor [22].

Antibody phage-display is a powerful *in vitro* selection technology capable of producing fully human antibodies against human antigens. A flowchart of the main steps in phage-display technology is present in Fig. 1.

This technique can be used to direct antibodies towards desired epitopes, due to the biochemical control available during selection conditions. Solution-phase phage display typically produces antibodies with non-linear (conformational) epitopes. Thus, intricate macromolecular cross-domain binding might be hypothetically achieved through this technology, an ideal scenario for an ADAM inhibitor [11]. In fact, antibodies have been produced through phage display, due to recent technical advances, capable of recognizing multiple distinct antigens [23] and different conformations of the same antigen [24,25].

Table 1
Monoclonal antibodies currently in use in anti-cancer immunotherapy, targets and respective cancer types, as well as date of approval both by the Food and Drink Administration and by the European Medicines Agency.
Adapted from Chames, P., et al. Br. J. Pharmacol, 2009 [9] and Oldham, R. K. and Dillman, R. O. Journal of Clinical Oncology, 2008 [10].

Monoclonal antibodies used in cancer immunotherapy					
Generic name	Commercial name	Target	Cancer type	FDA approval	EMEA approval
Rituximab	Rituxan	CD20	Non-Hodgkin's lymphoma	26/11/1997	2/6/1998
Trastuzumab	Herceptin	Erb B2 (HER-2)	Breast	25/9/1998	28/8/2000
Alemtuzumab	Campath	CD52	Chronic lymphocytic leukemia	7/5/2001	6/7/2001
Cetuximab	Erbitux	EGFR	Colorectal	12/2/2004	29/6/2004
Panitumumab	Vectibis	EGFR	Colorectal	27/9/2006	19/12/2007
Bevacizumab	Avastin	VEGF	Colorectal	26/2/2004	12/1/2005