Seminars in Cancer Biology 35 (2015) S185–S198

Contents lists available at ScienceDirect

Seminars in Cancer Biology

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

Review

Immune evasion in cancer: Mechanistic basis and therapeutic strategies

Dass S. Vinay[a], Elizabeth P. Ryan[b], Graham Pawelec[c], Wamidh H. Talib[d], John Stagg[e], Eyad Elkord[f], Terry Lichtor[g], William K. Decker[h], Richard L. Whelan[i], H.M.C. Shantha Kumara[i], Emanuela Signori[j], Kanya Honoki[k,1], Alexandros G. Georgakilas[l,1], Amr Amin[m,n,1], William G. Helferich[o,1], Chandra S. Boosani[p,1], Gunjan Guha[q,1], Maria Rosa Ciriolo[r,1], Sophie Chen[s,1], Sulma I. Mohammed[t,1], Asfar S. Azmi[u,1], W. Nicol Keith[v,1], Alan Bilsland[v,1], Dipita Bhakta[q,1], Dorota Halicka[w,1], Hiromasa Fujii[k,1], Katia Aquilano[r,1], S. Salman Ashraf[x,1], Somaira Nowsheen[y,1], Xujuan Yang[o,1], Beom K. Choi[z], Byoung S. Kwon[a,z,*]

[a] Section of Clinical Immunology, Allergy, and Rheumatology, Department of Medicine, Tulane University Health Sciences Center, New Orleans, LA, United States
[b] Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO, United States
[c] Center for Medical Research, University of Tübingen, Tubingen, Germany
[d] Department of Clinical Pharmacy and Therapeutics, Applied Science University, Amman, Jordan
[e] Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Faculté de Pharmacie et Institut du Cancer de Montréal, Montréal, Québec, Canada
[f] College of Medicine & Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates
[g] Department of Neurosurgery, Rush University Medical Center, Chicago, IL, United States
[h] Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX, United States
[i] Department of Surgery, St. Luke's Roosevelt Hospital, New York, NY, United States
[j] CNR, Institute of Translational Pharmacology, Rome, Italy
[k] Nara Medical University, Kashihara, Nara, Japan
[l] Physics Department, School of Applied Mathematics and Physical Sciences, National Technical University of Athens, Athens, Greece
[m] Department of Biology, College of Science, United Arab Emirates University, Al Ain, United Arab Emirates
[n] Faculty of Science, Cairo University, Egypt
[o] University of Illinois at Urbana Champaign, Urbana, IL, United States
[p] Creighton University, Omaha, NE, United States
[q] School of Chemical and Bio Technology, SASTRA University, Thanjavur, India
[r] Department of Biology, University of Rome "Tor Vergata", Rome, Italy
[s] Ovarian and Prostate Cancer Research Trust Laboratory, Guildford, Surrey, United Kingdom
[t] Purdue University Cancer for Cancer Research, West Lafayette, IN, United States
[u] Karmanos Cancer Institute, Wayne State University, Detroit, MI, United States
[v] University of Glasgow, Glasgow, United Kingdom
[w] New York Medical College, Valhalla, NY, United States
[x] Department of Chemistry, College of Science, United Arab Emirates University, Al Ain, United Arab Emirates
[y] Mayo Graduate School, Mayo Medical School, Mayo Clinic, Rochester, MN, United States
[z] Cancer Immunology Branch, Division of Cancer Biology, National Cancer Center, Goyang, Gyeonggi, Republic of Korea

ARTICLE INFO

Article history:
Available online 25 March 2015

Keywords:
Cancer
Immune evasion
T cells
Therapy

ABSTRACT

Cancer immune evasion is a major stumbling block in designing effective anticancer therapeutic strategies. Although considerable progress has been made in understanding how cancers evade destructive immunity, measures to counteract tumor escape have not kept pace. There are a number of factors that contribute to tumor persistence despite having a normal host immune system. Immune editing is one of the key aspects why tumors evade surveillance causing the tumors to lie dormant in patients for years through "equilibrium" and "senescence" before re-emerging. In addition, tumors exploit several immunological processes such as targeting the regulatory T cell function or their secretions, antigen

* Corresponding author at: R&D Center for Cancer Therapeutics, National Cancer Center, Goyang, Gyeonggi-do 410-769, Republic of Korea. Tel.: +82 31 920 2531; fax: +82 31 920 2542.
E-mail address: bskwon@ncc.re.kr (B.S. Kwon).
[1] These authors contributed to the cross-validation activity.

http://dx.doi.org/10.1016/j.semcancer.2015.03.004

presentation, modifying the production of immune suppressive mediators, tolerance and immune deviation. Besides these, tumor heterogeneity and metastasis also play a critical role in tumor growth. A number of potential targets like promoting Th1, NK cell, γδ T cell responses, inhibiting Treg functionality, induction of IL-12, use of drugs including phytochemicals have been designed to counter tumor progression with much success. Some natural agents and phytochemicals merit further study. For example, use of certain key polysaccharide components from mushrooms and plants have shown to possess therapeutic impact on tumor-imposed genetic instability, anti-growth signaling, replicative immortality, dysregulated metabolism etc. In this review, we will discuss the advances made toward understanding the basis of cancer immune evasion and summarize the efficacy of various therapeutic measures and targets that have been developed or are being investigated to enhance tumor rejection.

1. Introduction

Cancer remains one of the leading causes of death globally, with an estimated 12.7 million cases around the world affecting both sexes equally. This number is expected to increase to 21 million by 2030. The immune system interacts intimately with tumors over the entire process of disease development and progression to metastasis. This complex cross talk between immunity and cancer cells can both inhibit and enhance tumor growth and is now classified as a hallmark of cancer [1]. The balance of these actions between and across the hallmarks determines the eventual outcome, which in the case of clinically overt cancer results from evasion of the destructive elements of the immune response by the tumor. Mechanisms resulting in evasion of immune attack include the selection of tumor variants resistant to immune effectors (sometimes designated "immunoediting") and progressive formation of an immune suppressive environment within the tumor. Although considerable knowledge has been accumulated on how tumors avoid immune destruction, discovering effective cancer therapies still remains a daunting task for the researcher and clinician. In this report, we will briefly present an overview of how tumors evade immune surveillance by focusing on how the immune system reacts to the development of tumors, how certain cancers evade immunity, and what measures can be taken to eradicate cancer. We will address important aspects of tumor and host immune interactions as set out below.

2. Tumors and immunity

The involvement of the host immune system in cancer progression is well established, although greater emphasis has been placed on tumor eradication by immunity than tumor immune potentiation, which may be equally important. These interactions between the immune system and the tumor occur through complex events that usually eventually climax either in successful tumor eradication or immune evasion by the tumor [2].

2.1. Relationship between tumor formation and immune responses

Tumor development and survival is a chaotically governed process involving the interplay between cancer cells, normal stromal cells and host defense mechanisms. Several other factors such as cellular changes due to infection or disease-induced stress may also contribute to tumor growth or tumor suppression. Generally, $CD8^+$ cytotoxic T cells (CTL) and $CD4^+$ helper T (Th)1 cells curb cancer development via mechanisms commonly involving their production of interferon (IFN)-γ and cytotoxins [3] but other factors such as chronic inflammation may override these effects to promote cancer development [4,5]. For example, the risk of overt hepatocellular carcinoma (HCC) appears to be closely linked to the duration of the Hepatitis B and C viral-induced inflammatory state [6–9]. Compelling evidence has also documented, both in animal tumor models and in human cancers, that chronic inflammation plays a critical role in the development of colon and pancreatic cancers [6]. Therefore, when beneficial acute responses fail to resolve tumors/cancer, lingering chronic inflammation can lead to promotion of tumor cell growth and angiogenesis [6,10]. In addition, ongoing activity due to autoimmune disease has also been shown to support development of many cancers including lymphoma [6,10–12].

2.2. Tumor progression and immunity

Vital fundamental discoveries made over the last few decades have unequivocally shown that the immune system plays a critical role in maintaining an equilibrium between immune recognition and tumor development with a dual capacity to both promote and suppress tumor growth. These discoveries collectively support the concept of "immunoediting" and help to explain why tumors can sometimes lie dormant in patients for years before re-emerging, and why tumors grow despite the host having a fully functional immune system [13]. During cancer immune editing, the immune system is able to recognize and destroy the most immunologically vulnerable cancer cells because they present tumor antigens, resulting in their elimination [14]. Nonetheless, due to genetic instability, constant tumor cell division can generate with reduced immunogenicity that can evade immune elimination. This state of production of new tumor cell variants balanced by the elimination has been dubbed "equilibrium", during which the cancer cells continue to divide, accumulating mutational changes by chance or in response to immune-induced inflammation. Thus, a balance between immune control and tumor growth is maintained, giving the appearance of tumor dormancy [15]. However, these processes eventually enable tumors to impair the capacity of the immune system to eradicate them by immune suppressive effects or by loss of target antigen expression. It is at this stage that tumor escape occurs, resulting in overt clinical cancer. Nonetheless, there may also be conditions under which tumor cells are truly dormant, for example by induction of "senescence". In this case, they would be likely to remain dormant permanently, as replicative senescence is generally believed to be irreversible [16].

2.3. Factors that tumors exploit to avoid immune responses

2.3.1. Regulatory cells

Immune suppression in the tumor microenvironment, mediated by $CD4^+CD25^+$ $FoxP3^+$ regulatory T cells (Tregs), or other types of suppressive cells, seems to be a major mechanism of tumor immune escape and can be a crucial hurdle for tumor immunotherapy [17]. A number of studies have shown that tumor-derived Tregs have comparatively higher suppressive activity than naturally occurring Tregs [18,19]. Tregs are drawn into the tumor microenvironment via tumor cell-mediated chemokine production [20,21]. Evidence