Pharmacology & Therapeutics 142 (2014) 339–350

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: B. Teicher

Epigenetic drugs as immunomodulators for combination therapies in solid tumors

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ARTICLE INFO

Available online 30 December 2013

Keywords:
DNA methylation
Histone post-translational modifications
Immunostimulatory antibodies
Immunotherapy

ABSTRACT

Continuously improving knowledge of the fine mechanisms regulating cross-talk between immune cells, and of their multi-faceted interactions with cancer cells, has prompted the development of several novel immunotherapeutic strategies for cancer treatment. Among these, modulation of the host's immune system by targeting immunological synapses has shown notable clinical efficacy in different tumor types. Despite this, objective clinical responses and, more importantly, long-term survival are achieved only by a fraction of patients; therefore, identification of the mechanism(s) responsible for the differential effectiveness of immune checkpoint blockade in specific patient populations is an area of intense investigation. Neoplastic cells can activate multiple mechanisms to escape from immune control; among these, epigenetic reprogramming is emerging as a key player. Selected tumor-associated antigens, Human Leukocyte Antigens, and accessory/co-stimulatory molecules required for efficient recognition of neoplastic cells by the immune system have been shown to be epigenetically silenced or down-regulated in cancer. Consistent with the inherent reversibility of epigenetic silencing, "epigenetic" drugs, such as inhibitors of DNA methyltransferases and of histone deacetylases, can restore the functional expression of these down-regulated molecules, thus improving the recognition of cancer cells by both the innate and adaptive immune responses. This review focuses on the immunomodulatory activity of epigenetic drugs and on their proposed clinical use in novel combined chemo-immunotherapeutic regimens for the treatment of solid tumors.

Contents

Abbreviations: 5-AZA-CdR, 5-aza-2′-deoxycytidine; APC, antigen presenting cell; APM, Antigen Processing Machinery; CIITA, class II transactivator; CpG, cytosine–guanine dinucleotide; CTA, Cancer Testis Antigen; CTL, Cytotoxic T lymphocyte; DNMT, DNA methyltransferase; DNMTi, DNMT inhibitor; EGCG, (−)-epigallocatechin-3-gallate; ER, endoplasmic reticulum; ESCC, esophageal squamous cell carcinoma; FASL, FAS ligand; GC, gastric cancer; HAT, histone acetyltransferase; HATi, HAT inhibitor; HDAC, histone deacetylase; HDACi, HDAC inhibitor; HDM, histone demethylase; HLA, Human Leukocyte Antigen; HMT, histone methyltransferase; HMW-MAA, high molecular weight melanoma-associated antigen; IFN, interferon; MBD, methyl-CpG-binding proteins; NK, Natural Killer; SB, sodium butyrate; TAA, tumor-associated antigen; TAP, transporter associated with antigen processing; TCT, T cell receptor; Th, T helper; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R, TRAIL receptor; TSA, trichostatin A; TSG, tumor suppressor genes; VPA, valproic acid.

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0163-7258/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.12.015

1. Introduction

Neoplastic transformation is sustained by a series of genetic, epigenetic and regulatory alterations that frequently also result in de novo expression or over-expression of tumor-associated antigens (TAA), eventually recognized as non-self by the host's immune system (Buonaguro et al., 2011). This notion has prompted major research efforts aimed at understanding the subtle mechanisms regulating the activity of the immune system and its fine interaction with cancer cells; as a consequence, different immunotherapeutic approaches are finally proving effective in treating cancer. Among these "host immune-modulation" strategies, the anti-CTLA-4 antagonistic immunostimulatory monoclonal antibody (ipilimumab) and the autologous cellular vaccine Sipuleucel-T have recently been shown to improve significantly the survival of melanoma and prostate cancer patients, respectively, and have been approved by the FDA and the EMA (Sharma et al., 2011). These achievements clearly identify immunotherapy as a valid therapeutic strategy for cancer patients; however, its overall effectiveness is still far from optimal since only a minority of treated patients achieves long-term clinical benefit (Ascierto et al., 2011; Di Giacomo et al., 2013; Wolchok et al., 2013). Therefore, in spite of substantial progress, it is essential to identify the mechanism(s) underlying the failure of a large proportion of cancer patients to benefit from modulation of the host immune system. An important limiting aspect is the plethora of immune escape strategies used by neoplastic cells to survive their interaction with the host's immune system. Several strategies modulating the host immune system have proven effective in counteracting the ability of cancer cells to impair priming and/or activation of effector T cells, as well as the induction of tolerance or anergy. However, several immune-escape mechanisms that suppress or down-regulate key molecules required for the efficient recognition and destruction of cancer cells by immune effectors (see below and Fig. 1) are intrinsic to transformed cells and, therefore, can be targeted only by

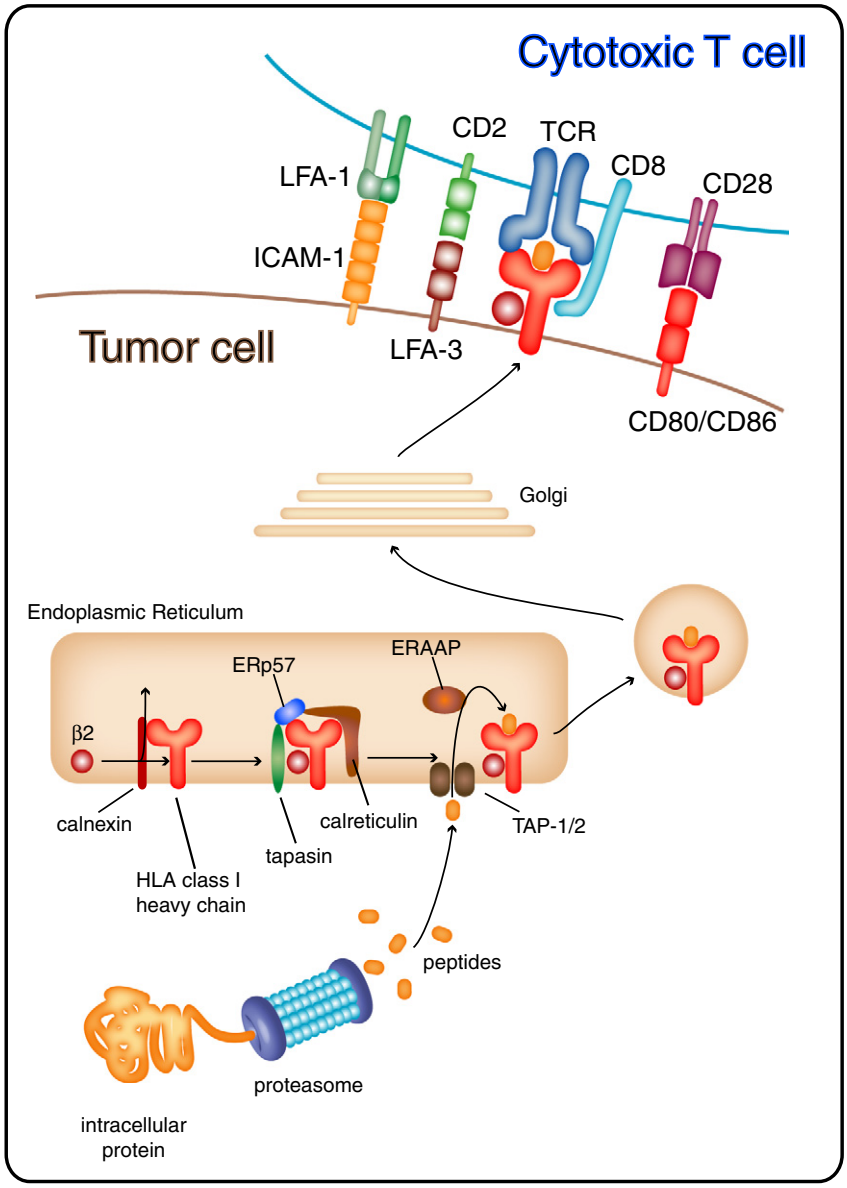

Fig. 1. CTL recognition of cancer cells. CTLs recognize cancer cells by the engagement of antigen-specific TCRs on CTLs, with the tumor antigen presented on the surface of target cells as peptide associated with HLA class I molecules. Cytosolic tumor antigens are degraded to peptides via the ubiquitin/proteasome pathway, and are then transported to the ER lumen by the TAP1/2 heterodimer, where they are further trimmed to their final length by the ERAP1 and 2 aminopeptidases. In the ER, the HLA class I heavy chain associates with β2-microglobulin (b2), giving rise to a partly folded HLA class I molecule. This is then loaded with peptide, assisted by the chaperone molecules ERp57, tapasin and calreticulin. The trimeric HLA class I heavy chain/β2-microglobulin/peptide is finally delivered to the cell surface via the trans-Golgi apparatus. In addition to engagement of HLA class I/peptide by the TCR, CTL activation and cytotoxicity require additional stimulatory signals provided by interactions between co-stimulatory/accessory molecules (CD80, CD86, LFA3) on the antigen presenting cells and activating receptors on the CTL (e.g., CD2, CD28, LFA1).