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Synergizing immunotherapy with molecular-targeted anticancer treatment

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The therapeutic opportunity for anticancer kinase inhibitors (KIs) that block cell-signaling pathways is materializing. Yet, these molecular-targeted therapies are not tailored to be allies of the immune system, and often antagonize it despite generating antigenic activity. KIs usually offer an incomplete cure and one culprit is the lack of synergy between the drug and the immune system, a problem that is magnified when the therapeutic context involves HIV-1-induced immunosuppression (AIDS). We outline a strategy to fulfill the therapeutic imperative of recruiting cooperative immune responses. Accordingly, we propose a method to redesign anticancer drugs to harness the antigenic products of drug-induced apoptosis of tumor cells, thus eliciting an adjuvant immune response.

Introduction

Small molecules such as kinase inhibitors (KIs) that interfere selectively with cell-signaling pathways represent a therapeutic opportunity in cancer treatment [1–11]. Promising as they are, most drug-based anticancer therapies are incomplete and do not provide a decisive cure [12]. A well-known culprit for failure in the long run arises from the somatic evolution of patterns of drug resistance that often materialize as site mutations. Such somatic mutations compromise the affinity of the drug for its target or increase the affinity for the kinase natural ligand ATP, in the case of ATP-competitive inhibitors [12]. A far less acknowledged culprit for the failure of drug treatment arises because these targeted therapies are typically not tailored to operate as an ally of the immune system, and often antagonize it despite generating antigenic activity [13–16]. Largely discovered through trial and error, KIs are often of limited applicability because drug treatments are marred by episodes of relapse and by the development of drug resistance and intolerance [12,17]. As said, one culprit for this incomplete success is the lack of synergy between the drug and the immune system, with the latter often incapacitated at crucial junctures owing to antagonistic effects generated by the drug [13,14,18–21]. Thus, a therapeutic requirement arises from the need to recruit cooperative immune responses concomitant with the molecular-targeted treatment. The goal is to design anticancer drugs that inhibit targeted cellular functions and steer the immune system to harness the antigenic products of the drug-induced apoptosis of tumor cells. To fulfill this need for therapeutic integration, we propose redesigns of anticancer drugs that fulfill three constraints: (i) nanomolar activity against anticancer targets; (ii) reversal of tumor-induced immunomodulation; and (iii) removal of drug-induced immunosuppressive activity.

The drug design strategies introduced to address the therapeutic imperative of immunosynergy have the potential to revolutionize cancer treatment and the understanding of the adaptive immune response by steering it with molecular-targeted therapy. We are counting on the premise that, by restoring the adaptive immune response to drug-induced antigenic activity, we shall be able to create synergies that will reciprocally empower the immune system and drug-based anticancer treatment. Novel possibilities to harness and manipulate the immune system will probably transpire from the evaluation of immunosynergic drugs.

Therapeutic shortcomings of anticancer drugs that suppress the adaptive immune response

Undesired cross-reactivity modulating the immune response

In practice, the level of molecular fine-tuning required to redesign an anticancer drug into an immunosynergic drug cannot be achieved within the drug discovery paradigm based on trial and

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error and high-throughput screening [17,22]. Rather, a rational design approach is needed [23]; an arena where novel molecular filters can be exploited to control drug specificity better [24,25]. Thus, an unprecedented control of specificity [17] is required to design therapeutic agents capable of discriminating between cancer-related targets and immunosuppressive targets. The reward in building immunosynergic molecular therapies through rational design is potentially immense, because these targeted therapies will have a formidable ally – the immune response – in their anticancer activity.

Well-established anticancer KIs like imatinib [1–3] or dasatinib [4–9] are also known to be directly immunosuppressive [13,14,18–21] through their powerful blockade of upstream signaling in the adaptive immune response and, yet, as shown in this study, they hold promise as chemical scaffolds that can be turned into immunosynergic drugs. The choices are justified because these KIs are nanomolar inhibitors of the major anticancer target c-KIT [2,3,8,9], the kinase of the stem cell factor (SCF) receptor, and hence the KI treatment is expected to have the additional effect of reversing tumor-induced immunosuppression, at least in certain tumor environments where tumor-secreted SCF is deployed to hijack the immune system [26]. The latter effect is promoted by the accumulation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), the development and activation of which requires the SCF expressed by the tumor cells. However, imatinib and dasatinib are also direct immunosuppressants [13–15,18–21], and this role is clearly antagonistic to their anticancer activity, thus requiring careful removal through a molecular remodeling of the parent compounds using stringent selectivity filters [23–25].

More precisely, these KIs are powerful (nanomolar) inhibitors of two crucial kinases implicated as upstream signal transducers controlling the immune response: lymphocyte-specific protein tyrosine kinase (LCK) and colony-stimulating factor 1 receptor (CSF1-R) [17,22]. In fact, dasatinib is the most powerful inhibitor of LCK known to date (K_d = 0.2 nM) [22]. Specifically, LCK is a signal transducer for the signaling cascade that originates in the CD4 and CD8 receptors expressed on the surface of T cells in antigen-triggered T cell differentiation (http://www.genome.jp/kegg-bin/show_pathway?map=hsa04660&show_description=show) and in natural killer (NK) cell-mediated cytotoxicity (KEGG, release 8/2/2013, http://www.genome.jp/kegg-bin/show_pathway?map=hsa04650&show_description=show) [27]. By contrast, the CSF1-R kinase is implicated in the development of the monocyte/macrophage (M/M) lineage (http://www.genome.jp/kegg-bin/show_pathway?map=hsa04640&show_description=show) [27]. Hence, both KIs suppress antigen-specific T cell effector functions and NK cytotoxicity and inhibit the hematopoietic development of crucial components of the immune response.

Thus, imatinib and dasatinib are likely to hamper the adaptive immune response triggered by the strong antigenic activity they generate and compromise the antigen presentation by precluding macrophage development. The profound inhibition of all antigen-specific T cell effector functions at therapeutically relevant concentrations has been mechanistically tracked down to the early blockade of signal transduction events promoted by LCK inhibition [13,14]. In fact, LCK is central in the transduction of T cell receptor (TCR) signaling in response to MHC-I and MHC-II antigen presentation that ultimately promotes T cell differentiation and proliferation. Thus, the drug-induced immunosuppressive effects caused by LCK inhibition – purposely engineered in the case of dasatinib [28] – actually betray the purpose of these drugs as anticancer agents, possibly enabling the development of episodes of relapse and drug resistance and impacting the frequency of opportunistic infections. In the case of dasatinib, the original drug discovery pursuits seemed to focus squarely on modulating the immune response [28]. The repositioning of dasatinib as an anticancer agent seemed to have arisen as an afterthought, because the precursor drug imatinib showed cross-reactivity against LCK as well as the cancer-associated targets Bcr-Abl, c-KIT and platelet-derived growth factor receptor (PDGFR). Furthermore, the LCK-related immunosuppression by both KIs is reinforced by the blockade of macrophage development – and thereby antigen presentation – caused by CSF1-R inhibition (both compounds are nanomolar inhibitors of CSF1-R).

These immunoantagonistic effects are ostensibly at odds with the need to maintain an uncompromised immune response to fight cancer, unless the kinases targeted for immunosuppression also happen to be relevant anticancer targets. Thus, the immunosuppressive effects are likely to impede a lot of the ongoing efforts to apply these KIs to combat cancers other than hematologic malignancies, where immunosuppression could become adjuvant. Even in those applications for which FDA approval has been obtained [i.e. the treatment of chronic myelogenous leukemia (CML) and Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph+ALL); http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021588s024lbl.pdfatypical; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm231409.htm], opportunistic infections have been reported in patients treated at therapeutic doses [19].

Potentially immunosuppressive anticancer drugs identified from kinome-wide screening

A kinome-wide screening of KIs [17,22] reveals that potential side-effects and immunosuppressive complications due to nanomolar inhibition of LCK (dissociation constant K_d <50 nM) are likely to be a concern for several compounds of therapeutic interest. Thus, a significant drug-induced impairment of adaptive immune responses, mostly affecting T cell and NK cell activation, is readily expected for the following KIs: NVP-AST487 (Novartis, K_d = 11 nM); nintedanib (BIBF-1120, Vargatef®, Boehringer-Ingelheim, K_d = 6.2 nM); crizotinib (Xalkori®, Pfizer, K_d = 30 nM); dasatinib (Sprycel®, Bristol-Myers Squibb, K_d = 0.2 nM); foretinib (GSK1363089, GlaxoSmithKline, K_d = 6 nM); imatinib (Gleevec®, Novartis, K_d = 40 nM); nilotinib (Tasigna®, Novartis, K_d = 47 nM); PD-173955 (Parke-Davis, K_d = 1.1 nM); bosutinib (SKI-606, Bosulif®, Wyeth/Pfizer, K_d = 0.59 nM); NVP-TAE684 (Novartis, K_d = 49 nM); and vandetanib (Caprelsa®, AstraZeneca, K_d = 17 nM) [22].

Although the anticancer activity is a desired clinical outcome for these KIs, the reported structural similarities between LCK and validated anticancer targets like c-KIT, PDGFR and Src-family kinases introduce extremely undesirable cross-reactivities. In fact, although these KIs are being actively evaluated as anticancer agents, their nanomolar inhibition of LCK truly compromises the immune system, depriving the patient of a key endogenous resource to fight the disease. This adverse aspect of treatment seems to have been overlooked (except in the cases of imatinib and dasatinib as indicated previously). Therefore, this review

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