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Perspective

The future of immune checkpoint combinations with tumor-targeted small molecule drugs

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Immune-checkpoint blockade (ICB) has transformed the landscape of cancer treatment. However, there is much to understand around refractory or acquired resistance in patients in order to utilize ICB therapy to its full potential. In this perspective article, we discuss the opportunities and challenges that are emerging as our understanding of immuno-oncology resistance matures. Firstly, there has been remarkable progress made to understand the exquisite overlap between oncogenic and immune signaling pathways. Several cancer-signaling pathways are constitutively active in oncogenic settings and also play physiological roles in immune cell function. A growing number of precision oncology tumor-targeted drugs show remarkable immunogenic properties that might be harnessed with rational combination strategies. Secondly, we now understand that the immune system confers a strong selective pressure on tumors. Whilst this pressure can lead to novel tumor evolution and immune escape, there is a growing recognition of tumor-intrinsic dependencies that arise in immune pressured environments. Such dependencies provide a roadmap for novel tumor-intrinsic drug targets to alleviate ICB resistance. We anticipate that rational combinations with existing oncology drugs and a next wave of tumor-intrinsic drugs that specifically target immunological resistance will represent the next frontier of therapeutic opportunity.

Introduction

Immune-checkpoint blockade (ICB) has transformed cancer treatment paradigms; however, the majority of patients are either refractory to treatment or eventually acquire resistance. The understanding of ICB therapy resistance is progressing rapidly, with several emerging concepts shaping the directions of the field. It is clear that many tumor-targeted drugs exert remarkably potent impacts on immune cells that may be either beneficial or detrimental. Moreover, the immune system exerts a significant selective pressure on tumors that confers unique signaling pathway dependencies. Neither of these concepts had been anticipated before the advent of immunotherapy because tumor cells were generally studied in isolation, but they guide us towards the next frontier of therapeutic opportunities.

Combination of immune-checkpoint blockade with tumor-targeted drugs

Treatment of metastatic cancer relies on combination approaches to minimize resistance and enhance the duration of response [1,2]. The integration of ICB with tumor-targeted therapies revealed unanticipated cross-talk between oncogenic and immunological signaling networks. For example, ICB combination with Mitogen-activated protein kinase (MAPK) pathway inhibitors was beneficial in pre-clinical models [3]. This finding was unexpected because MAPK signaling is important for T-cell development and effector activation [4]. Detailed mechanistic experiments revealed that MHC-I-dependent antigen presentation is suppressed by MAPK or upstream KRAS driven oncogenic signaling, whereas immunosuppressive PDL-1 and CD73 proteins are induced [5–7]. Thus, KRAS/MAPK pathway inhibition seems to exert an overall net benefit on tumor cell intrinsic

Table 1. The immunological effects of immune-checkpoint blockade in combination with small molecule tumor-targeted drugs

Combination inhibitor class	Exemplar combination partners and furthest clinical development status of combination	Proposed immunological mechanisms and key references
KRAS/MAPK pathway	RAF/MEK (Ph3 — NCT02967692) Sotorasib (Ph2 — NCT04185883)	Enhancement of MHC-I antigen presentation. Suppression of CD73 and PDL-1 expression.
MTOR/PI3K pathway	Everolimus (MTOR allosteric) (Ph1b — NCT03095274; NCT02890069) Vistusertib (preclinical) Idelalisib, AZD8835 (preclinical)	Promote antigen-presenting cell immunometabolism. Enhance T-effector/memory survival.
EGFR	Erlotinib, Gefitinib Osimertinib (Ph1/2 — NCT02039674; NCT02454933)	Preclinical combinatorial synergy with anti-PD1, direct mechanistic link unclear [31]. Resulted in potentially elevated interstitial lung disease [15].
ALK	Crizotinib (Ph1/2 — NCT02393625)	Crizotinib promotes immunogenic cell death of cancer cells [32]. Severe hepatic toxicities reported in early phase clinical trials [33].
FGFR	Erdafitinib (Preclinical)	FGFR pathway inhibition showed combination benefit with anti-PD1 in a preclinical mFGFR2 driven autochthonous lung cancer model, associated with increased T-cell infiltration [34]. Precise mechanistic links with the immune system are unknown.
CDK4/6	Abemaciclib (Preclinical)	Activation of endogenous retrovirus enhances immunogenicity, and suppression of Treg proliferaton [35].
IGF1R	PQ401 and genetic knockout - Preclinical	IGF/IGF1R pathway antagonists show combination benefit with anti-PD1. Mechanistic links to ICB are unknown [36].
Poly-specific tyrosine kinase (TKI)	Axitinib, Cabozantinib, Lenvatinib (approved — NCT02853331, NCT03141177, NCT02501096)	Modulation of the tumor microenvironment and enhancement of immunogenic cell death (increased interferon signaling, promote NK cell killing and reduced suppressive macrophage activity) [37–39].
DNA-damage response	PARP inhibitors; Olaparib, Rucaparib (Ph3 — NCT03737643, NCT01968213)	Immunogenic cell killing releases innate-immune agonists (e.g. STING) [40].
Epigenetic	BET (Ph2 — NCT04471974) HDACi (Ph1/2 — NCT02805660) EZH2 (Ph1/2 — NCT03854474)	Suppression of PDL-1 [41]. Modulation of transcriptome changes the peptide repertoire to enhance tumor immunogenicity [42].
iAP antagonists	Xevinapant (Ph1/2 — NCT04122625)	Lowering apoptotic threshold and sensitization to immune-mediated killing [43]

immunogenicity, a hypothesis that is currently under clinical evaluation (NCT02967692). These data neverthe-less imply that tumor-selective MAPK inhibition would be advantageous, to eliminate potentially negative effects on T-cells. Notably, oncogene-mutant-selective KRAS G12Ci showed excellent preclinical combination benefit with ICB in preclinical models where MAPK activation is driven by KRAS G12C mutation [8], and this combination is currently under clinical evaluation (NCT04185883).

Inhibitors of phosphoinositide 3-kinase (PI3K) and downstream AKT/Target of Rapamycin (MTOR) signal-ing pathways also represent another prominent class of oncogene targeted therapies being investigated in com-bination with ICB. PI3K/AKT/MTORi were developed as tumour-targeted agents, given pathway alterations are reported in 38% of solid tumors [9]. However, PI3K/MTOR pathway inhibitors show remarkable immunomo-dulatory properties. Ali et al. showed that inhibition of the PI3Kδ isoform could acutely deplete immunosup-pressive regulatory T-cells from the tumor microenvironment [10]. We extended these findings, showing the clinical PI3Kα/δ inhibitor AZD8835 enhances cytotoxic effector functions of conventional T-cells [11]. Inhibitors of MTOR also combine well in ICB combination, but subtleties are revealed when comparing the associated immune effects. For example, dose-dependent inhibition of T-cell proliferation is observed with MTOR but not PI3K inhibition, and MTORi additionally promotes innate-immune inflammatory cytokine profiles [11–13]. PI3Ki/MTORi combinations with ICB have not been widely explored in the clinic, and further evaluation is warranted.

Whilst we highlight MAPK and PI3K/mTOR examples, many analogous findings reinforce a continuum of shared signaling between tumor cells and the immune system that extends to additional oncogenic pathways
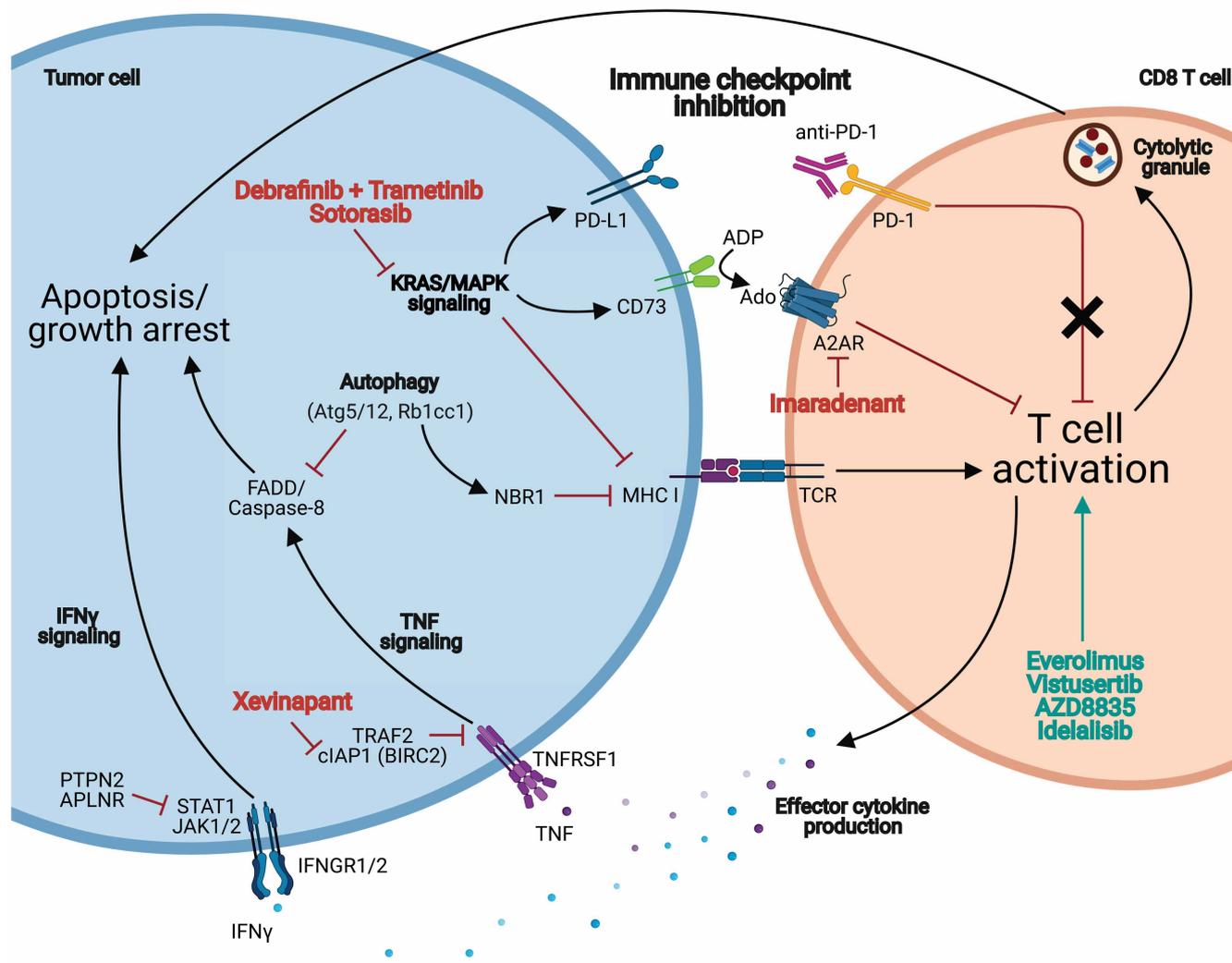
Figure 1. Mechanisms of immune-evasion by tumors and opportunities for novel therapeutic development with tumor-targeted therapies.
Key mechanisms involved in immune evasion or resistance are shown, in addition to clinical inhibitors that can modulate the pathways (depicted in red or teal text). A common involvement of antigen presentation, immune-checkpoint, IFNγ, TNF, cytolytic and autophagy pathways has been observed in functional genomics screens, which are typically associated with cell-mediated immunity. Not all pathways or targets are druggable with available inhibitors, which provides a roadmap for future drug discovery efforts.

(Table 1). Synergies between ICB and broadly active tumor targeting agents such as poly-specific tyrosine kinase inhibitors and DNA-damage pathway inhibitors are of significant interest due to their wide-clinical relevance [14]. Notably, not all combinations will be clinically feasible, exemplified by challenges in combining ICB with EGFR inhibitors that led to potentially increased incidence of interstitial lung disease [15]. Careful consideration of combinatorial mechanisms, overlapping biomarkers, and optimization of dose/scheduling should be prioritized to maximize the probability for these combinations to translate clinically. Given that oncogenic signaling can directly control the immunogenicity of a tumor, combination studies in the relevant genetic context represents a focused patient selection paradigm, as exemplified by KRAS/MAPK. In contrast, it is notable that direct immune-intrinsic potentiation would not preclude the extension of a novel combination beyond conventional oncogene-dependent patient populations, as may be the case for PI3K/MTOR inhibitors. Deep understanding of the cellular and molecular combinatorial mechanisms is critical before patient selection can be considered.

Tumor-intrinsic resistance to immune-mediated killing

Complimentary to harnessing tumor-targeted therapies to augment immunity, studies are uncovering the signaling pathways contributing to immune-evasion in tumors.

Mutation of the interferon gamma (IFNγ) signaling pathway represents a major mechanism of clinical ICB resistance [16,17]. IFNγ is a T-cell-derived cytokine that signals through the JAK/STAT pathway to directly restrict tumor growth, and indirectly promote upregulation of MHC-I-dependent antigen presentation. The important role for IFNγ is recapitulated in preclinical CRISPR screens performed with both human and mouse melanoma cells co-cultured with antigen specific T-cells, where IFNγ pathway attenuation promoted tumor persistence [18,19]. Similarly, an *in vivo* CRISPR screen using the B16 mouse model revealed IFNγ pathway enriched hits in tumors resistant to anti-PD-1 [20]. These studies identified well-known IFNγ pathway members including *Jak1/2*, *Stat1* and *Ifngr1/Ifngr2* as resistance hits, in addition to newly identified negative regulators such as *PTPN2* and *APLNR* which might represent novel therapeutic targets [18–20].

Systematic exploration of IFNγ-independent mechanisms of immune-evasion revealed an important role for the proinflammatory/cytotoxic cytokine TNF, which promotes bystander killing of tumors by T and NK-cells [21]. The TNF pathway exhibits complex feedback dynamics, and the ablation of negative pathway regulators *Traf2* and *Birc2* lowered the threshold of tumor cell apoptosis by TNF [22]. Historically, TNF administration resulted in unacceptable toxicities when delivered systemically in the clinic, despite exhibiting broad efficacy in preclinical tumor models [23]. An ability to selectively sensitize tumors to TNF-mediated killing would open up intriguing possibilities to widen the therapeutic index for TNF agonist therapies.

Beyond conventional cytotoxic effector signaling, perhaps a more unexpected role for autophagy has emerged. CRISPR-mediated knockout of autophagy pathway genes including *Atg12* enhanced cytotoxic killing of a broad panel of syngeneic mouse tumors [24]. Two additional studies corroborate these findings, implicating additional autophagy pathway members *Atg5* and *Rb1cc1* in immune resistance [25,26]. Autophagy is a cellular recycling process, which physiologically dampens intracellular damage to mitigate cell stress [27]. The exact mechanism through which autophagy promotes immune-evasion remains to be elucidated, however, autophagic flux reportedly limits TNF-mediated tumor cell apoptosis through regulation of the FADD/caspase-8 complex [26], and reduces antigen presentation via NBR1-mediated lysosomal degradation of MHC-I in pancreatic cancer [28]. Autophagy may, therefore, represent an emergent point of integration between tumor cell stress and immune cross-talk.

Collectively, it is becoming clear that the immune system exerts strong selective pressures on tumor cells and immune resistance is associated with a novel spectrum of cancer dependencies (Figure 1). Whilst functional genomics screens have started to reveal common immunomodulatory nodes that are broadly important in cancer, we must still consider that the oncogenic context is key. There remains an opportunity for functional genomics screening to better inform on diverse resistance mechanisms in systems harboring discrete, clinically relevant oncogenic drivers.

Conclusions

Since the first approvals of ICB, remarkable progress has been made to understand immune-resistance mechanisms. A unifying theme has emerged whereby classical oncogenic driver genes or pathways exhibit unexpected roles to promote immunosuppressive profiles. With hindsight, this may seem intuitive, given that immune-evasion is a central hallmark of oncogenesis [29]. Nonetheless, these findings are conceptually discrete from a purely immune-editing paradigm, where immune escape by tumors is driven solely by passive selective pressures conferred by immune cells [30]. Leveraging existing tumor-targeted therapies dosed and scheduled in a way to mitigate for deleterious effects on immune cells will maximize the therapeutic potential for such combinations in the near-term.

A second major theme is that whilst immune-evasion might be driven by core oncogenic signaling, the downstream functional dependencies and resistance pathways diverge. Tumor-intrinsic evasion mechanisms are best revealed under conditions that mimic immunological pressure, which is an area that has only recently received attention by the research community. Many of the emergent immunological resistance pathways are classically involved in cell-mediated immunity, however, with the newfound power of functional genomics, key signaling nodes are being deciphered. These efforts reveal a deep array of novel drug targets that will drive a subsequent wave of innovation to tackle ICB resistance.

Competing Interests

J.S. and C.S. are employees and shareholders of Bristol Myers Squibb.

Author Contributions

J.S. and C.S. co-wrote the manuscript.

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Abbreviations

ICB, Immune-checkpoint blockade; IFNγ, interferon gamma; MAPK, Mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase.

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