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Therapeutic opportunity in innate immune response induction by oncogene-targeted drugs

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“Importantly, the ability of oncogene-targeted inhibitors to induce this innate immune response indicates that oncogenes contribute to the cancer hallmark of immune evasion through mechanisms that are more direct than generally appreciated”

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Rapid reprogramming in residual disease induces innate immune signaling

Modern targeted cancer therapeutics include tyrosine kinase inhibitors (TKIs) that block oncogenic driver receptor tyrosine kinases (RTKs) such as EGFR and EML4 – anaplastic lymphoma kinase (ALK) in lung adenocarcinoma, as well as MAPK pathway-directed agents against mutant BRAF in multiple solid tumors. This has markedly increased cancer patient survival when delivered in a manner consistent with the tenets of precision medicine [1,2]. Still, in the majority of cases, incomplete elimination of cancer cells yields residual disease comprised of drug-tolerant persisters [3,4], which serves as a reservoir from which outgrowth of resistant clones eventually occurs. Over the last decade, major advances have occurred in defining the precise molecular mechanisms driving acquired resistance and therapeutic failure of first-line oncogene-targeted drugs [4,5]. While this has spurred the development of superior second- and third-generation inhibitors that further extend cancer patient's lives, these drugs have not yet provided long-term cancer control or cures. As reviewed by Glickman and Sawyers [4], serial monotherapy failed as a therapeutic strategy for combating HIV, even with the best drugs. Rather, successful management required upfront combinations of drugs to increase the depth of response and prevent or reduce acquired resistance [3,4]. Successful deployment of similar combination strategies with oncogene-targeted drugs will require a full understanding of the rapid signaling responses within residual tumors.

In this regard, the literature supports the ability of oncogene-targeted drugs to induce rapid and profound transcriptional reprogramming resulting in increased expression of bypass signaling pathways that decrease dependence of the cancer cells on the targeted oncogene [5,6]. This tumor cell autonomous view of inhibitor-induced reprogramming provides strong rationale for combining primary oncogene-targeted drugs with agents that block the emergent resistance-inducing bypass pathway. The clinical success of combining an MEK inhibitor (MEKi) with a BRAF inhibitor in melanoma therapy to prevent bypass signaling with the BRAF inhibitor, alone, is an example of rational deployment of mechanistic understanding of oncogene inhibitor-induced reprogramming [7].

Beyond these well-defined cancer cell autonomous actions, studies reveal that inhibitors of oncogenic RTK-MAPK pathways induce an innate immune response involving myriad chemokines, cytokines, antiviral genes and MHC genes where many are components of interferon (IFN)-stimulated gene-expression programs [8–11]. Importantly, the ability of oncogene-targeted inhibitors to induce this innate immune response indicates that oncogenes contribute to the cancer hallmark of immune evasion through mechanisms that are more direct than generally appreciated. The literature supports that this RTK-MAPK inhibitor-induced inflammatory response represents a normal epithelial homeostatic program that is frequently retained in carcinoma cells arising from distinct epithelial tissues [10,11]. Analysis of on-treatment melanoma and lung adenocarcinoma specimens demonstrates

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robust BRAF inhibitor and TKI-mediated transcriptional activation of multiple programs including IFN response pathways [8,12] and CD8⁺ T-cell infiltration [13]. Likewise, cetuximab increases CD8⁺ T-cell infiltration in head and neck cancers [14]. Thus, through tumor cell non-autonomous pathways, the immune microenvironment may directly participate in the therapeutic response to precision drugs such as TKIs and MEKi's. Moreover, the innate immune response elicited by oncogene-targeted drugs is not limited to chemokines and cytokines involved solely in recruitment and activation of anti-tumor immune cells. Rather, a broadly orchestrated program including both pro- and anti-tumorigenic paracrine signaling probably occurs. As an example, we previously demonstrated that EGFR-specific TKIs broadly induce the immune suppressive cytokine, TGFβ2, in head and neck cancer cell lines [15]. By contrast, increased expression of CXCL10, a potent chemotactic factor for effector immune cells [16], is more limited in these cell lines [17].

Oncogene-targeted drug-induced innate immune signaling provides precedent for immunotherapy combinations

Immunotherapies that target CTLA4 or the PD1/PD-L1 proteins disrupt distinct mechanisms of immune evasion and yield striking anticancer activity, albeit in a subset of patients. Notably, lung adenocarcinomas driven by mutated EGFR and EML4-ALK fusions that are enriched in 'never smokers' exhibit little or no response to the presently approved immunotherapeutics [18]. It has been postulated that a T-cell-inflamed tumor microenvironment (TME) associates with immunotherapy sensitivity where a molecular signature for the inflamed state includes T-cell-specific transcripts, chemokines and innate IFN response genes [19,20]. The critical chemokines that promote T-cell infiltration into tumors (such as T-cell inflammation) include CXCL9 and CXCL10 that engage CXCR3 on T cells [19]. A distinct, but overlapping IFNγ signature has also been recently reported that predicts sensitivity of head and neck squamous cell carcinoma (HNSCC) to immunotherapy better than PD-L1 levels [20]. Logically, tumors that exhibit response to immunotherapies are also more highly infiltrated with CD8⁺ cytotoxic T cells, natural killer cells, dendritic cells and other well-known anti-tumor immune cells.

In light of this ability of oncogene-targeted agents to induce an innate IFN response that includes T-cell-attracting chemokines and increased antigen presentation, combining immunotherapeutics with oncogene-targeted drugs represents an attractive approach to increasing the response relative to either, alone. In fact, a dizzying number of clinical studies testing combinations of EGFR or ALK-specific TKIs and immunotherapeutics have been initiated [21]. Although premature to form conclusions on efficacy of the combinations relative to either monotherapy, increased incidence of adverse events including pulmonary and liver toxicities has been observed, frequently requiring termination of the treatment [21].

Conclusion & knowledge gaps

The failure of oncogene-targeted agents to yield long-term cancer control or cures highlights the need for novel combination therapy strategies in precision cancer medicine. Because an IFN response gene signature within tumors is clearly associated with sensitivity to immunotherapies, discovering pharmacological approaches that induce T-cell inflammation within the TME has clear promise. While the research community supports advancement of rigorous preclinical studies to provide rationale for clinical investigations, the advent and approval of immunotherapy has led to an 'Immunotherapy Gold Rush' [22]. As of 2017, there were 940 immuno-oncology agents in clinical development and another 1064 in preclinical phase. Moreover, 3042 interventional and active clinical trials are evaluating these clinical-stage immunotherapies with a target of enrolling 577,076 patients [23]. It is likely that the majority of clinical trials presently exploring immune therapies in a combination format will not provide deep insight into fundamental mechanism, regardless of whether they succeed or fail. Identifying precise tumor-cell intrinsic signal pathways and the dominant chemokines and cytokines that mediate the cancer cell-TME conversation must be explored at the basic mechanistic level to identify novel targets, biomarkers of predicted response and strategies to limit adverse events. Certainly, the number of approved immunotherapies with molecular targets distinct from blockade of PD1/PD-L1 interactions will grow. Thus, comprehensive and deep investigation of the basic signaling mechanisms that drive the transcriptional induction of this innate immune response by oncogene-targeted inhibitors must be prioritized to identify novel therapeutic targets beyond PD1/PD-L1 for rational combination with precision medicines. For example, combining oncogene inhibitors with antagonists of pro-tumorigenic, immune suppressive chemokines and cytokines or intentionally enhancing expression of anti-tumor chemokine/cytokine activity may permit specific innate and adaptive immune cells to productively participate in the elimination of solid tumors with oncogene-targeted drugs.

The oncogene inhibitor-induced chemokine/cytokine cascade and increased MHC expression support a hypothesis that this innate response invokes the direct participation of immune cells in the therapeutic response to RTK-MAPK pathway inhibitors. Consistent with this hypothesis, EGFR mutant lung cancer patients exhibited increased peripheral natural killer cells and IFN γ levels after 4 weeks of gefitinib treatment while circulating IL6 levels decreased, especially in gefitinib-sensitive patients [24]. Published studies with murine tumor models demonstrated that MEKis improved the tumor cell killing capacity of immune cells but failed to identify the site of action of the agents [25]. A full understanding of the magnitude and kinetics (sustained versus transient) of this inhibitor-induced response will be relevant to the functional communication with the immune microenvironment, but also instruct how immunotherapies should be introduced into a combination. Also, the association of these variables with the degree of therapeutic response in patients may yield insight into the observed variability in patient responses to precision medicine, even within an oncogene-defined subset. Does variable induction of innate immune signaling underlie the range of tumor shrinkage responses noted in a waterfall plot? Preclinical deployment of accurate murine models of oncogenic RTK-MAPK driven cancers in syngeneic mice [26] would allow direct assessment of the role of specific immune cells in the targeted therapeutic response.

Finally, the precise signal transduction mechanisms mediating the innate immune response within tumor cells treated with oncogene-targeted drugs deserve deeper exploration with the rationale that novel drug targets may emerge, which can add to the arsenal of agents for enhancing immune surveillance of cancers. While a number of studies have documented an innate immune response resulting from RTK-MAPK inhibition in keratinocytes [10] and primary tumors [8,12,13], the mechanism(s) mediating this response remains ill defined. Does the RTK-MAPK pathway directly suppress transcription of chemokine and cytokine transcripts needed to recruit anti-tumor immune cells, or does inhibition of MAPK signaling indirectly result in activation of specific stress signaling pathways that activate IFN-stimulated genes? Also, it is important to determine if the inhibitor-induced innate immune response is specific to oncogenic RTK-MAPK pathways or is observed following inhibition of PI3K/AKT/MTOR or Wnt/ β -catenin pathways as well.

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