Combination immuno-oncology therapy with immune checkpoint blockers targeting PD-L1, PD-1 or CTLA4 and epigenetic drugs targeting MYC and immune evasion for precision medicine

Masaru Katoh

Department of Omics Network, National Cancer Center Tokyo, Japan

Correspondence to: Masaru Katoh. Department of Omics Network, National Cancer Center, 5-1-1 Tsukiji, Chuo-ward, Tokyo 104-0045, Japan. Email: mkatoh-kkr@umin.ac.jp.

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Therapeutics targeting epigenetic regulators (1-3), immune modulators (4-6) and receptor tyrosine kinases (7-9) have emerged as promising drugs for cancer patients who are refractory to conventional chemotherapy, radiotherapy or surgery (Figure 1). These cutting-edge therapeutics, together with next-generation sequencing (NGS) technologies that produce bulk genomics-related data as commodities of clinical medicine, have led to a gradual shift toward personalized or precision medicine. Whole genome sequencing comprehensively detecting alterations in common and rare cancer-related genes and cancer gene panels detecting alterations in approximately 300 common cancer-related genes are representative NGS-based sequencing (10-12). In current practice, personalized medicine involves using NGS-based diagnostic tests to select patients and time points for targeted therapy; in the future, precision medicine will involve utilizing multiple layers of omics data to optimize benefit-risk balance for targeted therapy (10). Lung cancer is one of the most common malignancies in the world (13). Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases, and NSCLCs can be sub-classified into lung adenocarcinoma, lung squamous cell carcinoma and other types of cancer. Epidermal growth factor receptor (EGFR) inhibitors (afatinib, erlotinib, gefitinib and osimertinib) and immuno-oncology drugs (atezolizumab, nivolumab and pembrolizumab) are representative targeted therapeutics approved for the treatment of NSCLC patients (14-16). Because recurrence and adverse effects are unavoidable even when cutting-edge targeted therapies are administered, the use of a combination of different categories of drugs is a rational strategy to enhance the benefits and reduce the drawbacks of targeted therapy.

Epigenetic regulation of transcription and phenotypes involves chromatin-dependent mechanisms, such as methylation of genomic DNA and post-translational modification of histones (1-3). Because chromatin consists of genomic DNA wrapped around histone octamers, closed and open chromatin states are fine-tuned via DNA methylation and histone modification. In closed chromatin or heterochromatin, transcription factors cannot access genomic DNA; such chromatin is found in transcriptionally repressed regions, which are characterized by methylation of histone H3 lysine 9 (H3K9) and hypermethylation of genomic DNA. In contrast, in open chromatin or euchromatin, transcription factors cannot access genomic DNA; such chromatin is found in transcriptionally active regions, which are characterized by tri-methylation of H3K4 and H3K36 and hypomethylation of genomic DNA. CpG hypermethylation in the promoter regions of tumor suppressor genes induces the silencing of these genes, whereas genetic alterations in various epigenetic regulators, such as ASXL1, ASXL2, BAPI, DNMT3A, EZH2, IDH1, IDH2, MLL1, MLL3, NDS1, NDS2, NDS3, SMARCA4 and
**Figure 1** Multi-stage carcinogenesis, genomics testing and targeted cancer therapy. Genetic predisposition (germline alterations), chronic infection and life style, such as alcohol drinking and tobacco smoking, are involved in progression to pre-malignant stages of carcinogenesis, whereas epigenetic dysregulation, genetic alterations (germline and somatic) and immune evasion are involved in progression to more advanced stages of carcinogenesis. Chemotherapy, radiotherapy and surgical operation are conventional cancer therapies. By contrast, epigenetic drugs, immuno-oncology drugs and receptor tyrosine kinase (RTK) inhibitors or anti-RTK monoclonal antibodies (mAbs) have emerged as promising targeted cancer therapies. Cancer gene panels detecting alterations in approximately 300 common cancer-related genes and whole genome sequencing comprehensively detecting alterations in common and rare cancer-related genes are next-generation sequencing (NGS)-based genomics testing. Genomics testing is necessary to select patients and time points for targeted therapy.

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*TET2*, are involved in human carcinogenesis (1,2,17-23). Epigenetic dysregulation plays a pivotal role in human carcinogenesis. Bromodomain and extra-terminal (BET) inhibitors, DNA methyltransferase (DNMT) inhibitors, histone deacetylase (HDAC) inhibitors, histone lysine demethylase (KDM) inhibitors and histone lysine methyltransferase (KMT) inhibitors have been developed as drugs that target epigenetic regulators (1-3).

Immuno-oncology therapeutics are generally classified into inhibitors of immunosuppressive ligands or receptors (immune checkpoint blockers) and activators of immunostimulatory receptors (immunostimulatory agents) (4-6). CTLA4 (CD152), LAG3 (CD223), PD-1 (CD279/PDCD1), TIGIT and TIM3 (CD366/HAVCR2) are representative immunosuppressive receptors, whereas ICOS, TNFRSF4 (CD134/OX40), TNFRSF9 (CD137/4-1BB) and TNFRSF18 (CD357/GITR) are representative immunostimulatory receptors.
Immunogenomic analyses have revealed that CTLA4, LAG3 and PD-1 are major immunosuppressive receptors in various types of human cancers and that TIGIT and TIM3 are additional immunosuppressive receptors that function in a tumor type-dependent manner (24). PD-1 ligand 1 (PD-L1/CD274) on cancer cells, macrophages, myeloid-derived suppressor cells and stromal cells in the tumor microenvironment interacts with PD-1 receptor on T cells to induce immune evasion via the inhibition of PI3K-AKT, RAS-MAPK and calcineurin-NFAT signaling. Blockade of this immunosuppressive signaling using monoclonal antibodies (mAbs) against PD-L1 or PD-1 induces the activation, differentiation and/or proliferation of tumor-infiltrating T cells via de-repression of the PI3K-AKT, RAS-MAPK and calcineurin-NFAT signaling cascades. Anti-PD-L1 mAbs (atezolizumab, avelumab and durvalumab), anti-PD-1 mAbs (nivolumab and pembrolizumab) and an anti-CTLA4 mAb (ipilimumab) are immune checkpoint blockers that have been approved for the treatment of cancer patients, whereas other immunomodulatory therapeutics that target 4-1BB, GITR, ICOS, LAG3, OX40, TIGIT and/or TIM3 are being accessed in clinical trials or preclinical research (4-6).

Durable partial or complete responses to immune checkpoint blockers, including pembrolizumab and nivolumab, have been observed in approximately 20% of NSCLC patients and 31-44% of melanoma patients (25); however, immune checkpoint blockade therapies have been associated with adverse events, including pneumonia in 4.7% (43/915) of cancer patients (26) and anecdotal rapid progression of cancer or hyperprogressive disease in 9.2% (12/131) of cancer patients (27). Expression of PD-L1 ligand (28) and/or clonal neoantigen on tumor cells (29) and mismatch repair (MMR) deficiency (30) have been reported as biomarkers associated with preferable response to immune checkpoint blockers, whereas higher tumor burden (31), loss of neoantigen expression on tumor cells (32), escape mutations in the interferon signaling cascade in tumor cells (33) and upregulation of alternative immunosuppressive receptors on T cells (34) are biomarkers associated with poor response to immune checkpoint blockers. Comprehensive genotype-immunophenotype analyses should be performed in companion studies of clinical trials to generalize the mechanisms of durable response to, resistance against or severe adverse effects of immuno-oncology therapy in various types of human cancers. Further fine-tuning of the benefit-risk balances of immuno-oncology drugs is necessary for the application of these drugs as part of a precision oncology platform.

Recently, Topper et al. reported preclinical research on combination epigenetic therapy for NSCLC that evaluated (I) synergistic effects of a DNMT inhibitor (azacitidine) and an HDAC inhibitor (ITF-2357, MGCD-0103 or MS-275), especially the combination of azacitidine and ITF-2357, on cells from a panel of NSCLC cell lines and (II) epigenetic therapy-induced MYC downregulation, interferon signaling activation and CCL5, HLA-A and HLA-B upregulation in tumor cells, as well as downregulation of PD-1 and CTLA4 and upregulation of CCR7 in CD8+ tumor-infiltrating lymphocytes, in mouse models of lung cancer (35). Topper et al. postulated that depletion of the oncoprotein MYC and removal of immune evasion might explain the mechanisms by which epigenetic therapy involving DNMT and HDAC inhibitors produces anti-tumor effects. In contrast, Zheng et al. screened 97 approved oncology drugs and found that only the HDAC inhibitor romidepsin induces upregulation of the chemokines CCL5, CXCL9 and CXCL10 with T cell-attracting potential in mouse and human lung cancer cell lines (36). Zheng et al. demonstrated synergistic anti-tumor effects of romidepsin and anti-PD-1 mAb in mouse lung cancer models, and proposed upregulation of T cell-attracting chemokines and interferon-γ as mechanisms underlying the synergistic effects of the HDAC inhibitor and immune checkpoint blocker. These two reports clarified cross-talk between epigenetic dysregulation and immune evasion during lung cancer progression and emphasized a rational strategy involving the use of a combination of epigenetic drugs and immuno-oncology drugs for cancer therapy.

Immune checkpoint blockers can be combined with epigenetic therapeutics and other therapeutics (Figure 2), including alternative immune checkpoint blockers, cancer vaccines, conventional chemotherapy, immunostimulatory agents, macrophage inhibitors, metabolic modulators, natural killer cell inhibitors, radiotherapy, receptor tyrosine kinase inhibitors and regulatory T (Treg) cell inhibitors (6). For example, the following combination epigenetic immuno-oncology therapies are in clinical trials for cancer patients: an anti-PD-L1 mAb (atezolizumab) and a DNMT inhibitor (azacitidine) [ClinicalTrials.gov identifier: NCT02508870]; an anti-PD-L1 mAb (atezolizumab) and a DNMT inhibitor (guadecitabine) [ClinicalTrials.gov identifier: NCT0179943]; an anti-PD-1 mAb (pembrolizumab) and a DNMT inhibitor (CC-486) [ClinicalTrials.gov identifier: NCT02546986]; an anti-PD-1 mAb (pembrolizumab) and an HDAC inhibitor (entinostat)
Upregulation of MYC and downregulation of CCL5, CXCL9, CXCL10, HLA-A and/or HLA-B in pretreatment tumor samples might be predictive biomarkers of response to combination epigenetic immuno-oncology therapies, because DNMT and HDAC inhibitors synergistically revert immune evasion via MYC repression and reciprocal de-repression of CCL5, HLA-A and HLA-B (35) and
HDAC inhibitors exert anti-tumor effects via de-repression of the chemokine CCL5, CXCL9 and CXCL10 (36). MYC is transcriptionally upregulated via genetic alterations in MYC, including gene rearrangement, gene amplification and focal amplification of the super-enhancer region (37), and activation of the WNT, Notch and other signaling pathways; it is post-translationally stabilized via PI3K-AKT and RAS-MAPK signaling activation (38). MYC activates its target genes to regulate a variety of cellular processes, such as proliferation, metabolism, survival and apoptosis, in a context-dependent manner (38,39). Taken together, these facts suggest that certain tumors with constitutive MYC overexpression might be resistant to epigenetic therapy-induced MYC repression and that epigenetic therapy-induced MYC repression might not always lead to upregulation of CCL5, HLA-A or HLA-B in tumor cells and the subsequent correction of immune evasion. Whole-genome sequencing and transcriptome analyses of tumor cells and immuno-phenotype analyses of the tumor microenvironment are necessary to precisely predict responders to epigenetic immuno-oncology therapies.

In conclusion, clinical trials and companion studies to develop the most effective combination immuno-oncology therapy and identify biomarkers that predict therapeutic benefits and risks of adverse effects are necessary to optimize the benefit-risk balance of precision medicine for cancer patients in the future.

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Footnote
Conflicts of Interest: The author has no conflicts of interest to declare.

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