Positive Attributes of Anti-TERT CD4 T-Helper Type 1 Immune Responses in Melanoma

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Nardin et al’s (2021) study on melanoma reports anti-TERT CD4 T helper type (Th) 1 responses in more than half of patients. Besides indicating a trend for improved survival, increased anti-TERT CD4 Th1 responses predicted better outcomes for patients treated with immune checkpoint inhibitors. Thus, harnessing systemic anti-TERT CD4 Th1 responses together with tumor-specific elevation of telomerase can potentially open new avenues for biomarkers and treatment in melanoma.

In a new article of the Journal of Investigative Dermatology, Nardin et al., 2021 report the prevalence and clinical significance of systemic CD4 T helper type (Th) 1 responses against telomerase reverse transcriptase subunit (TERT) peptides in patients with melanoma. In a prospective study based on 156 patients with melanoma, anti-TERT CD4 Th1 immune responses were observed in more than half of patients, a proportion higher than reported earlier for other cancers. Furthermore, patients with thinner melanomas and American Joint Committee on Cancer (AJCC) stage I showed positive anti-TERT CD4 Th1 responses more frequently than patients with thicker and AJCC stage II melanomas. In line with its role as a mediator of immune evasion, patients with BRAF V600 mutation had lower anti-TERT CD4 Th1 responses than those with wild-type BRAF. Consistent with observations in other cancers, anti-TERT CD4 Th1 responses at baseline were associated with a trend for better survival, particularly in stage III and stage IV patients.

Harnessing systemic anti-TERT CD4 Th1 responses in conjunction with tumor-specific elevation of TERT can potentially open new avenues for biomarkers and treatment in melanoma.

In perhaps the most exciting observation, in the cohort of patients treated with anti-PD1 and anti-CTLA4 immune checkpoint inhibitors, anti-TERT CD4 Th1 responses before the onset of treatment were more frequent in responders than in nonresponders. The presence of anti-TERT CD4 Th1 responses in that subgroup that benefited was associated with better progression-free survival as well as overall survival (Nardin et al., 2021).

TERT, in conjunction with an RNA component (TERC), constitutes the telomerase holoenzyme that maintains telomeric repeats at chromosomal ends to impart unlimited replicative potential to tumor cells (Rachakonda et al., 2021). Stabilization of critically short telomeres through telomerase upregulation allows tumors to escape replicative senescence and continue cell division through the stages of cancer progression. Telomerase is crucial for the self-renewal of stem and progenitor cells. Its deficiency leads to bone marrow failure and other debilitating disorders in the setting of congenital mutations in the genes encoding the holoenzyme components and their associated proteins (Rachakonda et al., 2021). Although TERT is repressed in most somatic tissues, this rate-limiting telomerase component is overexpressed in over 90% of human cancers, and it is critical to immortalizing human cells. Ectopic expression of TERT, together with simian virus 40 large T antigen and RAS oncoproteins, reportedly leads to tumorigenic transformation of human cells (Hahn et al., 1999). An overarching presence of TERT selectively in cancer cells has prompted both conventional and immune-targeted therapeutic considerations with less than optimal success.

Because of its ubiquitous expression in tumors, TERT has been probed for its antigenicity and immunogenicity (Zanetti, 2017). Early on, evidence showed that TERT is immunogenic and could expand cytotoxic CD8 T cells in the peripheral blood of patients with cancer. Short peptides derived from TERT bound to major histocompatibility complex (MHC) class I molecules constitute targets for antigen-induced CD8 cytotoxic T lymphocytes. In vitro, TERT protein has been shown to be immunogenic for peripheral T lymphocytes harvested from healthy individuals and patients with cancer, suggesting that TERT-reactive T-cell precursors are present in blood. CD4 T cells are also important in generating antitumor immune responses through multiple mechanisms, and they can eliminate tumor cells either directly or by altering the tumor microenvironment. Tumor-reactive CD4 T cells ensure efficient effector cytotoxic T lymphocyte recruitment at the tumor site. Antitumor protection by CD4 Th1 cells is facilitated by the
production of cytokines (Dosset et al., 2020). TERT-derived peptides that bind to multiple MHC class II alleles are produced endogenously in cancer cells, expanding the role of TERT antigen within the context of tumor immunity. The identification of MHC II–binding TERT peptides led to the role of systemic CD4 T cells in lung cancer, where detection of functional anti-TERT CD4 Th1 cells in blood at baseline proved to predict clinical response to chemotherapy (Godet et al., 2012). In addition, using TERT-derived universal cancer peptides, several groups identified CD4 Th1 responses in several cancers, including melanoma, leukemia, renal cell carcinoma, and lung, colon, and liver cancers (Laheurte et al., 2016).

Several factors confound the complex interaction between the immune system and cancer, leading to variable responses in patients treated with immune checkpoint targeting agents. Whereas some patients exhibit durable clinical responses, others do not respond or develop resistance over time. For example, mAbs that target the PD1–PDL1 pathway have shown objective responses in 31–44% of patients with melanoma and in a lesser proportion in non–small cell lung cancer and renal cell cancer. Similarly, the antibody that blocks CTLA4 showed a response rate of about 11% and prolonged overall survival in about 22% of patients with melanoma (Topalian et al., 2016). Thus, identification of additional reliable biological markers that can predict responses and outcomes of immune checkpoint inhibitor treatments in melanoma and other cancers remains an important goal. The findings by Nardin et al., 2021 that responders had more frequent anti-TERT CD4 Th1 responses and fared better with respect to survival adds to the list of durable immune-specific biomarkers for predicting immune checkpoint treatment outcomes. As hypothesized, increased anti-TERT CD4 Th1 responses may reflect enhanced patient immune responsiveness, which is in line with previous findings in melanoma, including the predictive value of vitiligo, a disease with a predisposing genetic background to autoimmune processes (Nardin et al., 2021).

However, the potential of anti-TERT CD4 Th1 responses in cancers remains incompletely understood and elucidated in melanoma-specific telomerase regeneration. Although telomerase reactivation in tumors occurs through several mechanisms, in melanoma and other cancers arising from tissues with low rates of self-renewal, TERT is upregulated through somatic acquisition of mutations within the promoter of the gene encoding the reverse transcriptase subunit. The TERT promoter mutations that are now the most frequent noncoding mutations in human cancers create de novo binding sites for ETS transcription factors, resulting in massive epigenetic changes on the mutant allele, leading to monosomic TERT expression (Figure 1). Somatic TERT promoter mutations have emerged as markers of poor outcome, defining patients with reduced survival in several cancers and linking transcription of TERT with oncogenic pathways. TERT promoter mutations in thyroid and colon cancer and melanoma cell lines over the background of activated BRAF trigger strong apoptosis-induced cell death on treatment with MAPK inhibitors that abolish the growth of tumors in vivo (Rachakonda et al., 2021).

Tumors with TERT promoter mutations are invariably associated with statistically significant increased transcription of the telomerase reverse transcriptase subunit and higher levels of TERT protein (Rachakonda et al., 2021). It has been argued that increased TERT would generate more peptides, making tumor cells preferentially susceptible to T-cell killing (Zanetti, 2017). That should also logically lead to elevated anti-TERT CD4 Th1 responses. Although the increased frequency of TERT promoter mutations in melanoma was previously shown to be associated with increased Breslow thickness and tumor stage, in their study, Nardin et al., 2021 observed an inverse association between the frequency of anti-TERT CD4 Th1 responses and Breslow thickness, tumor stages, and BRAF mutations (Rachakonda et al., 2021). However, higher anti-TERT CD4 Th1 responses align with improved prognosis with an increased presence of brisk tumor-infiltrating lymphocytes in thinner tumors (Thomas et al., 2013). The question of whether the TERT promoter mutations exert immune suppression remains to be settled. On one hand, TERT promoter mutations occur more frequently over the background of oncogenic BRAF or NRAS mutations, and the hypothesized immune suppression could possibly be due to mutated BRAF. However, it has also been documented that cell lines with TERT promoter mutations exhibit gene expression characteristics dominated by epithelial to mesenchymal transitions and MAPK activation signaling, generating distinct tumor environments and intercellular interactions (Stern et al., 2020).
The observation of elevated anti-TERT CD4 Th1 response frequencies in patients with melanoma opens up a range of options in terms of biomarkers for immune checkpoint inhibitors. The critical role of CD4 Th1 cells in antitumor immunity already argues for a new impetus for cancer vaccines with enhanced effectiveness by modulating tumor environments. Many TERT-derived peptide vaccines have already been the subject of clinical studies in several cancers with durable T-cell memory responses and increased survival in immune responders but without improvement in overall survival (Zanetti, 2017). However, utilizing such vaccines in conjunction with elevated basal anti-TERT CD4 Th1 responses and TERT promoter mutations requires additional exploration that could be crucial to identifying patients with melanoma who could potentially benefit from such treatments in a personalized approach. In addition, the approach has the possibility of broader application to include cancers with high frequencies of TERT promoter mutations together with immune checkpoint inhibitors to suppress negative immune regulation.

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**CONFLICT OF INTEREST**
The authors state no conflict of interest.

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