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Editorial

A Novel Role for Tazarotene-induced Gene 1 in Suppressing Melanoma Growth — Schlafen 11

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Retinoic acid is the active metabolite of vitamin A. It binds to the retinoic acid receptor (RAR) and retinoid X receptor (RXR) to regulate the expression of downstream genes, thereby influencing cell proliferation, differentiation, and apoptosis. Although retinoic acid is effective in preventing the development of melanoma, its high affinity for both RAR and RXR results in a lack of specificity. Consequently, patients who take retinoic acid may experience severe side effects, such as liver damage, teratogenic effects, or neurological issues, making it unsuitable for widespread use. Tazarotene is a third-generation synthetic retinoid that primarily targets RAR-β and RAR-γ subtypes and is mainly used as a topical medication in clinical practice. In sporadic case studies, treatment with a 0.1% tazarotene gel for 6 to 8 months in patients with melanoma *in situ* resulted in disease remission without observed recurrence [1]. In a randomized controlled trial evaluating the treatment of melanoma *in situ* using either imiquimod alone or imiquimod combined with 0.1% tazarotene gel, the response rate for patients treated with imiquimod alone was 64% (27 of 42 patients achieved remission), while the response rate for those receiving combination therapy was 78% (29 of 37 patients achieved remission) [2]. Additionally, patients in the combination therapy group showed a significant increase in systemic inflammation markers compared to those treated with imiquimod alone (mean 2.3 vs. 1.8). This indicates that tazarotene enhances immune responses in patients, potentially boosting the immune system's ability to target and eliminate tumor cells [2]. To date, 87 clinical trials investigating the use of imiquimod for treating melanoma *in situ* have collectively analyzed 1133 cases, with some studies also incorporating the combination of imiquimod and 0.1% tazarotene gel. The rates of histological clearance and clinical clearance were 56.9% and 43.2%, respectively. However, due to variations in study methodologies (such as differences in drug administration timing), statistical analysis to determine the efficacy of imiquimod and whether tazarotene provides an additive effect remains inconclusive [3].

After binding to RAR-β/γ, tazarotene not only acts as an AP1 and type I interferons (IFNs) antagonist but also induces the expression of three distinct genes: tazarotene-induced gene 1–3 (*TIG1–TIG3*). Among these, *TIG1* and *TIG3* are considered the most important retinoic acid-regulated genes involved in the modulation of cancer cell growth. TIG1 was initially isolated from skin tissues treated with retinoic acid derivatives. Amino acid sequence analysis identified TIG1 as a transmembrane protein, with its C-terminal amino acid structure resembling latexin. Latexin is the only carboxypeptidase inhibitor found in mammals. *TIG1* is highly expressed in well-differentiated prostate and colorectal tissues but has low or no expression in various cancers, including hepatocellular carcinoma, prostate cancer, head and neck cancer, nasopharyngeal carcinoma, gastric cancer, and colorectal cancer, suggesting that *TIG1* may function as a tumor suppressor gene. A recent study by Meng Liu *et al.* [4] identified *TIG1* as a promising biomarker for melanoma. In melanoma, genetic mutations in *TIG1* may lead to the production of dysfunctional or inactive proteins, while methylation of the *TIG1* promoter may result in the silencing of TIG1 expression, ultimately leading to reduced TIG1 protein levels in melanoma cells. When TIG1 is expressed in melanoma cells, it exhibits multiple tumor-suppressive effects, including: promoting immune cell infiltration, particularly macrophages and T cells (especially type 1 T helper cells); downregulating cyclin D1 and cyclin E, thereby inhibiting cell cycle progression; upregulating p53, B-cell lymphoma 2-associated X protein (Bax), and Bcl-2 homologous antagonist/killer (Bak), leading to cell apoptosis and inducing light chain 3 II and p62 expression, triggering autophagy [4]. The authors proposed that TIG1 induces apoptosis, cell cycle arrest, and autophagy by upregulating intracellular reactive oxygen species (ROS) levels. Additionally, in our recent study, we identified 101 genes with significant transcriptional changes in melanoma cells expressing TIG1. Among them, two genes exhibited particularly distinct changes ($\log_2$ fold change >5): *TIG1* itself and Schlafen 11 (*SLFN11*) [5]. Beyond gene expression, we

also observed that when A2058 melanoma cells express *TIG1*, they also induce SLFN11 protein expression (data not shown). Schlafen family gene expression is regulated by type I IFNs and downstream JAK kinase signaling pathways [6]. Meng Liu *et al.* [4] reported that *TIG1* enhances Th1 cell-mediated immune responses. Collectively, these findings suggest that *TIG1*-driven SLFN11 upregulation may be linked to its role in interferon activation.

The putative DNA/RNA helicase SLFN11 exhibits a causal relationship with the ability of cancer cells to respond to DNA-damaging agents. SLFN11 is widely expressed in colon cancer, ovarian adenocarcinoma, sarcoma, small cell lung cancer, and breast cancer, making it a potential biomarker for predicting the response to DNA-damaging agents in clinical trials. SLFN11 detects stressed replication and induces irreversible replication blockage during unplanned DNA re-replication or replication stress, thus serving as a crucial regulator of the cellular response to DNA damage. Recent research by Boon and colleagues indicates that when cellular DNA is damaged under conditions of extreme stress, the *SLFN11* gene shuts down the protein synthesis machinery in the ribosomes, allowing cells to bypass the p53 pathway and undergo cell death [7]. Additionally, retinoic acid synergizes with the DNA alkylating agent dacarbazine to promote apoptosis in melanoma cells [8]. This suggests that retinoic acid may alter the cellular stress environment or enhance the effects of therapeutic agents under stress conditions, thereby increasing DNA alkylating agent efficacy. When SLFN11 detects single-stranded DNA within the cell, it not only directly regulates cell growth by triggering related responses but also activates innate immune responses through its RNase activity [9]. SLFN11 also enhances the cytotoxic effects of immune cells on cancer cells by increasing type I IFN and IFN-γ signaling [10]. Furthermore, SLFN11 expression is associated with immune activation in the tumor microenvironment of various cancers [11]. In hepatocellular carcinoma (HCC), SLFN11 expression is linked to the effectiveness of immune checkpoint inhibitors (ICIs). It is upregulated in ICI-responsive tumors, while tumors lacking SLFN11 show increased immunosuppressive macrophage infiltration and faster progression. The absence of *SLFN11* activates the Notch pathway, promoting chemokine (C-C motif) ligand 2 (CCL2) production, macrophage migration, and M2 polarization, which enhances PD-L1 expression through NF-κB activation. Blocking CCL2 signaling and M2 polarization can improve anti-PD-1 therapy efficacy in *SLFN11*-deficient tumors [12]. Furthermore, SLFN11 expression correlates with immune cell infiltration and immune checkpoint expression, making it a potential biomarker for monitoring immune therapy responses [13].

In the study by Liu *et al.* [4], the effects of TIG1 expression on melanoma cells could be explained by the upregulation of ROS, but this does not account for the chemotactic effects on various immune cells within tissues. Additionally, patients with melanoma *in situ* treated with imiquimod combined with 0.1% tazarotene exhibited a higher inflammatory response in tissues compared to those treated with imiquimod alone [2]. Tazarotene induces another important tumor suppressor gene, TIG3, which also has the potential to promote cell differentiation and inhibit cancer cell growth. However, there are no reports indicating that TIG3 expression in cells promotes immune cell chemotaxis. These findings suggest that the increased inflammatory response in patient tissues following tazarotene treatment may be related to TIG1 expression. The infiltration of T cells and macrophages in cells expressing TIG1 may be associated with TIG1-induced SLFN11 expression.

Although the mutation rate of p53 in melanoma cells is relatively low (ranging from 10–19%), its activity is often compromised due to various interfering factors [14]. When p53 is inactivated, TIG1-induced SLFN11 expression offers an alternative pathway to inhibit cancer cell growth, providing a target for drug development. However, during the progression of some melanomas, the expression level of retinoic receptors decreases [15]. The loss of RAR expression leads to the ineffectiveness of tazarotene in activating downstream genes, including *TIG1*. Therefore, RAR expression in melanoma tissues may serve as a useful biomarker for predicting the effectiveness of tazarotene treatment.

Abbreviations

RAR, retinoic acid receptor; RXR, retinoid X receptor; IFNs, interferons; *TIG1*, tazarotene-induced gene 1; *TIG3*, tazarotene-induced gene 3; Bax, B-cell lymphoma 2-associated X protein; Bak, Bcl-2 homologous antagonist/killer; ROS, reactive oxygen species; SLFN11, schlafen family member 11; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; CCL2, chemokine (C-C motif) ligand 2.

Author Contributions

Conceptualization, FMT, CHW and LKW; Original draft, CHW, LKW, and FMT; Review & editing, References curation, FMT. All authors contributed to editorial changes in the manuscript. All authors reviewed the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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