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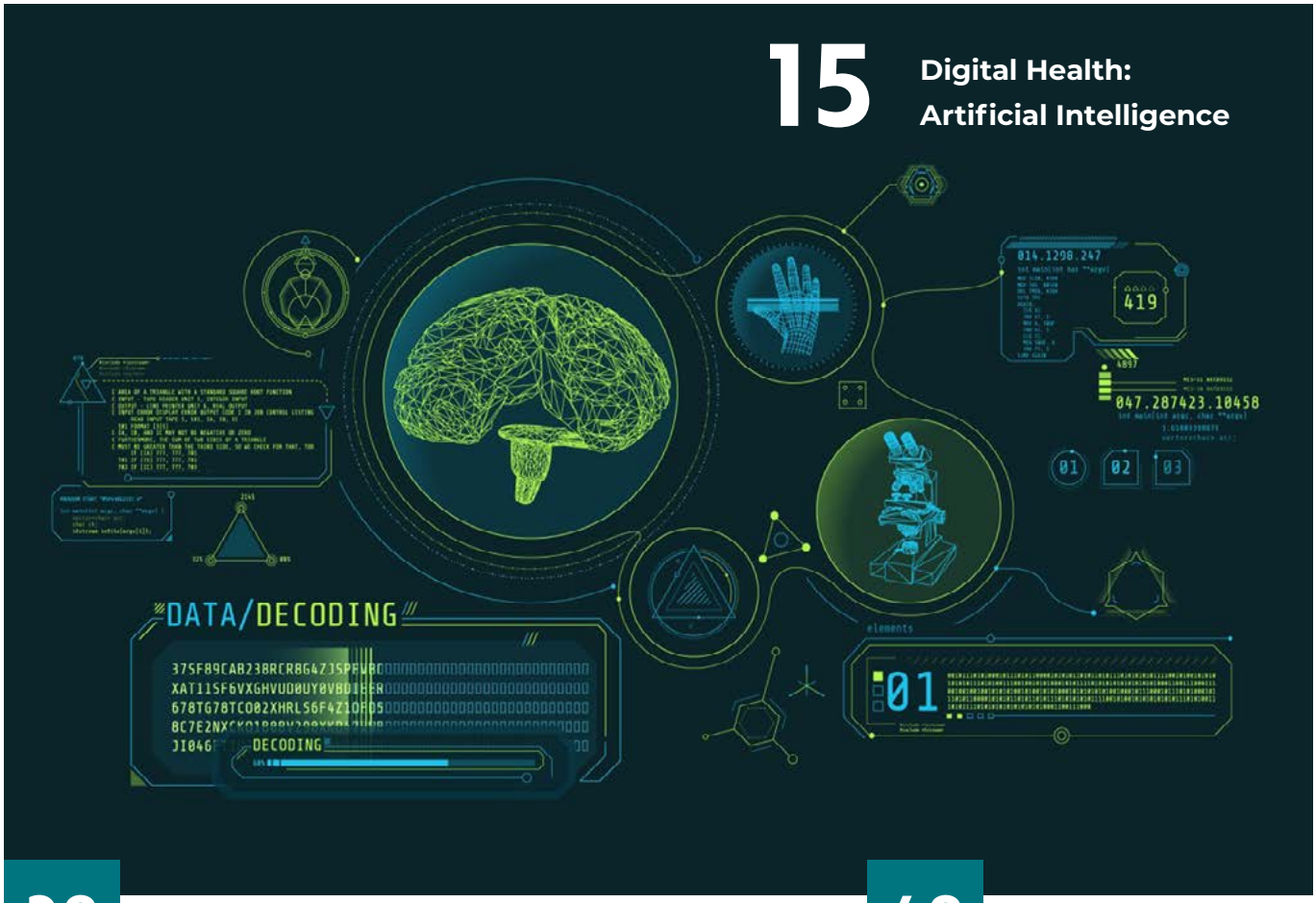

Société Suisse de Dermatologie et Vénéréologie
Società Svizzera di Dermatologia e Venereologia
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WHAT'S NEW

Adrogen Receptor Signaling: a Critical Factor of BRAFi/MEKi Resistance in Cutaneous Melanoma

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The present work was performed by Dr. Anastasia Samarkina and colleagues, including SKINTEGRITY.CH Principal Investigators Profs. Gian Paolo Dotto and Mitchell Levesque.

Maarten Schledorn
Scientific coordinator SKINTEGRITY.CH

Anastasia Samarkina. *Melanoma, arising from pigment-producing melanocytes, represents the most aggressive form of skin cancer. Roughly 50 % of cutaneous melanoma cases stem from activating BRAFV600 mutations, which fundamentally control melanoma growth, survival, and differentiation potential. Specific BRAF/MEK inhibitors (BRAFi/MEKi) rapidly regress patient tumors. However, nearly all patients experience relapse within two years, often developing resistance not only to these inhibitors but also to immunotherapies. This underscores the urgent need to devise strategies to prevent and overcome resistance.*

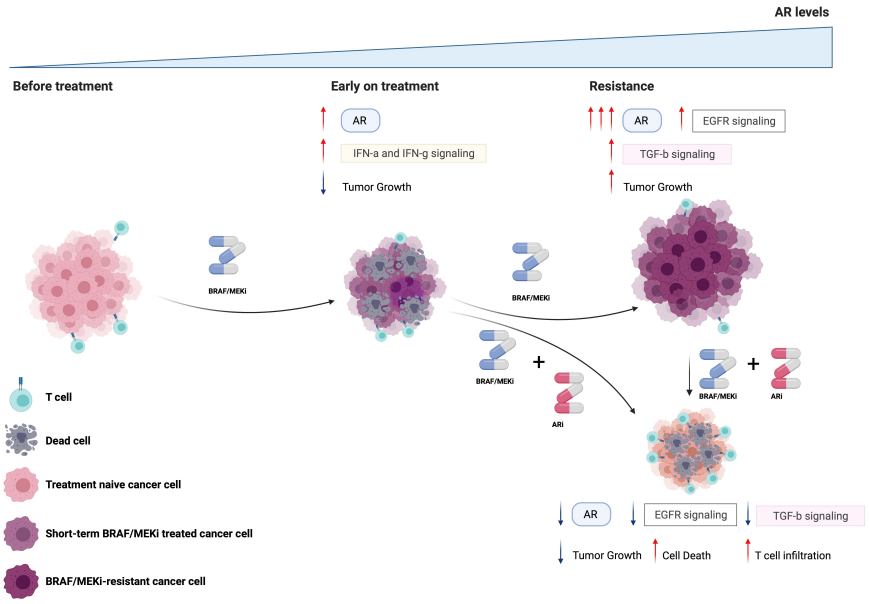
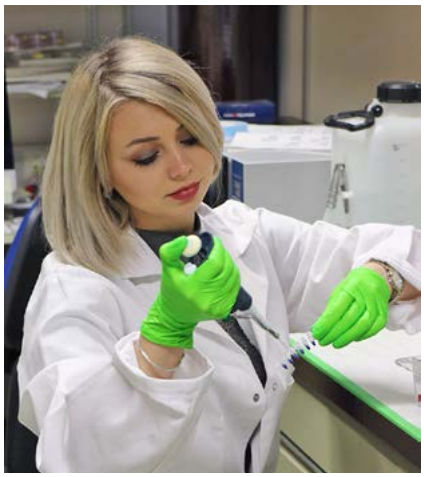


Figure 1: Graphical abstract of the study. Treatment of melanoma cells with BRAFi/MEKi increases AR expression. Early on BRAFi treatment (48h), AR levels increase accompanied by heightened inflammatory (IFN-α and IFN-γ) signaling pathways and reduced cell proliferation. In BRAFi/MEKi-resistant melanoma cells, AR levels peak, fueling resistance via increased EGFR and TGF-β signaling. Pharmacological inhibition of AR with receptor antagonists (ARi) reduces the expression of EGFR and TGF-β signaling genes, impedes BRAFi-resistant cell growth, triggers cell death, and increases intratumoral T cell infiltration. Created using BioRender.com (2020).

A recent study by Samarkina *et al.* explores the complex interplay between androgen receptor (AR) signaling and the response to BRAFi/MEKi-targeted therapy in cutaneous melanoma. Our study reveals that elevated AR signaling promotes BRAFi/MEKi resistance in cutaneous melanoma via an adaptive mechanism. The study finds that AR levels rise rapidly during BRAFi/MEKi treatment and remain elevated in BRAFi-resistant cells. As AR levels increase during BRAFi treatment, distinct gene sets are modulated. During the first 48h of BRAFi treatment, we observe the upregulation of canonical AR signaling in drug-naïve melanoma cells, along with heightened inflammatory and apoptotic pathways. Under chronic BRAFi treatment, elevated AR signaling drives the induction of drug resistance via EGFR and TGF-β signaling axes. These pathways are clinically relevant as they have been shown to contribute to the emergence of therapy resistance in multiple clinical and preclinical settings. Our analysis further extends to these multiple studies, consistently associating AR activity with EGFR and TGF-β signaling pathways in BRAFi-resistant melanoma cells, preclinical models of BRAFi/MEKi resistance, and patient cohorts. Importantly, we also find that AR overexpression alone is sufficient to render cells BRAFi resistant. AR-overexpressing cells overcome BRAFi-induced growth suppression and cell death while maintaining apoptosis, inflammatory, and antigen presentation transcriptional programs at low levels. These pathways are relevant as the induction of proinflammatory and cell death programs is necessary to activate the immune system and eradicate tumors. In line with this, our *in vivo* data reveal that pharmacological treatment with AR inhibitors of BRAFi-resistant melanomas inhibits tumor growth, increas-

es cell death, and boosts intratumoral CD8+ T cell levels. Similarly, AR inhibition suppresses the emergence of drug-tolerant melanoma cells, blunts the proliferation of BRAFi-resistant cells, induces cell death, and decreases the expression of resistance markers in melanoma cells in *in vitro* settings.

The AR is expressed in various cell types, and AR signaling has been implicated in tumorigenesis in various cancer types, including prostate, breast, bladder, and liver. Until recently, only a handful of studies have investigated the implications of AR signaling in melanoma. Our previous findings established an important role for basal AR signaling during melanoma cell proliferation, DNA repair, and tumorigenesis in both male and female melanomas. Genetically or pharmacologically inhibiting AR was shown to induce DNA damage and limit tumorigenesis of melanoma cells. These properties render the inhibition of AR signaling an attractive target for improved management of treatment-naïve melanoma. Our present work adds a new dimension to AR activity in human melanoma, demonstrating that AR signaling induces transcriptional changes in melanoma cells that drive targeted drug resistance. Our data are further strengthened by clinical and preclinical data showing an association between AR activity and BRAFi/MEKi resistance in both males and females. Since BRAFi/MEKi elevate AR expression in melanoma cells, promoting therapeutic resistance, suppressing AR through receptor antagonists emerges as a potential therapeutic strategy to combat drug resistance in cutaneous melanoma, regardless of sex.



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Reference

Samarkina A, Youssef MK, Ostano P, Ghosh S, Ma M, Tassone B, Proust T, Chiorino G, Levesque MP, Goruppi S & Dotto GP (2023). Androgen receptor is a determinant of melanoma targeted drug resistance. Nat Commun, 14(1), 6498. DOI 10.1038/s41467-023-42239-w