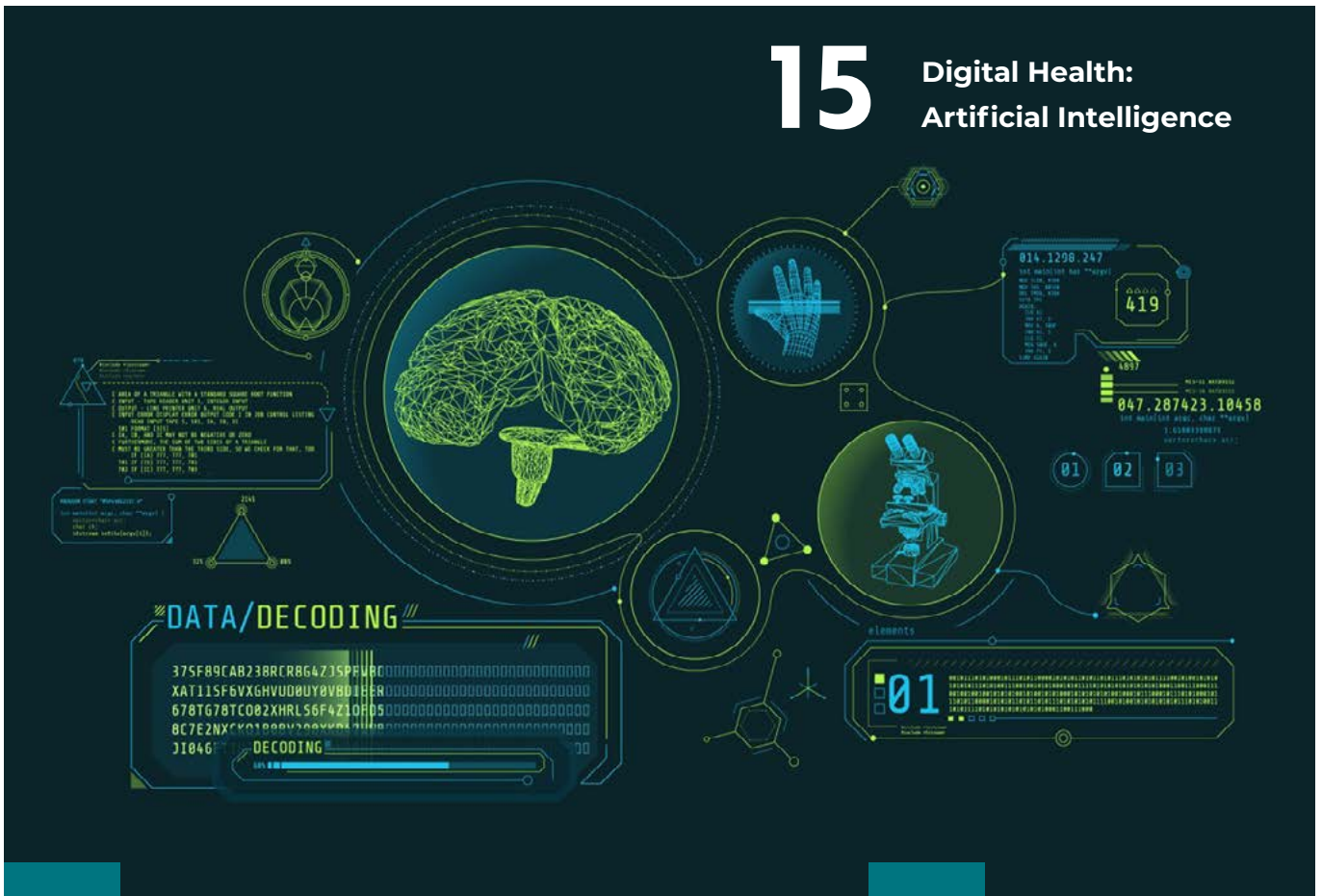


DERMATOLOGICA HELVETICA



15 Digital Health: Artificial Intelligence

28

SYD: Die Weiterbildung Facharzt
Dermatologie & Venerologie in der Schweiz
SYD: La formation continue de spécialiste
en dermatologie et vénéréologie en Suisse

48

Awards 2024
Awards 2024



Société Suisse de Dermatologie et Vénéréologie
Società Svizzera di Dermatologia e Venereologia
Swiss Society of Dermatology and Venereology
Schweizerische Gesellschaft für Dermatologie und Venerologie

WHAT'S NEW

Androgen 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.

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

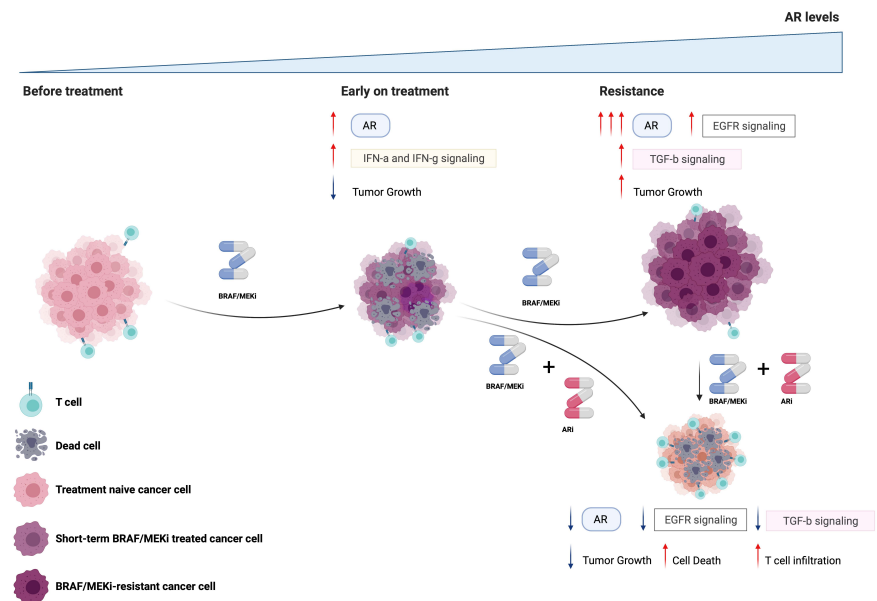


Figure 1: Graphical abstract of the study. Treatment of melanoma cells with BRAFi/MEKi increases AR expression. Early on BRAFi treatment (48h), AR levels increase accompanied by heightened inflammatory (IFN-α and IFN-γ) signaling pathways and reduced cell proliferation. In BRAFi/MEKi-resistant melanoma 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).

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 stud-

ies, 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 mel-

anoma. 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 expres-



sion 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.

Author

Anastasia Samarkina, PhD
 Past: PhD Candidate, Department of Immunobiology, University of Lausanne (UNIL), Lausanne, Switzerland
 Present: Postdoctoral Scholar, Department of Dermatology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco (UCSF), San Francisco, USA

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

GERÖTETE UND ENTZÜNDETE HAUT¹
 atopische Dermatitis¹
 allergische Hauterkrankungen¹
 AKUTE UND CHRONISCHE EKZEME¹
 Juckreiz¹
 60g Creme
 BioMed[®]
 Juckreizstillend, antiallergisch entzündungshemmend
 antipruriginöses, anti-allergisches anti-inflammatorisches
 Levomenolum
 Heparinum natricum
 WIRKT spürbar.^{1,2}
 KASSEN-ZULÄSSIG³

Bestellen Sie Ihren Derma Survival Guide und viele weitere hilfreiche Unterlagen.



Sensicutan[®]
 Levomenolum, Heparinum natricum

Bei entzündlichen, juckenden und allergischen Hauterkrankungen.¹

Sensicutan[®] Creme
 Z: Levomenol, Heparin-Natrium in einer O/W Emulsion. I: Entzündliche, nicht-infektiöse, stark juckende und allergische Hauterkrankungen z. B. akute und chronische Ekzeme, atopische Dermatitis. D: >3 J.: 2x tgl. auftragen. KI: Überempfindlichkeit auf einen der Inhaltsstoffe. VM: Nicht auf offene Verletzungen und Schleimhäute auftragen. IA: keine bekannt. S/S: Nach Rücksprache mit dem Arzt. UW: Sehr selten: Überempfindlichkeitsreaktionen der Haut, allergische bzw. pseudoallergische Reaktionen. P: Tube 80 g¹. Kat. D. Ausführliche Angaben siehe www.swissmedicinfo.ch. *kassenzulässig V02.0921

Referenzen: 1. Sensicutan[®]. www.swissmedicinfo.ch, abgerufen am 01.01.2023. 2. Arenberger P et al. Effect of topical heparin and levomenol on atopic dermatitis: a randomized four-arm, placebo-controlled, double-blind clinical study. *J EADV* 2011; 25(6): 688–694. 3. BAG Spezialitätenliste. www.spezialitaetenliste.ch, abgerufen am 01.01.2023. Die Referenzen sind auf Anfrage erhältlich.