RESEARCH HIGHLIGHT

An exploitable Achilles heel of MITF?

Carolina Silva[1,2] and Ze'ev A. Ronai[1]✉

© The Author(s) under exclusive licence to Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences 2022

Cell Research (2023) 33:195–196; https://doi.org/10.1038/s41422-022-00762-3

Microphthalmia-associated transcription factor (MITF) has been implicated in melanoma development and progression. In a study published in *Cell Research*, Liu et al. suggest that inhibition of MITF via targeting of its dimer interface may provide a novel therapeutic modality.

As the master regulator of melanoma biogenesis, microphthalmia-associated transcription factor (MITF) coordinates survival, differentiation, proliferation, invasion, senescence, metabolism, and DNA damage repair in both melanocytes and melanomas.[1] MITF is subject to tight regulation at the levels of translation, transcription, and post-translational modification, and its activity does not always correlate with protein expression levels. When active, MITF binds to specific DNA motifs resulting in the transcriptional activation of genes implicated in numerous cellular functions. The rheostat model of MITF activity, supported by independent studies, suggests that low activity is associated with proliferation, dedifferentiation, and invasion. In contrast, high activity is associated with differentiation and reduced proliferation.[1] Importantly, MITF activity depends on post-translational protein modifications that vary within tumors and between primary and metastatic melanomas. Thus, one needs to carefully identify melanomas that may be amenable for MITF targeting.

In this issue, Liu et al. report that MITF adopts a hyperdynamic structure that leaves it vulnerable to dimer disruption as means of therapeutic targeting.[2] Alignment of the MITF sequence with other E box-binding transcription factors identified a 3-amino acid (aa) insertion in the leucine zipper region within the basic helix-loop-helix leucine zipper domain that is required for MITF–DNA binding. The authors demonstrated that the 3-aa insertion increases the conformational dynamics of MITF dimer (Fig. 1). A high-throughput screening campaign led to the identification of the small molecule TT-012, which disrupted MITF dimerization and DNA-binding activity. This finding was confirmed using an AlphaScreen assay that was developed to monitor MITF dimerization. TT-012 was shown to preferentially inhibit tumor cells expressing high levels of MITF, as demonstrated in experiments with human and mouse melanoma (and non-melanoma) cell lines in culture and by in vivo inhibition of $MITF^{hi}$ B16F10 melanoma growth and metastasis.[2]

Can the targeting of MITF dynamic structure, as shown here by Liu et al., offer a novel therapeutic modality for melanoma? To answer this question, several additional assessments will be required. First, the utility of TT-012 should be demonstrated in a large cohort of human and mouse melanoma models harboring different genetic drivers (i.e., N-Ras or B-Raf mutations) in vivo. A plethora of melanoma cell lines of both human and mouse origin are currently available, and it will be important to establish the effectiveness of TT-012 in as diverse sets of human melanomas as possible. The availability of patient-derived xenografts, as exploited in the present study, also provides a valuable model to assess large cohorts of human melanomas harboring different phenotypes for in vivo effectiveness. Next, considering the increasing number of studies demonstrating a role for MITF in modulating the tumor microenvironment, including immune system components,[3] it is important to assess the effect of TT-012 in immunocompetent and immunocompromised mouse models, especially.

One of the key characteristics of melanoma is its plasticity, which allows it to adapt to harsh environmental growth conditions, establish resistance to therapy and exhibit a strong propensity to metastasize.[4,5] Would targeting MITF provide a long-sought solution to overcome these hurdles in melanoma treatment? For example, would TT-012 overcome the therapy resistance that has been associated with increased MITF expression and activity? Would co-administration of TT-012 with targeted or immune therapies prevent the emergence of resistance?

Similarly, several important questions pertain to MITF's role in skin pigmentation as in DNA damage response.[6] Would TT-012-mediated inhibition of MITF impact the early steps in melanomagenesis? The demonstration by Liu et al. that TT-012 limits B16F10 metastasis is consistent with the known involvement of MITF in melanoma invasion and metastasis.[7] However, extending this observation to other melanoma models may be challenging because most human melanomas do not metastasize in mouse models. Nevertheless, a comprehensive assessment of the efficacy of MITF dimer-disrupting compounds will likely be aided by the availability of an increasing number of metastatic mouse melanoma models.

The MITF rheostat model, including the upstream regulators and downstream effectors, has been the subject of intense studies.[1,8] Thus, transcriptional changes observed upon TT-012 treatment should represent known gene expression signatures, a readout that could further reflect on the state of melanomagenesis, in culture and in vivo.

Overall, the study by Liu et al. represents an important advance for the therapeutic targeting of melanomas. Considering the plasticity and variability of melanomas, this newly identified approach is likely to be clinically important, even if it is restricted to a select tumor cohort. The current study may also have important implications beyond MITF, given that genetic perturbations in key regulatory genes are a common occurrence in cancer.[9,10]

[1]Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA. [2]The University of São Paulo, São Paulo, Brazil. ✉email: zeev@ronailab.net

Published online: 23 December 2022

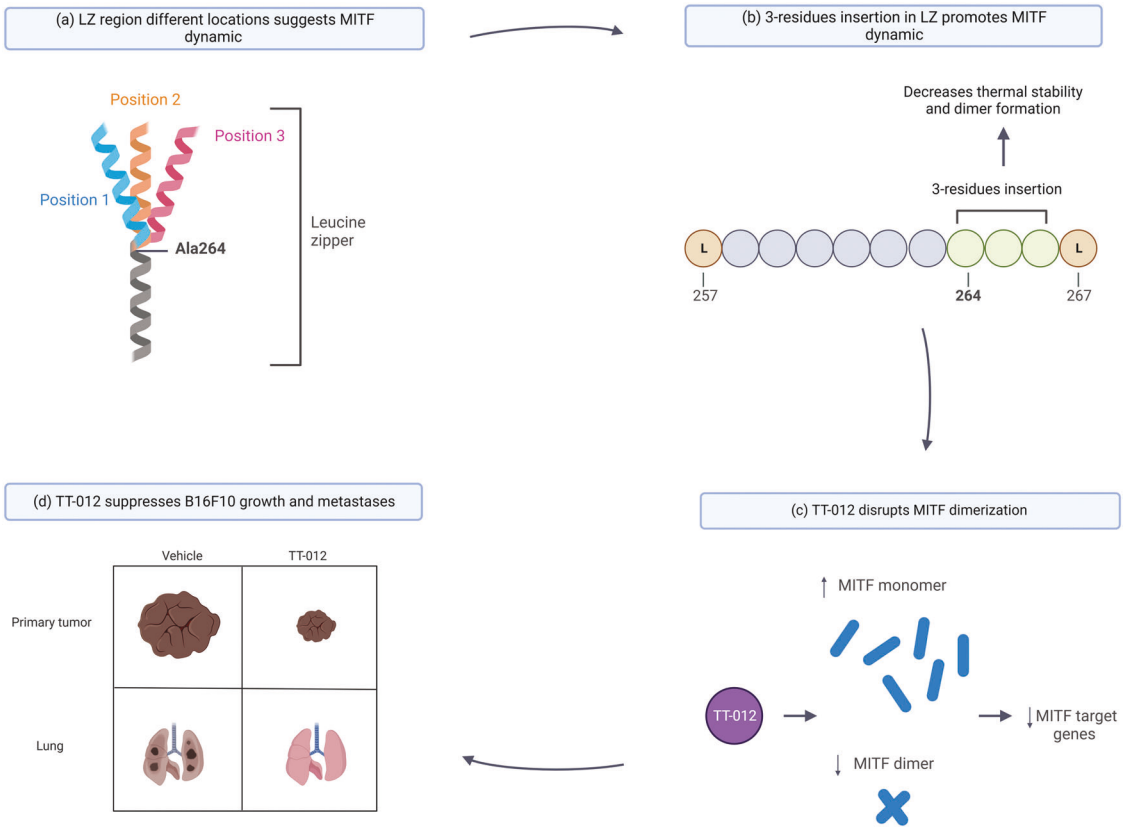

Fig. 1 The hyperdynamic interface of MITF represents a vulnerability to pharmacological dimer disruption. a–d Schematic representations of various aspects of MITF. The three locations (i.e., distinct conformations indicated in colored positions) are adjacent to Ala264 in the leucine zipper (LZ) (**a**). The 3-residue insertion in the LZ (**b**). TT-012-mediated disruption of MITF dimerization (**c**). TT-012 administration in vivo suppresses tumor growth and metastasis of B16F10, a MITF^{hi} melanoma cell line (**d**). Figure is created with BioRender.

REFERENCES

1. Goding, C. R. & Arnheiter, H. *Genes Dev.* **33**, 983–1007 (2019).
2. Liu, Z. et al. *Cell Res.* https://doi.org/10.1038/s41422-022-00744-5 (2023).
3. Ballotti, R., Cheli, Y. & Bertolotto, C. *Mol. Cancer* **19**, 170 (2020).
4. Falletta, P., Goding, C. R. & Vivas-García, Y. *Front. Cell Dev. Biol.* **10**, 3389 (2022).
5. Vivas-Garcia, Y. et al. *Mol. Cell* **77**, 120–137 (2020).
6. Nguyen, N. & Fisher, D. E. *Pigment Cell Melanoma Res.* **32**, 224–236 (2019).
7. Johannessen, C. M. et al. *Nature* **504**, 138–142 (2013).
8. Smith, M. P. et al. *Pigment Cell Melanoma Res.* **32**, 280–291 (2019).
9. Pich, O. et al. *Cancer Cell* **40**, 458–478 (2022).
10. Malapelle, U. et al. *Crit. Rev. Oncol. Hematol.* **169**, 103536 (2021).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ze'ev A. Ronai.

Reprints and permission information is available at http://www.nature.com/reprints