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RESEARCH HIGHLIGHT

Treating leukemia: differentiation therapy for mIDH2 AML

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While the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) in the treatment of acute promyelocytic leukemia (APL) has been a remarkably successful example for differentiation therapy of cancer, the recently developed therapeutics of mutant IDH2 (mIDH2)-associated leukemia by specific mIDH2 inhibitors is launching another promising campaign. Interestingly, a recent study in *Cell Research* by Mugoni et al. demonstrated a sensitivity of the mIDH2 leukemia to the APL-like ATRA/ATO combination therapy, narrating a convergence of two tales.

APL used to be the most dangerous leukemia, but it has become a curable disease in just a few decades. This historical transition was started by introducing ATRA into APL treatment in 1985, and further effected by the use of ATO in 1990s.[1] While both ATRA and ATO as single agents had been very effective in inducing high complete remission rates, a combination of ATRA and ATO achieved much better results[1] (Fig. 1a). Mechanistically, ATRA binds to the RARα portion of the leukemogenic PML-RARα fusion protein, dissociates co-repressors from PML-RARα and reactivates silenced genes, thereby resuming differentiation of the APL cells. Conversely, ATO binds to the PML portion of PML-RARα and triggers SUMOylation, ultimately resulting in PML-RARα degradation, which largely accounts for the ATO-induced APL cell apoptosis and differentiation. Furthermore, wild-type PML also plays a role, as the ATO-bound PML restores PML-nuclear bodies (PML-NBs) that were initially disrupted in APL cells; this PML-NB re-formation activates p53 and, likely through coupling with reactive oxygen species (ROS) signaling pathway, contributes to cell apoptosis and senescence, which is required for long-term therapeutic response[2] (Fig. 1b).

The development of mIDH-based targeted therapy may represent another historical success, especially considering that it takes <10 years for the mIDH2 inhibitor, AG-221 (also known as enasidenib or Idhifa), to gain an FDA approval for treating relapsed or refractory acute myeloid leukemia (AML) (2017), since the first identification of *mIDH1* in glioblastoma (2008) and then *mIDH2* in leukemia (2010) (Fig. 1a). The *IDH* genes encode enzymes that convert isocitrate to α-ketoglutarate (α-KG) in the central metabolic pathways. Hot spot mutants of IDH1/2 acquire a neomorphic activity in reduction of α-KG to 2-hydroxyglutarate (2-HG). The 2-HG competitively inhibits some α-KG-dependent dioxygenases, including the TET family of 5-methylcytosine hydroxylases and the Jumonji C domain-containing histone demethylases, both of which closely link the mIDH1/2 with aberrant epigenetic regulation. A common characteristic shared by the treatment of APL and mIDH2 AML is the central role of cell differentiation, which is convincingly indicated by terminal myeloid differentiation of leukemic cells in vivo during the treatment with ATRA/ATO and AG-221.[3] Therefore, the AG-221 treatment of mIDH2 AML may provide another example for differentiation therapy of cancer, although the underlying mechanism is largely unknown.

Notably, the clinical trial of AG-221 for relapsed/refractory AML showed that the overall response rate was 40.3% and that many of the responding patients eventually relapsed.[3] To understand the mechanism underlying the resistance/relapse, several studies analyzed the 2-HG level, *mIDH2* allele burden and clonal evolution in the responding and resistant cases.[4–6] It was somewhat surprising that neither 2-HG level nor *mIDH2* allele burden correlated with clinical response.[4] Clonal evolution analysis implicated various pathways into the acquired resistance/relapse,[5] including an emergence of second-site mutations in IDH2 that interfere with the AG-221 binding to the IDH2 dimer.[6]

In complement with these patient-based studies, Mugoni et al. developed a unique mIDH2 AML mouse model, which may reflect an intrinsic resistance of the patients to mIDH2 inhibition.[7] It was interestingly observed that, during serial transplantation, the AML evolved from an mIDH2-dependent (first and second transplantation) to an mIDH2-independent status (third transplantation).[7] Like the AG-221-resistant patients, the mIDH2-independent leukemia progression was not slowed down by mIDH2 inhibition, despite a decrease of 2-HG.[7] Aiming at identification of targetable vulnerabilities of the mIDH2-independent AML, Mugoni et al. performed metabolic, genomic and transcriptomic comparison of the second and third transplanted AMLs, and observed several molecular features that may characterize the mIDH2 independence (Fig. 1b): (i) a significant increase of ROS that may cause a genotoxic stress in the third transplanted AML; (ii) enrichment of the Tretinoin/ATRA response pathway in the third recipients; (iii) suppression of the LSD1 histone demethylase in mIDH2 AML; and (iv) upregulation of Pin1 prolyl isomerase in the third transplantation.[7] While the increased ROS and the enrichment of the Tretinoin/ATRA pathway immediately suggest vulnerabilities to ATO and ATRA sensitivities, the LSD1 suppression and Pin1 upregulation also imply the same vulnerabilities, because previous studies have shown that LSD1 inhibition sensitizes AML to ATRA-induced differentiation[8] and that Pin1 functions as a direct target of ATRA and thereby plays a role in differentiation.[9] However, it remains to be clarified whether other factors, especially those playing important roles in APL, also contribute to these effects. For example, whether the wild-type RARα (or its homologues RARβ/γ) and PML, the direct targets of ATRA and ATO, exert functions in the ATRA/ATO sensitivity? Also, since a previous study showed that C/EBPα is important for sensitizing mIDH1 AML to ATRA,[10] does C/EBPα (or C/EBPβ/ε) do the same in mIDH2 AML? Although some of these factors were analyzed by western blot showing unchanged or decreased protein levels at the mIDH2-independent stage,[7] their functions may not necessarily be reflected by protein levels and therefore merit further investigation (Fig. 1b).

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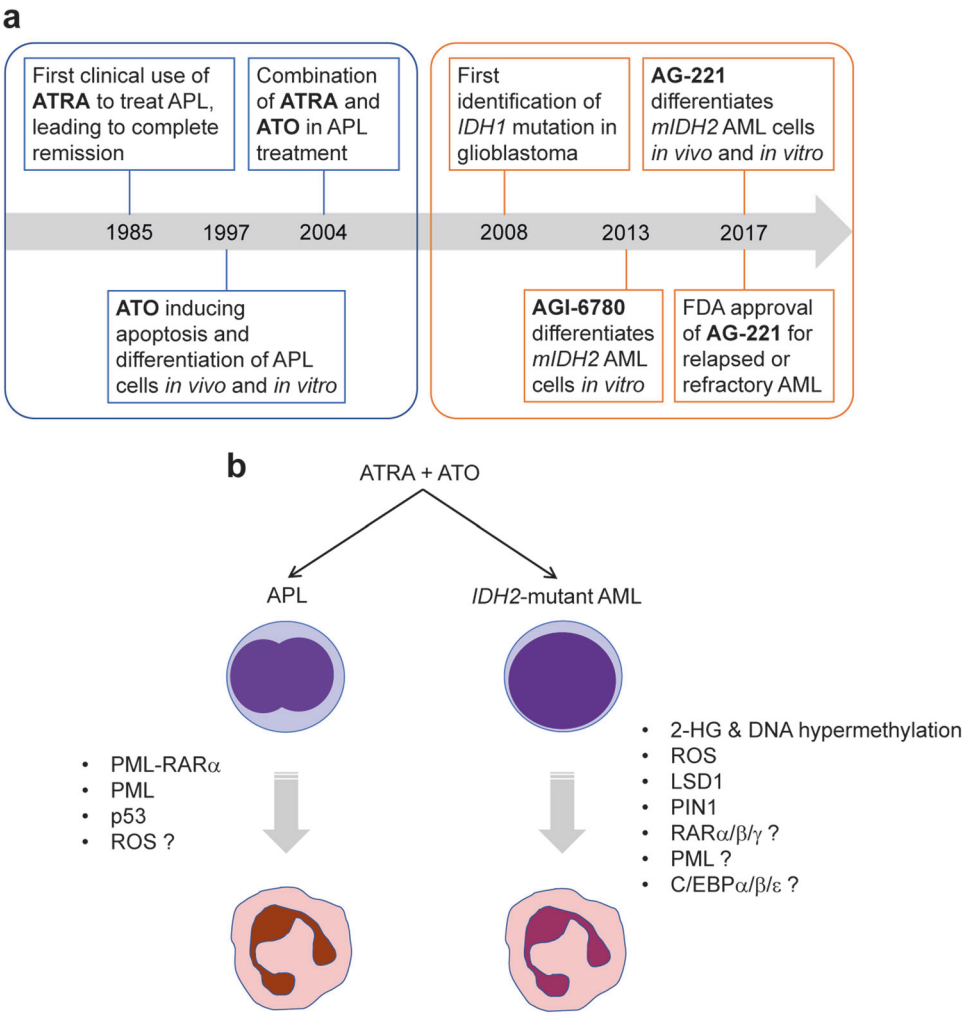

Fig. 1 A convergence of two tales. **a** Timeline of the development of the ATRA/ATO and mIDH2-based therapeutics. **b** ATRA/ATO combination therapy induces myeloid differentiation of both APL and mIDH2 AML cells, implying common feature(s) between these two subtypes of AML. Key factors that regulate these differentiation processes are listed; question marks denote potential regulatory factors that have not been confirmed

Based on the mechanistic studies, Mugoni et al. tested ATRA, ATO, and ATRA/ATO combination treatment of various mIDH2 AML cellular and mouse models.[7] Importantly, the ATRA/ATO treatment showed promising efficacy in the human primary AML cells and in the transgenic and PDX mouse models. Notably, in both mouse models, differentiation syndrome (DS) occasionally occurred as a result of induced myeloid differentiation. Interestingly, the DS is typically seen in APL patients treated with ATRA and/or ATO, but it has recently been reported to occur in the mIDH2 AML patients treated with AG-221 and therefore named as "IDH-inhibitor–associated differentiation syndrome (IDH-DS)" following the widely used term "retinoic acid syndrome (RAS)".[3] Thus, together with the herein described DS in the mIDH2 AML mice treated with ATRA/ATO, these observations clearly suggest the importance of differentiation in these therapies and imply common feature(s) between these two subtypes of AML.

In summary, Mugoni et al. used a unique mouse model mimicking emergence of mIDH2 independence during leukemia progression and discovered targetable vulnerabilities conferring sensitivity to the ATRA/ATO combination therapy. These vulnerabilities were validated in the human primary AML cells and PDX mouse models, providing an alternative therapeutic strategy for the mIDH2 AML. Of note, given that AG-221 has already been shown to induce differentiation and exert appreciable clinical efficacy, a direct comparison between AG-221 and ATRA/ATO in their activities and mechanisms would be highly plausible. Finally, based on the herein demonstrated therapeutic efficacy of the ATRA/ATO combination therapy of the mIDH2 AML cellular/mouse models, and given that the safety of the ATRA/ATO regimen has been fully evaluated, a clinical trial should be in reasonable prospect, setting for a potential expansion of the differentiation therapy concept beyond APL to benefit more cancer patients.

REFERENCES

1. Wang, Z. Y. & Chen, Z. *Blood* **111**, 2505–2515 (2008).
2. de The, H., Pandolfi, P. P. & Chen, Z. *Cancer Cell* **32**, 552–560 (2017).
3. Stein, E. M. et al. *Blood* **130**, 722–731 (2017).
4. Amatangelo, M. D. et al. *Blood* **130**, 732–741 (2017).
5. Quek, L. et al. *Nat. Med.* **24**, 1167–1177 (2018).
6. Intlekofer, A. M. et al. *Nature* **559**, 125–129 (2018).
7. Mugoni, V. et al. *Cell Res.* https://doi.org/10.1038/s41422-019-0162-7 (2019).
8. Schenk, T. et al. *Nat. Med.* **18**, 605–611 (2012).
9. Wei, S. et al. *Nat. Med.* **21**, 457–466 (2015).
10. Boutzen, H. et al. *J. Exp. Med.* **213**, 483–497 (2016).