

absent responses to vaccination against SARS-CoV2 and cannot abandon social distancing and masking precautions.

In the end, there is no advantage from prolonged maintenance in indolent lymphomas, and 2 years should remain the standard duration if maintenance rituximab is offered. The MabCute trial thus supports that extended dosing of rituximab is both too much, and also not enough to offer cure or improve overall survival. Future studies should focus on identifying the minimum number of maintenance doses needed to improve outcomes, particularly in light of a pandemic threat.

Disclosures

No conflicts of interest to disclose.

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An exciting RXRA mutant revives interest in retinoids for acute myeloid leukemia

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doi:10.3324/haematol.2021.279152

The idea that "one size fits all" is obviously outdated for acute myeloid leukemia (AML) therapy: tomorrow's treatments will depend on phenotypically or genetically defined subtypes. The most striking example is acute promyelocytic leukemia (APL), driven by the PML-RARA fusion protein. In APL, a subtype that accounts for 5% of cases of AML, a combination of two targeted agents, all *trans*-retinoic acid (ATRA) and arsenic trioxide, cures over 90% of patients through PML-RARA driver degradation, differentiation and restoration of PML-dependent senescence.¹ These clinical successes have spurred attempts to harness the power of retinoids in other cancers. Unfortunately, ATRA treatment alone remains poorly effective in most non-APL AML.²

Retinoid signaling is complex and still incompletely understood.³ ATRA acts primarily through heterodimeric complexes of retinoic acid receptors (RAR) assembled with retinoid X receptors (RXR). These RXR are key heterodimerization partners of many class-II nuclear receptors and may be ligand-dependent transcription factors or

silent receptors, allowing sequence-specific DNA recognition.⁴ Hence, therapeutic targeting of RXR could be a strategy to activate targets under the control of the RXR/RAR transcriptional complex. However, in principle, RXR/RAR signaling cannot be activated by RXR ligands alone, at least in part because co-repressors remain firmly bound to RAR. This may be modulated by other signaling cascades/second messengers, such as cAMP.⁵

In AML, this simple view has been challenged. RXR ligands (rexinoids, such as bexarotene) may exert some differentiating effects *ex vivo* and *in vivo*.^{5,6} Hematopoietic cells and some AML express endogenous RXRA ligands.^{7,8} Two recent studies have revived interest in RXRA signaling in AML. The first demonstrated that, in AML driven by KMT2A-MLLT3, rexinoids partially suppressed AML growth and triggered differentiation.⁸ Moreover, genetic ablation of RXR accelerated AML growth, while concomitant activation of both RXRA and RARA precipitated differentiation or apoptosis. It is hoped that dual activation of these key regulators may harness retinoids more effi-

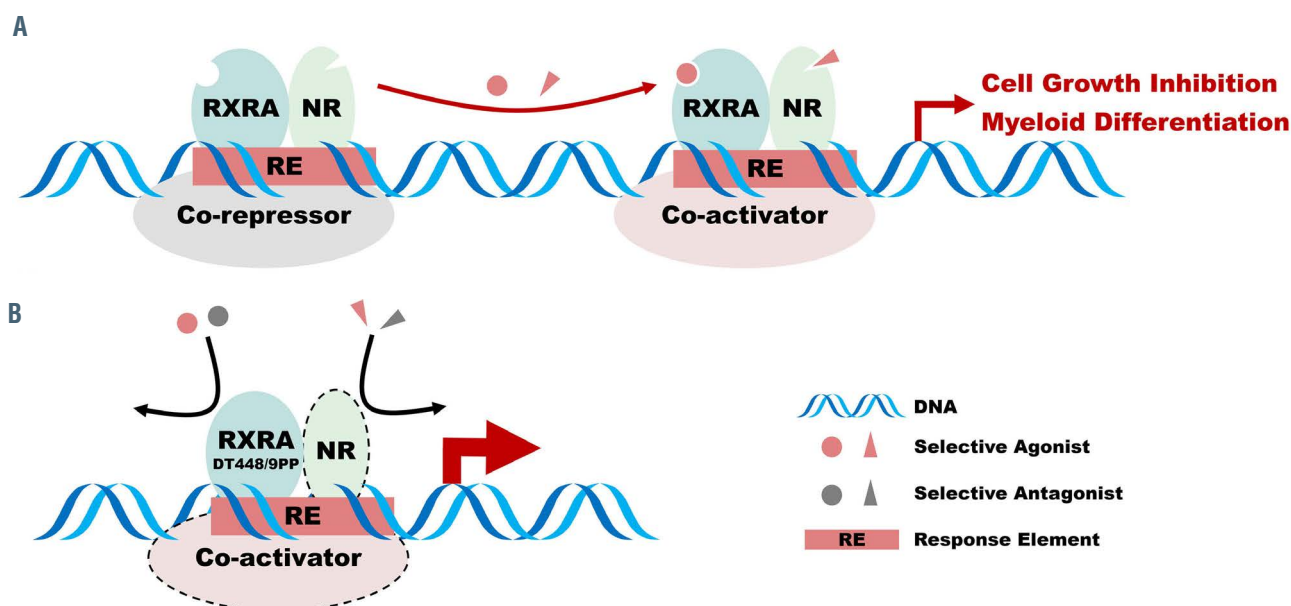


Figure 1. Schematic summary of the effects of constitutively active RXRA DT448/9PP. (A) Under normal circumstances, the transcriptional activity of RXRA heterodimerized with other nuclear receptors (NR), including RARA, remains silent, because of co-repressor binding. Selective agonists activate RXRA/NR-driven transcription, resulting in cellular differentiation and growth arrest. (B) Mutations of residues 488/9 in RXRA allow potent ligand-independent transcriptional activation and drive differentiation.

ciently in AML.² In the second study, published last year in *Haematologica*, di Martino *et al.* report a serendipitously identified activating mutation in RXRA (RXRA DT448/9PP), which potently activates rexinoid/retinoid downstream signaling and suffices to induce terminal differentiation of KMT2A-MLLT3-transformed cells.⁹ The C-terminal helix 12 or AF-2 helix of RXRA, is a critical determinant of ligand-dependent transcriptional activity through control of co-activator/co-repressor binding. Surprisingly, di Martino *et al.* demonstrated that RXRA DT448/9PP overexpression resulted in enhanced transcriptional activity leading to multiple features of differentiation, notably loss of colony-forming ability, in KMT2A-MLLT3-transformed AML cells. Amazingly, this constitutively active RXRA variant binds co-activators completely independently of ligands. Accordingly, transactivation could not be abrogated or further boosted by selective antagonists of RXR or other nuclear receptors, or their agonists, respectively (Figure 1).

These intriguing observations imply that even though rexinoids and retinoids synergize for myeloid differentiation of those AML,⁸ more profound "unconventional" activation by RXRA can initiate terminal differentiation. This master transcriptional regulatory complex deserves further studies to mechanistically decipher how it can become so potent in the absence of ligands. Issues of partner proteins, post-translational modifications or non-coding RNA, all come to mind. Whatever the molecular mechanism, these observations suggest that the RXRA/RARA axis, when super-activated, has the potential to initiate terminal differentiation of some AML cells. Further studies should determine which AML exhibit this exquisite sensitivity to RXRA signaling. This re-emerging

theme of retinoid sensitivity in non-APL AML² could be particularly important in the context of combinations of treatment, particularly with decitabine, as encouraging clinical trials have been published recently,¹⁰ with more likely to come.

Disclosures

No conflicts of interest to disclose.

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