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Haematologica 2021 [Epub ahead of print]

Citation: Hugues de Thé and Fang Qiu. An exciting RXRA mutant revives interest for retinoids in acute myeloid leukemia. Haematologica. 2021; 106:xxx

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

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"One size fits all" is obviously over for acute myeloid leukemia (AML) therapy: cures for tomorrow will depend on the phenotypically- or genetically-defined subtypes. The most striking example is acute promyelocytic leukemia (APL; ~5% of AML) driven by the PML-RARA fusion protein, where the combination of two targeted agents, all trans-retinoic acid (ATRA) and As2O3, cures over 90% of APL 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 primarily acts through heterodimeric complexes of retinoic acid receptors (RARs) assembled with retinoid X receptors (RXRs). These RXRs are key heterodimerization partners of many class-II nuclear receptors (NRs) and may be ligand-dependent transcriptional factors or silent receptors, allowing sequence-specific DNA recognition.4 Hence, therapeutic targeting of RXRs could be a strategy to activate targets under the control of the RXR/RAR transcriptional complex. Yet, in principle, RXR/RAR signaling cannot be activated by RXR ligands alone, at least in part, because co-repressors remain firmly bound to RAR. Yet, this may be modulated by other signaling cascades/second messengers, such as cAMP.5

In AML, this simple view has been somehow challenged. RXR ligands (rexinoids, such as Bexarotene) may exert some differentiation ex vivo or in vivo.5,6 Hematopoietic cells and some AMLs express endogenous RXRA ligands.7,8 Two recent papers have revived interest in RXRA signaling in AML. The first one demonstrated that, in AML driven by KMT2A-MLLT3, rexinoids partially suppressed AML growth and triggered differentiation.8 Moreover, genetic ablation of RXRs accelerated AML growth, while concomitant activation of both RXRA and RARA precipitated differentiation or apoptosis. Dual activation of these key regulators carries hopes to more efficiently harness retinoids in AML.2 In the second
one (this issue), 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. 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. demonstrate 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 from ligands. Accordingly, transactivation could not be abrogated or further boosted by selective antagonists of RXR or other NRs, or their agonists, respectively (Figure 1).

These intriguing observations imply that even though rexinoids and retinoids synergize for myeloid differentiation of those AMLs, 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 RNAs, all come to mind. Whatever the molecular mechanism, these observations suggest that the RXRA/RARA axis, when super-activated, bears the potential to initiate terminal differentiation of some AML cells. Further studies should decipher which AMLs exhibit this exquisite sensitivity to RXRA signaling. This re-emerging theme of retinoid sensitivity in non-APL AML could be particularly important in the context of combinations, particularly with Decitabine, as encouraging clinical trials have been recently published, with likely more to come.

References


Legend

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 NRs (including RARA) remains silent, because of co-repressor binding. Selective agonists awake 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.