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Don't Kill the WASP!

By Melania Tesio

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Anaplastic T-cell lymphoma is a rare but aggressive mature T-cell lymphoma. In 50% to 80% of the cases, these tumors harbor a t(2;5) chromosomal translocation generating a chimeric NPM-ALK gene whereby the anaplastic lymphoma kinase (ALK) domain is fused to the N-terminal part of nucleophosmin (NPM).[1,2] In a recent issue of Nature Medicine, Menotti et al provided novel insights into anaplastic large cell lymphoma (ALCL) development, revealing novel functions for the Wiskott-Aldrich syndrome protein (WASP).[3] In physiological conditions, this protein plays crucial roles during T-cell activation: following T-cell receptor (TCR) engagement, WASP is rapidly activated and recruited to the TCR complex to promote actin remodeling.[4] Menotti et al now demonstrate that WASP has an unexpected tumor suppressive role in ALCLs.

The researchers first observed that WASP was selectively decreased in ALK expressing ALCLs when compared to other T-cell lymphoma subtypes, including ALK negative ALCL cases. Molecular investigations further revealed that WASP selective down-regulation was driven by the ALK-mediated activation of STAT3 and C/EBP-beta, which repressed WASP transcription. To functionally explore the significance of these findings, the authors next used a murine model whereby the transgenic expression of NPM-ALK drives ALCL development with high penetrance. When these mice were crossed to WASP knock-out animals, lymphomagenesis accelerated. Supporting these data, the enforced expression of WASP in ALK expressing tumor cells reduced the proliferation of human cell lines and diminished lymphoma development in xenografts models, thus demonstrating that WASP acts a tumor suppressor in ALCLs.

The researches next explored the molecular basis underlying WASP tumor suppressive functions. They observed that WASP loss in NPM-ALK mice increased the levels of active GTP-bound CDC42 (cell division control protein 42 homolog), a GTPase involved in cellular transformation. In turn, CDC42 accumulation was crucial to promote lymphomagenesis as the conditional deletion of a CDC42 allele in NPM-ALK WASP deficient animals was sufficient to delay tumor development. In addition to accumulating CDC42, NPM-ALK WASP deficient lymphoma cells showed increased levels of phosphorylated ERK1/2, indicating that WASP negatively controls MAPK activation. Confirming these data, the enforced expression of WASP in ALK expressing xenografts decreased MAPK signaling.

Taken together, the findings by Menotti et al suggest a model whereby the ALK-mediated down-regulation of WASP promotes tumor development activating CDC42 and MAPK signaling (Fig. 1). This model is intriguing for 2 reasons. FIRST, it implies that in ALK driven T-cell lymphoma, where the TCR signaling is lost, WASP acts as tumor suppressor. This is in sharp contrast to other T-cell lymphoma types such as the peripheral T-cell lymphoma and angioimmunoblastic T-cell lymphoma, which retain the TCR expression and harbor pathogenic mutations in genes involved in the TCR signaling. In these tumors, WASP function is maintained as it is a crucial compenent of the TCR signaling and it may be lost only at later stages of tumor development to provide additional growth advantages once the tumor is already established. Second, Menotti's model suggests that ALK expressing tumors might be vulnerable to MAPK inhibition. Interestingly, MAPK pharmacological inhibition through the MEK inhibitor trametinib potentiated the activity of the ALK inhibitor crizotinib both in NPM-ALK lymphoma lines and in NPM-ALK WASP knock-out mice. Although these findings need to be extended to xenograft models, they are encouraging as they suggest that the combination of ALK and MEK inhibitors can be beneficial in ALK expressing lymphoma cases that poorly respond to crizotinib.

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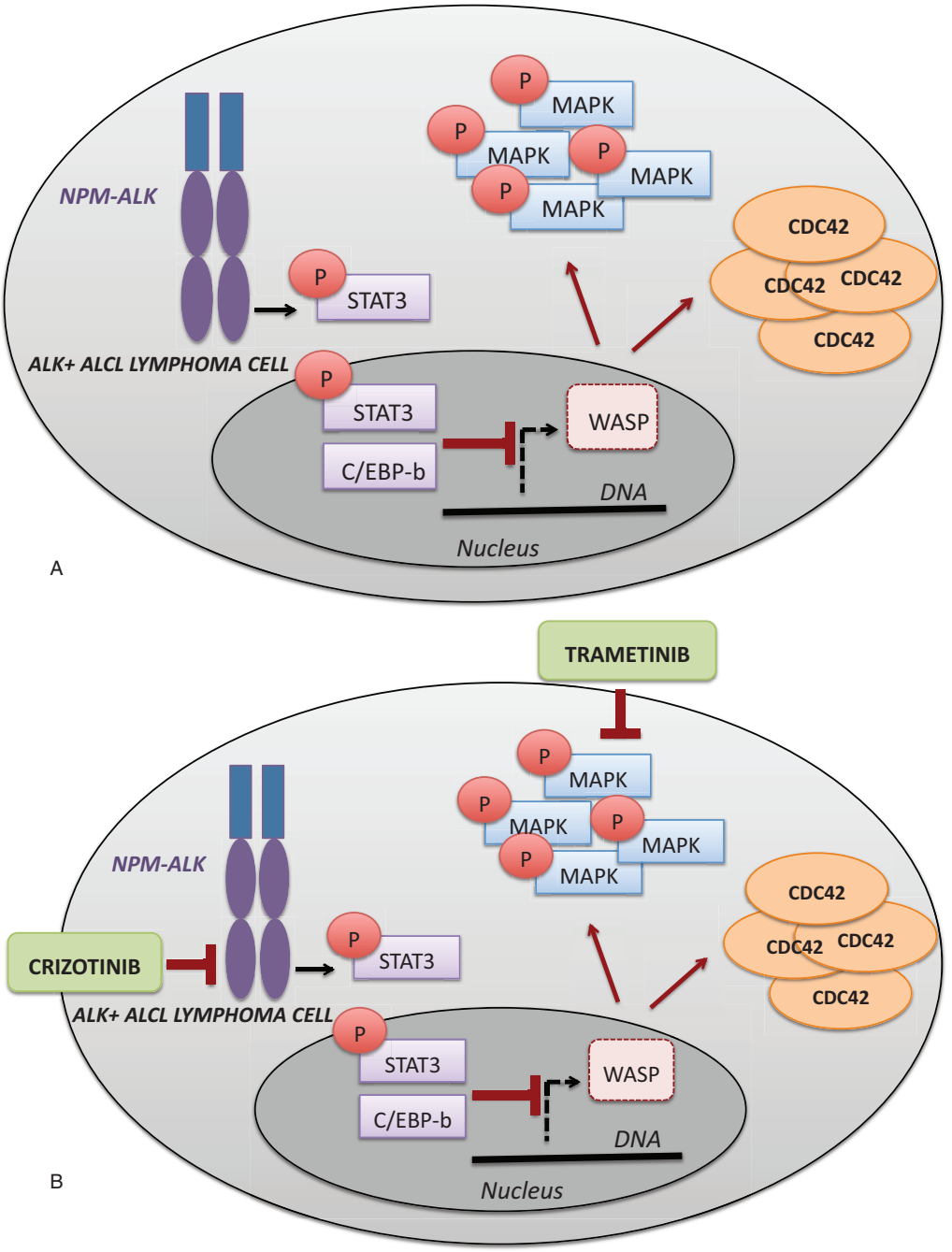

Figure 1. WASP role in the development of ALK expressing ALCLs. In ALK expressing ALCLs, ALK down-regulates WASP via STAT3 and C/EBP-beta mediated transcriptional repression. In turn, WASP loss drives lymphomagenesis by promoting CDC42 accumulation and MAPK signaling (A). As a consequence, ALK expressing ALCLs are vulnerable to the combined therapy with ALK and MEK inhibitors (B). ALCL = anaplastic large cell lymphoma, ALK = anaplastic lymphoma kinase, WASP = Wiskott-Aldrich syndrome protein.

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