POSTER 24: PML physiological functions are required for acute promyelocytic leukemia cure, independently from the immune system

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Introduction

PML/RARA fusion protein expression leads to acute promyelocytic leukemia through the disruption of nuclear structures called PML nuclear bodies. These domains modulate stress response, particularly senescence, through the recruitment and post-translational modifications of a variety of partner proteins. All-Trans Retinoic Acid (ATRA) and Arsenic Tri0xide (AT0), the current standard of care, cure the vast majority of patients, and both PML and PML/RARA have been identified as the direct targets of the treatment. However, the precise role of PML in APL cure still remains unclear. Previous work has failed to identify the actual functions of PML required for treatment response, including in innate immunity. Moreover, multiple studies have revealed the role of the immune system for therapy response and cure in cancer. Yet, any role of immunity in APL cure remains largely unexplored.

Material and method

We generated a variety of PML/RARA expressing mice in backgrounds where mutations in Pml abolish specific functions of PML (nuclear localization, partner recruitment or nuclear bodies formation). Then, APL blasts were transplanted in syngenic immunocompetent receivers to assess APL response to ATRA+ATO treatment. Transcriptomic analysis of treatment response was performed at different time points in these PML-mutant APLs. Finally, APL cells were transplanted in immunodeficient NSG mice and these mice were treated to assess the role of the immune system in APL cure.

Results and discussion

We found that Pml delays APL onset and aggressiveness in either untreated and treated acute transplant recipients. Critically, APLs defective for PML nuclear bodies formation or partner recruitment initially responded to ATRA + AT0 treatment, but quickly relapsed, while mice transplanted with Pml+/+ APL could be cured. Lilrb4 and Tnfrsf14, two immune checkpoint genes, were strongly deregulated in a Pml-dependent manner, but we failed to demonstrate interactions between APL blasts and immune cells upon treatment. Accordingly, highly immunodeficient mice transplanted with APL could still be cured with the ATRA+AT0 combination.

Conclusion

Our work demonstrates that PML nuclear body formation and partner recruitment are required for APL cure and that the later can be achieved without immune system involvement. These findings emphasize that a potent targeted therapy can cure cancer in an autonomous, immune system independent, manner.