A zebrafish model of MYC-driven acute myeloid leukemia reveals that neutrophil resistance to oncogenic transformation depends on their ability to promote PP2A-mediated MYC proteasomal degradation

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INTRODUCTION

Acute Myeloid Leukemia ("AML") is the most common acute leukemia in adults. The origin of the malignancy can be found in a different chromosomal translocation as well as in accumulated mutations in genes involved in hematopoietic proliferation and differentiation. The result is growth of poorly differentiated myeloid cells. Despite being considered a heterogeneous malignancy, AML possesses many genetic aberrations that nowadays can be classified as prognostic factors in myeloid leukaemia, including the overexpression of the MYC and the downregulation of the PP2A: both proteins are essential regulators of cell proliferation, apoptosis, and differentiation, and they, directly and indirectly, regulate each other's activity. With zebrafish able to develop almost any tumour type known from humans, we can follow the development of AML and verify the effects of different drugs in tumor development.

RESULTS: OVEREXPRESSION OF hMYC CAUSES A HYPERPROLIFERATION OF NEUTROPHILS

A) Representative images of WT and Lys:HsMYC larvae. B) Lys positive cells quantification in the tail region of WT and Lys:HsMYC larvae. We observed an early drastic expansion of neutrophils. The neutrophil number gradually declined to normal levels from 10 dpf onwards.

RESULTS: LOWER EXPRESSION OF PP2A SUBUNITS WAS DETECTED IN LYZ:HsMYC FISH

qPCR analysis of PP2A subunits in zebrafish larvae WT and Lys:HsMYC in a 2 to 10 days timeframe. Lower expression of three different subunits has been detected in Lys:HsMYC larvae.

RESULTS: PROTEASOME INHIBITION AFFECTS THE RUDIMENT OF NEUTROPHILS AFTER 10DPF

A) Representative images of WT and Lys:HsMYC larvae treated with MG132 (proteasome inhibitor). B) Lys positive cells quantification in the tail region of WT and Lys:HsMYC larvae. The inhibition resulted in the stabilization of myc protein levels and further expansion of transformed neutrophils.

RESULTS: THE PHARMACOLOGICAL ACTIVATION OF PP2A BLOCKS THE EXPANSION OF NEUTROPHILS

Lys positive cells quantification in the tail region of WT and Lys:HsMYC larvae after the treatment with PP2A activators at 3, 5, and 7 dpf. Pharmacological treatment with three different drugs inhibits the expansion of neutrophils.

CONCLUSION

Taken together, our data suggests a mechanism of direct interaction between MYC and the PP2A in the development of acute myeloid leukaemia.

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