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Hypoxia-driven WNT10A and WNT10B signalling: a new clue to make acute leukaemia initiating cells vulnerable

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Introduction:Overcoming resistance to chemotherapy is indeed the main therapeutic challenge in the treatment of T-cell acute lymphoblastic leukaemia (T-ALL). Several studies emerged from different groups evidence that restrained leukaemia cell populations have the exclusive ability to regenerate the complete phenotypic heterogeneity of the primary malignancy, and account for T-ALL resistance. Those unique cells, which possess the ability to self-renewal and differentiate, are commonly called “leukaemia initiating cells” (LICs). A better understanding of the molecular mechanisms that control LICs may reveal specific vulnerabilities, and may thus offer new opportunities to develop less toxic anti-T-ALL drugs.

Objectives:Our projectaimed at deciphering the role of a crosstalk between hypoxia,an integral component of the bone marrow (BM) microenvironment,and the WNT signalling pathway to support T-cell acute lymphoid leukaemia initiating cells (LICs).

Methodology:We have used Human and Mouse models of NOTCH-dependent T-ALL cells.

Results:Our results reveal a role for two hypoxia-target WNT ligands, WNT10A and WNT10B, in the maintenance of T-ALL LICs. In accordance with WNT10A and WNT10B acting as canonical WNT ligands, we have shown accumulation of transcriptionally active β-catenin restricted to LIC populations. Furthermore, our results clearly stay a dual role for hypoxia by also promoting the autocrine WNT10A/WNT10B signalling, which depends on cell surface sugar’s sulphation.

Conclusions:Our data raises the possibility to make LICs vulnerable by targeting the WNT10A/B signalling individually or in combination.

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