

Metabolic Transformation in Notch-Driven Acute Lymphoblastic Leukemia

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Abstract

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive, highly frequent type of hematologic tumor. Current treatments against T-ALL are recurrently associated with treatment resistance, severe toxicity and side effects. For the proposal and validation of more effective treatments, great efforts are dedicated to elucidate the molecular mechanisms leading to the origin and progression of this type of leukemia. In this short review, we briefly summarize some aspects of those molecular mechanisms, with an especial emphasis in the upregulation of the Notch signaling pathway and its consequences into cancer cell growth and cancer metabolism.

Keywords: Notch1; T-ALL; mTOR; Metabolic transformation

T-cell Acute Lymphoblastic Leukemia

T-cell acute lymphoblastic leukemia (T-ALL) is a genetically heterogeneous malignancy which appears upon the malignant transformation of a T-cell progenitor. It is an aggressive type of hematologic tumor which accounts for 15% of pediatric and 25% of adult acute lymphoblastic leukemia [1]. T-ALL patients present aggressive clinical features, including an increase in the level of circulating white blood cells and affected central nervous system. Nowadays, the regular treatment of T-ALL patients is based on high-doses of multi-agent chemotherapy, recurrently associated with severe toxicity and side effects. Although these protocols of intensified chemotherapy have significantly improved the outcome of patients, still 20% of childhood patients and the majority of adult patients do not survive due to resistant or relapsed disease [2]. Thus, a better understanding of the molecular basis of T-ALL origin and progression is essential for the proposal, design and validation of more specific, highly effective treatments against this type of leukemia. The main objective of contemporary research in pathobiology of T-ALL is to understand how frequently arising genetic lesions affect malignant transformation hallmarks, including cell growth and proliferation, cell survival and cellular bioenergetics [3]. The final goal should be to identify selectively targeted treatments against those elements to which the transformed T-cell have become addicted, including signaling pathways and metabolic processes.

The malignant transformation process of T-cells is very complex. It involves different genetic alterations during thymocyte development leading to the deregulation of cell growth, proliferation, differentiation, migration and survival of the T-cell. Originating mutations might arise in a haemopoietic stem cell, leading to multilineage developmental capacity. Transformed T-cells present clonal rearrangements in their T-cell receptor genes, and express antigen-receptor molecules resembling immature lymphoid progenitor cells within the early developmental stages of normal T lymphocytes. Genome-wide sequencing studies showed that, while some somatic mutations in T-ALL correlate preferentially with either children or adults, other genetic alterations are uniformly identified both in pediatric and adult T-ALL [4]. One example is the constitutive

activation of Notch1 signaling, present in a majority of T-ALL patients. First discovered in *Drosophila*, Notch1 was identified in humans through a t(7;9)(q34;q34.3) chromosomal translocation observed in some patients with T-ALL [5]. Since only 1% to 3% of patients of T-ALL were found to carry this translocation, the mechanistic role of Notch1 in the origin and development this malignancy was not clear. Later, it was found that other activating mutations leading to the upregulation of Notch1 pathway are present in more than 50% of the patients with T-ALL, underscoring the direct implication of Notch1 in the proliferation and survival of leukemia cells.

Notch and mTOR Signaling in T-ALL

Notch signaling plays an active role in many biological processes, including embryonic development, vascular formation, cell proliferation and cell survival. The human Notch family is constituted by four receptors (Notch1-4) located in the surface of the cell membrane, and five ligands (Dll1, Dll3, Dll4, Jagged1 and Jagged2) located on the surface of the neighboring cell, all ligands belonging to the Delta/Serrate/LAG-2 (DSL) family [6]. Notch receptors are expressed as heterodimeric peptides, including an extracellular subunit and a transmembrane subunit which interact through a heterodimerization domain present in both subunits. When a ligand of the DSL family binds to the extracellular domain of the Notch receptor, it induces sequential cleavages in Notch by an ADAM metalloprotease and by a γ -secretase, releasing the Notch intracellular domain (NICD) from the membrane [7]. NICD then translocates to the nucleus, interacts with specific DNA-binding proteins (CBF1/Suppressor of Hairless/LAG-1 and Mastermind/SEL-8) and activates the transcription of target genes, such as the two families of transcriptional factors HES and HEY (including HES1, HES5, HEY1 and HEY2). The analysis of Notch1-target genes and gene expression programs controlled by Notch1 showed that Notch1 promotes leukemic cell growth via direct transcriptional upregulation of genes involved in ribosome biosynthesis, amino acid metabolism including glutamine, protein translation, and nucleotide synthesis. However, Notch1 activation also follows an indirect mechanism to induce leukemic transformation through the upregulation of key target pathways, namely c-MYC pathway, PI3K/AKT/mTOR

pathway, and interleukin 7 receptor alpha chain. In addition, Notch1 activation increases G1/S cell cycle progression in T-ALL (through the upregulation of CCND3, CDK4, and CDK6 cell cycle genes) [8].

Despite the prominent oncogenic role of Notch signaling in T-ALL, the inhibition of Notch signaling using γ -secretase inhibitors (GSI) have only limited anti-leukemic activity against human T-ALL cell lines, exerting primarily a cytostatic effect with minimal or no apoptosis. Furthermore, early trials were hampered by excessive toxicity from off-target effects on the intestinal epithelial differentiation, resulting in dose-limiting diarrhea. GSI resistance can be induced by mutational loss of PTEN which leads to constitutive activation of the PI3K/AKT/mTOR pathway. Several lines of evidence connect Notch signaling with mTOR activation in T-ALL. mTOR is a conserved serine/threonine kinase which integrates several stimuli to regulate cell growth and metabolism. mTOR forms two functionally and structurally distinct complexes termed mTORC1 and mTORC2. mTORC1 regulates protein synthesis, ribosome biogenesis, nutrient uptake and autophagy in response to growth factors, amino acids, and cellular energy [9]. In response to amino acids, mTORC1 is activated by its translocation to the surface of the lysosomes, a process regulated by the Rag GTPases. Due to its central role in controlling cell growth and metabolism, mTORC1 is upregulated in many different types of tumors to sustain tumor growth. This upregulation of mTORC1 constitutes a critical step for the deregulation of cell signaling during malignant transformation. Intriguingly, GSI treatment suppresses the phosphorylation of multiple signaling proteins in the mTORC1 pathway, suggesting a mechanistic role of Notch signaling in the activation of mTORC1. Of note, simultaneous blockade of the mTORC1 and Notch pathway with small molecule inhibitors resulted in synergistic suppression of T-ALL growth [10]. Thus, this simultaneous inhibition has gathered some attention as a potential co-treatment strategy against T-ALL. However, the mechanistic connection between both pathways is not clear. While some results suggest a PTEN-dependent mechanism involving AKT activation [11], other results showed that the mechanism of mTORC1 activation is independent of both PTEN and AKT, and rather involves c-MYC activation [10].

Metabolic Transformation in Notch-driven T-ALL

The origin, development and progression of cancer require a set of modifications in the normal homeostasis of the cell known as malignant transformation. Among these modifications, changes in cellular metabolism and in cellular signaling are key elements. While signaling deregulation in cancer has been deeply studied during many years, metabolic changes during malignant transformation become a matter of intense research. However, most of the studies concerned the role of p53, cMYC, MYCN and AKT, and the metabolic impact of Notch signaling in cancer has not been investigated deeply yet. To date, several reports have shown bioenergetic changes in leukemic models, but no molecular explanation has been provided yet [12-14]. These reports highlighted the importance of aerobic glycolysis (the so-called "Warburg Effect") to sustain ATP production in T-ALL cells, showing a potentiation between glycolysis inhibition via 3-BrOP and mTOR inhibition by rapamycin in their ability to reduce T-ALL cell viability [12]. In addition, a recent report also showed that PTEN loss upregulates glycolysis and consequently rescues leukemic cell metabolism [15]. This report also identified glutaminolysis as a major node in cancer metabolism in T-ALL. Nowadays, a proper integration between metabolism and cell signaling in cancer cells is required to really understand the mechanisms by which these two components of malignant transformation interact, and ultimately, to find potential candidates that could be used for targeted therapies to specifically kill cancer cells.

As described above, Notch signaling is a major target in a very large percentage of lymphoblastic leukemia, as it is upregulated in more than 50% of the patients with T-ALL. Still, anti-cancer treatments targeting

Notch signaling fail due to treatment resistance and tumor relapse. Indeed, it is becoming clear that inherent or acquired resistance of tumor cells to treatment has limited the effectiveness of the majority of targeted therapies. A proposed solution to overcome this limitation is the use of molecular co-treatments, targeting more than one critical element for the tumor growth and survival. In this direction, one potential solution that has not received enough attention during the last years is the possibility of targeting essential aspects of both cell signaling and cell metabolism of the tumor. The main reason to explain why these kinds of therapies have been disregarded during the past years is simple: our knowledge about the crosstalk between cell signaling and cell metabolism in both normal and tumor cells is limited, and therefore the proposal of rationally designed co-treatments is currently inaccessible.

Concluding Remarks

In summary, much more effort is necessary to understand the molecular and cellular implications of Notch upregulation in T-ALL. The interconnection between Notch pathway and other major signaling pathways, such as mTOR, and with metabolic re-programing open the door to the definition of new "addictions" in Notch-driven T-ALL cells that might be used for the specific treatment of this type of leukemia. Further research should elucidate if metabolic reprogramming is not only a hallmark, but also an Achilles heel of Notch-driven leukemia.

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References

1. Van Vlierberghe P, Ferrando A (2012) The molecular basis of T cell acute lymphoblastic leukemia. *J Clin Invest* 122: 3398-3406.
2. Tremblay CS, Curtis DJ (2014) The clonal evolution of leukemic stem cells in T-cell acute lymphoblastic leukemia. *Curr Opin Hematol* 21: 320-325.
3. Pui CH, Robison LL, Look AT (2008) Acute lymphoblastic leukemia. *Lancet* 371: 1030-1043.
4. Peirs S, Van der Meulen J, Van de Walle I, Taghon T, Speleman F, et al. (2015) Epigenetics in T-cell acute lymphoblastic leukemia. *Immunol Rev* 263: 50-67.
5. Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, et al. (1991) TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* 66: 649-61.
6. D'Souza B, Meloty-Kapella L, Weinmaster G (2010) Canonical and non-canonical Notch ligands. *Curr Top Dev Biol* 92: 73-129.
7. Pancewicz J, Nicot C (2011) Current views on the role of Notch signaling and the pathogenesis of human leukemia. *BMC Cancer* 11: 502.
8. Tzoneva G, Ferrando AA (2012) Recent advances on NOTCH signaling in T-ALL. *Curr Top Microbiol Immunol* 360: 163-182.
9. Duran RV, Hall MN (2012) Regulation of TOR by small GTPases. *EMBO Rep* 13: 121-128.
10. Chan SM, Weng AP, Tibshirani R, Aster JC, Utz PJ (2007) Notch signals positively regulate activity of the mTOR pathway in T-cell acute lymphoblastic leukemia. *Blood* 110: 278-86.
11. Palomero T, Sulis ML, Cortina M, Real PJ, Barnes K, et al. (2007) Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. *Nat Med* 13: 1203-1210.

12. Akers LJ, Fang W, Levy AG, Franklin AR, Huang P, et al. (2011) Targeting glycolysis in leukemia: a novel inhibitor 3-BrOP in combination with rapamycin. *Leuk Res* 35: 814-820.
13. Renner K, Kofler R, Gnaiger E (2002) Mitochondrial function in glucocorticoid triggered T-ALL cells with transgenic bcl-2 expression. *Mol Biol Rep* 29: 97-101.
14. Ursini MV, Parrella A, Rosa G, Salzano S, Martini G (1997) Enhanced expression of glucose-6-phosphate dehydrogenase in human cells sustaining oxidative stress. *Biochem J* 323: 801-806.
15. Herranz D, Ambesi-Impiombato A, Sudderth J, Sánchez-Martín M, Belver L, et al. (2015) Metabolic reprogramming induces resistance to anti-NOTCH1 therapies in T cell acute lymphoblastic leukemia. *Nat Med* 21: 1182-1189.
16. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, et al. (2013) Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature* 496: 101-115.