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Mini Review

Glycogen Synthase Kinase-3β (GSK-3β) is a Critical Factor in Intracellular Signaling Pathways in Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is a common hematologic malignancy in children, teenagers, and young adults. The ALL development is a complex process, it includes the aberrant gene expression and the presence of chromosomal translocations. Chromosomal rearrangement have incidence in the cell maturation, proliferation and survival process. The treatment of ALL has shown high rates of effectiveness; however, the expression of biomarkers associated with the activation of cell signaling pathways is crucial to establish the prognosis of the disease. Glycogen synthase kinase-3β (GSK-3β) is a member of the serine/tyrosine kinase family with an important role in intracellular pathways signal; the GSK-3β transposition has been associated with changes in the transcriptional activity of nuclear factor kappa B (NF-kB) in blast cells. Nonetheless, others intracellular signaling pathways associated with the GSK-3β activity should participate in the ALL development.

Keywords: Acute lymphoblastic leukemia; GSK-3β; Prognostic

Introduction

ALL development is associated with deregulation in different points of the molecular signaling pathways associated with the hematopoiesis process. The main determinants of the LLA development of respect to cytogenetic pattern has been established, in this syndrome: t(1,19), t(4,11), t(12,21) and t(9,22) have been described. Moreover, the translocations induced an aberrant expression of the enzymes that regulate the intracellular signaling process [1].

The biomarkers associated with prognosis and treatment response in ALL in the last decade has been extensive. The use of kinase inhibitors of BCR/ABL gene as a molecular target in patients positive to the Philadelphia chromosome (Ph + ALL) is available, this occurs with a prevalence of 5% in children and 30 % in adults. [2,3] or ErbB, a promoter of survival signaling and cell proliferation expressed in B-cell lymphoblast [4,5].

ALL development has been associated with *JAK-STAT* aberrant expression. *JAK2* and *JAK1* mutations affect the regulation of intracellular processes of proliferation and survival [6,7]. *JAK* mutations and *CRLF2* over expression in patients with refractory leukemia have been identified and treatment with *JAK* inhibitors has shown favorable results. Alterations in *PI3K-AKT* and Ras-MAPK signaling path way sin hematological malignancies have been evaluated in different populations, hence its role in targeted therapies [8]. The inhibition of rapamycin in mammalian cells (mTOR) involved in the control of the transcription complex has been shown effective in the treatment of pediatric ALL [8-10].

However, glycogen synthase kinase-3β (GSK-3β) has been identified as an important regulator of NF-kB transcriptional activity, these effects should regulate the apoptosis in leukemic cells. In this review, there are molecular mechanisms associates with the critical role of GSK-3β in intracellular signaling pathways in ALL.

GSK-3B Regulates NF-Kb Activity in Mononuclear Cells of Bone Marrow

Glycogen synthase kinase (GSK-3) is a serine and tyrosine kinases family identified in skeletal muscle, GSK-3 participates in the culmination of glycogen synthesis. Over expression of GSK-3 has been demonstrated in metabolic disorders and different alterations of the differentiation and proliferation of hematopoietic stem cells [4]. There are two iso forms of GSK-3: the first of 51 kDa (GSK- 3α) and the second of 47 kDa (GSK-3β), Figure 1.

Recently GSK-3β has been associated with the regulation of NF-kB activity. The inhibition of GSK-3β decreases the activation pathway of NF-KB; this inhibition generates gene suppression and stimulates apoptosis *in vitro*. The importance of targeted molecular

therapies for each genetic abnormalities related with the process of multiplication of leukemic cells and have emerged in childhood ALL. The isolation of bone marrow aspirates for mononuclear cells has been used to detect GSK-3β by immune fluorescence in primary cell cultures. The inhibition of GSK-3β *in vitro* showed changes in the transcriptional activity of NF-kB and the induction of apoptosis of leukemic cells. The GSK-3β level was significantly accumulated in the nuclei of all leukemic cells and the cell death induced by the inhibition of GSK-3β was mediated by a down regulation of the transcriptional activity of NF-kB. GSK-3β inhibitors significantly decreased NF-kB expression, it suggesting that it is a new interesting target on ALL treatment [11].

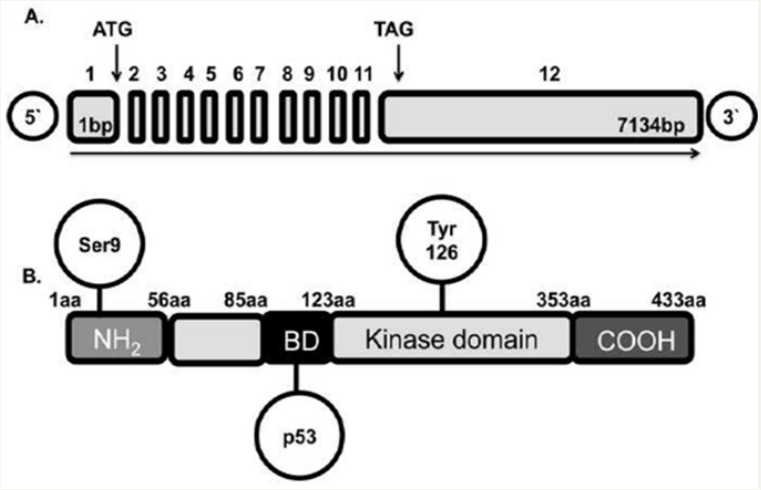

Figure 1: GSK-3β structure. A) The gene is compound of 12 exons. B) The protein has N-terminal and C- terminal extremes, a kinase domain and a BD region associated with a binding site to p53.

WNT Pathway is a Crucial Regulator of Proliferation and Survival Cell

GSK-3β regulates various signaling pathways for the expression of growth factor and affects a wide range of physiological processes, is an important component in the process of insulin signaling and *Wnt*. The relationship between activation pathways and dependent signaling GSK-3β concentrations determined the signaling pathway of insulin exerts a specific action on the glycogen synthase activity. Furthermore, *Wnt* increases cytosolic expression of beta catenin subunit; the formation of a GSK- 3β- axin complex may increase the expression of *Wnt* through different mechanisms and this activation is very important consider the role of *Wnt* in carcinogenesis and mechanisms of signal transduction [12].

Ribosomal Protein S6 Kinase 1 (S6K1) Regulation is Related with GSK-3β Activity

In cellular models, GSK-3βpromoted the activation of p70 subunit of ribosomal protein S6 kinase 1 (S6K1) by phosphorylation. S6K1 plays an important role in cellular processes mediated by insulin sensitivity; these including cell proliferation and proteins synthesis. Therefore, dysregulation of S6K1 contributes to the progression of different metabolic diseases. S6K1 has an important biological and clinical role; moreover is necessary to know the activation processes mediated by GSK-3β activity in the regulation, thus, it is an important regulator of cell proliferation and growth. The results establish the need to develop inhibitors of GSK-3β to treat diseases as diabetes, cancer and other age-related that are linked to inadequate regulation of S6K1 [13].

GSK-3β has been included to determine the pharmacological perspective, therefore intermediate in a number of signaling pathways including insulin/PI3 kinase and *Wnt* pathway [13,14]. GSK-3β Inhibition with lithium or by phosphorylation, activate signaling pathways generally has an apoptotic effect; GSK-3β targets are transcription factors (β- catenin, C -Jun, HSF -1, CREB) and cytoskeletal elements (Tau, MAP1B), determinants involved in metabolic processes. Intracellular GSK- 3βshould be inhibited by at least five different mechanisms, which are critical for the development of new inhibitors [15,16].

Perspectives

Thus, in acute lymphoproliferative disorders present in pediatric population, there are not described the molecular biomarkers of disease progression. The use of prognostic factors including biochemical-metabolic, clinical and molecular biomarkers should establish the risk of relapse; approximately half of patients who relapse have a favorable clinical prognosis and excellent response to initial treatment [17,18].

GSK-3β is involved in multiple molecular signaling pathways as PI3K/PTEN/Akt/mTOR and Ras / Raf / MEK / ERK. Moreover, should be considered as a prognostic marker of disease but as a potential target in the development of new treatments that seek to reduce the resistance to current chemotherapy, considering that their aberrant expression has been identified in patients with different types of cancer treatment instituted [19,20].

Inhibitors of GSK- 3β have become one of the most powerful tools in the treatment of pathophysiological processes in which the enzyme is an activator of other signaling pathways. The most

common inhibitors are small synthetic molecules that compete for ATP binding site [15-17]. Recently, Wang has reported that tetramethylpyrazine inhibits the proliferation of ALL cell lines decreasing in GSK-3β signaling, an interesting pharmacological perspective to development [20]. Layton et.al, report that NFKB relative expression levels, in comparison to the GSK-3β immune his to chemistry results of the bone marrow samples, showed a significant difference between positive and negative cases, these results suggest that GSK-3β may be a prognostic biomarker in childhood ALL [21].

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