An Overview of Expression of Livin Gene in Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia (ALL) represents approximately 80% of childhood leukemias, making it the most common childhood malignancy. Apoptosis is an autonomous process that involves the activation, expression, and regulation of a wide range of genes, leading to programed cell death to remove unwanted or abnormal cells. Livin/ML- IAP/BIRC7 is a member of the inhibitor of apoptosis proteins family, which plays a key role in the regulation of apoptosis and modulation of cell cycle and cell proliferation. Livin is over-expressed in several cancer types and presents an anti-apoptotic activity mediated mostly by the direct inhibition of caspase 3, but also of caspases 7 and 9 and DIABLO

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Introduction

Acute lymphoblastic leukaemia (ALL) is a disseminated malignancy of B- or T-lymphoblasts which imposes a rapid and accurate diagnostic process to support an optimal risk oriented therapy and thus increase the curability rate **(1).**

Acute lymphoblastic leukaemia (ALL) represents approximately 80% of childhood leukaemias making it the most common childhood cancer and a leading cause of cancer- related deaths among children **(2).**

Epidemiology

Most ALL cases occur in children, with an incidence of 3 to 4/100,000 in patients 0 to14 years of age and 1/100,000 in patients older than 15 years, in the United States. In children, ALLs represent 75% of all acute leukaemias (which in turn represent 34% of all cancers in this age group), with a peak incidence at 2 to 5 years of age **(3).**

In Egypt, the incidence of ALL is about 4 cases per 100,000 children accounting for about 20% of pediatric malignancies **(4).**

Livin (BIRC7, ML-IAP) is a member of the inhibitors of apoptosis (IAP) family, which plays crucial roles in apoptosis, cell proliferation and cell cycle control. Abnormal livin expression is sometimes detected during the process of cancer formation and/or progression. Thus livin research may provide an opportunity for the development of potential therapy for livin-relevant cancers **(5).**

Apoptosis is an active biological mechanism leading to programmed cell death.A tight regulation is required in biologic systems to ensure a delicate balance between life and death

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. The loss of apoptosis might result in the development of a wide variety of diseases , including cancers . A complex network of proapoptotic and antiapoptotic proteins that governs this tight regulation has been revealed and it is now possible to lay out a provisional apoptotic signaling circuity **(6).**

A family of intracellular antiapoptotic proteins that has become increasingly prominent in the field of cancer is the inhibitor of apoptosis protein (IAP) family. IAP family members are able to inhibit apoptpsis induced by a variety of stimuli mainly by binding and inhibiting specific caspases, primarily 3, 7 , 9 **(7).**

The role of IAPs family in apoptosis

Inhibitors of apoptosis proteins (IAPs) inhibit apoptosis through at least two of the major pathways for the initiation of caspase activation**:**

A. Mitochondrial pathway (intrinsic pathway) with cytochrome c.
B. The death receptor pathway (extrinsic pathway) with tumor necrosis factor (TNF) family of death receptors.

Inhibitor of apoptosis proteins (IAPs) also influence a third minor pathway in which granzyme B directly activates caspase 3 **(8).**

A. The mitochondrial (intrinsic) pathway of caspase activation:

The intrinsic mechanism of apoptosis uses the mitochondria and mitochondrial proteins. Cells with damaged DNA or upregulated oncogenes can stimulate this pathway **(9)**

Additional stimuli for this pathway include growth factor deprivation, surplus Ca2+, DNA-damaging molecules, oxidants and microtubule targeting drugs.The overall pathway is regulated by the BCL-2 family of proteins **(8).**Various apoptotic stimuli result in the upregulation of BH3-only proteins, which then activate both BAX and BAK**.** BAX is regulated by p53, a tumor suppressor gene, once activated, BAX and BAK oligomerize which leads to mitochondrial outer membrane permeabilization (MOMP). MOMP is the defining event of intrinsic apoptosis and is considered the point of no return. The permeabilization allows the release of intermembrane proteins like cytochrome c, second mitochondria-derived activator of caspase (SMAC). Upon the release of cytochrome c, the apoptosome is formed from cytochrome c, apoptotic protease-activating factor-1 (APAF- 1), dATP and procaspase-9. Within the apoptosome, procaspase-9 is converted into caspase- 9 which activates the executioner caspases-3 and -7 the executioner caspases quickly begin to break down proteins leading to cell death. **(8)**

There are additional steps to intrinsic apoptosis that ensure cell death. SMAC is released during apoptosis to inhibit inhibitor of apoptosis proteins (IAP) so that apoptosis proceeds once the apoptosome is formed **(8).** MOMP will also lead to cell death if caspases are not activated.

The permeabilization of the membrane leads to loss of mitochondrial function which leads to cell death. There are a few cells that can survive MOMP such as neurons. It has also been found that some cancer cells are able to elude death even after MOMP **(10).**

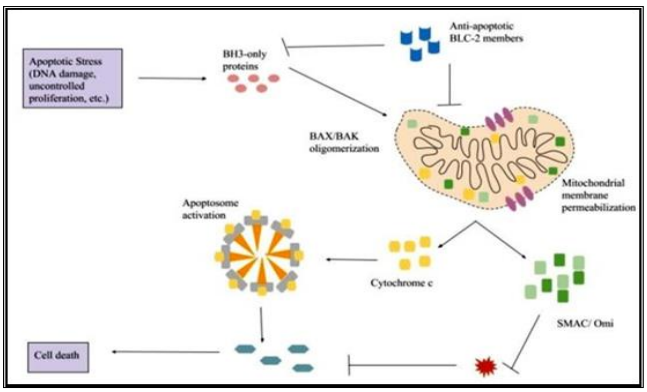

Figure (1): The pathway of intrinsic apoptosis. BH3-only proteins are upregulated in response to apoptotic stress. They activate BAX (BCL-2-associated X protein) and BAK (BCL-2 homologous antagonist killer) which oligomerize and results in mitochondrial membrane permeabilization. Cytochrome c, SMAC (second mitochondria-derived activator of caspase), and Omi are released and the apoptosome is formed from procaspase-9, dATP, cytochrome c, and APAF-1. Caspases are

then activated and begin to cleave cellular proteins resulting in apoptosis. Arrows represent activation and T bars represent inhibition **(10)**

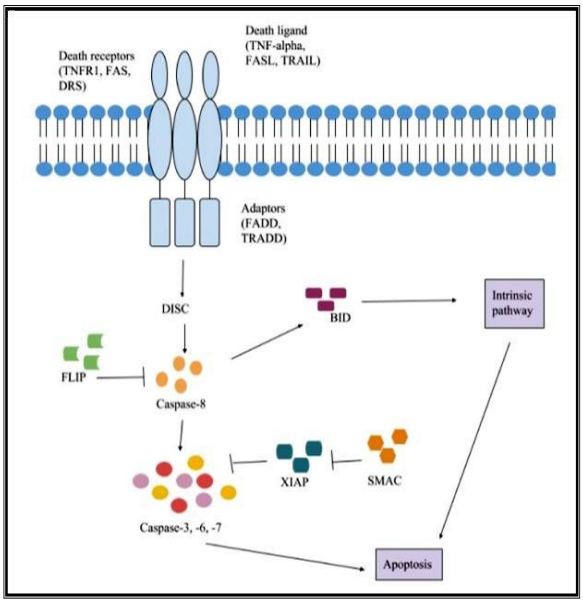

Figure (2): The extrinsic pathway begins with a death ligand docking on a death receptor. An adaptor protein binds to the receptor. DISC (death-inducing signaling complex) is formed c the adaptor protein and procaspases-8 and -10. Caspase-8 becomes activated which activates caspases-3, -6 and -7 and BID (BH3 interacting-domain death agonist). BID goes on to activate BAX and BAK which activates the intrinsic pathway. Caspases-3, -6 and -7 are the executioner caspases that result in cell death. Arrows represent activation and T bars represent inhibition **(8)**.

<u>The death receptor (extrinsic) pathway of caspase activation:</u>

The extrinsic pathway uses extracellular signals to induce apoptosis. Cell death signals, also known as death ligands, bind to tumor necrosis factor (TNF) family death receptors **(8).**

Some death ligands include Fas ligand (Fas-L), TNF-related apoptosis-inducing ligand (TRAIL) and tumor necrosis factor (TNF). An adaptor protein is recruited to the death receptor adaptor proteins include Fas-associated death domain (FADD) and TNF receptor- associated death domain **(9).**

Initiator procaspases-8 and -10 bind to the adaptor protein, forming the death-inducing signaling complex (DISC). The procaspases have a death effector domain (DED) that binds to the adaptor protein at its DED. Procaspases-8 and -10 are activated by DISC. Executioner caspases-3, -6 and -7 are then activated and begin the cleavage of proteins and the cytoskeleton leading to cell death. DISC is regulated by the inhibitor, c-FLIP, which is homologous to caspase-8, yet lacks caspase activity **(8).**

The extrinsic and intrinsic pathways converge after the activation of caspase 8. In the extrinsic pathway, the activation of caspase-8 leads to the activation of BH3 interacting- domain death agonist (BID), a BH3-only protein**. (8)**. The BID then activates and oligomerizes BAX and BAK and the intrinsic apoptotic pathway continues. This results in both pathways to continue to propagate through their typical course ensuring that apoptosis will occur **(8).**

Livin in Acute Lymphoblastic Leukemia

The over expression of livin protein in newly diagnosed children with acute leukaemia indicated that it could play an important role in carcinogenesis and progression of acute leukaemia **(11).**

The expression of *livin* α and *livin* β may be associated with the genesis and development of childhood acute leukaemia. It seems that the expression of *livin* α and *livin* β may be used as a molecular marker of childhood acute leukaemia **(12).**

Flotho et al. (13) found that that high expression of *livin* gene may be used as a marker of poor prognosis in acute lymphoblastic leukaemia. As *livin* gene has associations with risk group and response to chemotherapy.

El-Mesallamy et al. (14) showed that increased livin expression in adult ALL patients was associated with the presence of unfavorable prognostic factors at diagnosis. This suggests that high livin expression is associated with a slower apoptotic response of leukemic cells to apoptotic stimuli provided by chemotherapeutic agents and eventually associated with a lower EFS and OS.

Most studies on the clinical relevance of *livin* expression, albeit limited in number, have shown that *livin* is an antiapoptotic regulator; therefore, *livin* expression has been considered to be a poor prognostic factor in malignancies. Therefore, the observations from other studies were quite unexpected and suggest that the role of *livin* in the apoptosis system in leukemogenesis or in the maintenance of leukemic cells might be different from what has been previously recognized. The possible explanation of the favorable prognosis of *livin* expression is that the cleaved form of *livin* may serve as a proapoptotic regulator. A study showed that silencing of the *livin* ß-isoform, but not the α-isoform, by RNA interference blocked the growth of HeLa cells in clonogenic survival assays and sensitized the cells to various proapoptotic stimuli **(14).**

Yan et al. (12) showed that leukemic lymphoblasts preferentially express the α-isoform of *livin*, rendering them more susceptible to apoptosis **(**

Choi et al. (5) showed that livin expression in childhood ALL was, albeit not always, associated with the presence of favorable prognostic factors at diagnosis. In addition, Livin expression was associated with a favorable early response to chemotherapy.

They also noted that not only the livin expression rates but also the livin expression levels were higher in patients with favorable clinical features compared with those in patients with unfavorable clinical features.

These findings suggest that livin expression itself, not the expression level, is an important prognostic determinant in patients with childhood ALL.

Ibrahim et al. (4) found that Livin expression was strongly associated with better DFS, and OS rates in patients with childhood ALL (The better early bone marrow response to induction chemotherapy suggest that *livin* expression is associated with a faster apoptotic response of leukemic cells to apoptotic stimuli provided by chemotherapeutic agents and eventually associated with a better relapse-free survival**).** It was associated with an increased apoptotic response to methyl prednisolone treatment ex vivo, a rapid early treatment response in vivo, and more importantly, a very favorable treatment outcome. *Livin* expression retained independent prognostic significance in a multivariate analysis.

Shurtleff et al. (15) found that *livin* expression rate was significantly higher in patients with favorable prognostic factors. It is particularly interesting to note that the *livin* expression rate was very high in *t*(12, 21) and was very low in *t*(9, 22)/11q23 rearrangement, because these translocations are known to be strongly associated with the best and worst outcomes, respectively. Suggested that the expression of *livin* α and *livin* β may be associated with the genesis and development of childhood acute leukaemia. It seems that the expression of *livin* α and *livin* β may be used as a molecular marker of childhood acute leukaemia.

Kaspers et al. (16) found that *Livin* expression was strongly associated with better DFS, and OS rates in patients with childhood ALL. The better early bone marrow response to induction chemotherapy suggests that *livin* expression is associated with a faster apoptotic response of leukemic cells to apoptotic stimuli provided by chemotherapeutic agents and eventually associated with a better relapse-free survival.

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