Review Article

A ROLE OF TEC, A NON RECEPTOR TYROSINE KINASE AS APOPTOTIC REGULATOR

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ABSTRACT

There are many types of tyrosine kinase involved in intracellular mitogenic mechanism, particularly, Tec tyrosine kinase are involved in apoptosis pathway. Tec tyrosine kinases do not have any transmembrane domain so it is known as non receptor tyrosine kinase. There are various types of Tec tyrosine kinase like Txk, Btk, Itk, Rik and Bmx. These kinases have different protein or domain structure like PH domain, SH2 domain, SH3 domain TH domain and also chromosome localization. Tec tyrosine kinase is mainly expressed in spleen, liver, kidney and heart but low in many others tissues. Activation of Tec tyrosine kinase cause by the different molecule like PKCs, JAK, SFK and FADD. Regulation of Tec tyrosine kinase cause by CD+4 native cell and CD+4 activated cell, and also involve IL-12, IL-27, IFNγ, IL-18 and IL-4. There are various downstream and upstream regulators involved in Tec tyrosine kinase family. The role of Tec tyrosine kinase is Induction of Bcl-xL, Mitogenic signals in T-cells, Tec kinases as a RhoA regulator, Regulation of apoptosis, Control of c-fos transcription. There are various diseases produce due to lack of T-cell and B-cell like Behcet's disease, XLA and XID.

Keywords: Tyrosine kinase, Tec family, domain, myristoylation signals, apoptosis.

INTRODUCTION OF TEC TYROSINE KINASE

In intracellular mitogenic signaling mechanism, Protein tyrosine kinase (PTKs) play essential role in human. Many growth factor receptors like epidermal growth factor (EGF), nerve growth factor (NGF), stem cell factor (SCF) receptors themselves have intrinsic PTK activity. PTKs are designated as Non receptor type PTKs or cytoplasmic PTKs because many PTKs do not have transmembrane domain in their structure. Tec family is a part of Non receptor type PTKs.

The Tec family composed of five members, namely Tec, Btk, Itk/Emt/Tsk, Bmx and Txk/Rik. The molecular mechanism of Tec family kinase is regulation of growth/differentiation signals in vivo and also involve in calcium mobilization, RhoA activation and MAPK regulation[1].

Types of tec tyrosine kinase

- Inducible tyrosine kinase (ITK)

ITK play an essential role in T-cell activation and proliferation by expressed in T-cells, NK cells and mast cells. ITK is activated by stimulation of T-cell receptors and serves to amplify the TCR signaling cascade. Now a day ITK represents a novel potential target for anti inflammatory therapy in a variety of indication such as psoriasis and allergic asthma.

- Bruton tyrosine kinase (BTK)

It is a first Tec tyrosine kinase, which represents the prototypic family member in this regard. Btk is involved in formation of numerous types of complexes important in regulating B-cell functions depending on intracellular localization and translocation.

- TXK tyrosine kinase

RIK/TXK is primarily expressed in T lymphocytes and TXK do not have any pleckstrin homology (PH) domain near the amino terminus but instead of this they contain a distinctive cysteine string motif. Because of alternative initiation of translation from the same cDNA, RIK proteins produce a two isoforms. The initiated protein species lacks the cysteine string motif and present in nucleus. The larger form is cytoplasmic and when it is palmitolated and mutation of its cysteine string motif is carried out then palmitoylation and migration of protein to the nucleus is occurs. Therefore, cysteine string motif is responsible for the determinant of both fatty acid modification and protein localization for the larger isoform of RIK which suggest the RIK regulation is differ from the other Btk family kinase.

- Bone Marrow Chromosome X (BMX)

It is responsible for the downstream target of PI-3 kinase in BMX and expressed in myeloid cells, arterial endothelium and epithelial cells but limited in tissue distribution. Cytokines and other growth factors are activated by BMX through the PI-3 kinase and implicated in cellular functions, including differentiation, motility and apoptosis[2].

MOLECULAR CLONING OF TEC TYROSINE KINASE

Expression of Tec members in tissue

Tec tyrosine kinase is mainly expressed in spleen, liver, kidney and heart but low in many others tissues[3]. Btk is abundant in myeloid and B-cell lineages. BMX have a relatively wide in hematopoietic as well as non hematopoietic organs. TXK and RIK are mainly expressed in T-cell.

Table 1: Chromosome localization

Kinase	Chromosome localization
Tec	4p12
Btk	Xq22
Itk	5q31-32
Bmx	Xp22.2
Txk	4p12

From Table-1 it should be noted that Tec and Txk genes are assigned to the same locus chromosome 4p12 so Tec and Txk genes are closely localized in mice at long arm of chromosome 5.Similarly, both Bmx and Btk genes are localized on the X chromosome, and the amino acid sequence of Bmx is most closely homologous to that of Btk. So that, these two genes are similarly generated in evolution by gene duplication[4-6].

PROTEIN STRUCTURE OF TEC KINASE

Protein structure of Tec kinase resembles to that of Src family with some differences like they carry a unique NH3 terminal domain of amino acid which is followed by a Src homology (SH3) domain, SH2 domain and a kinase domain.SH3 domain responsible for binding site of polyproline helices. Now recently studied that the SH3 binds intramolecularly to the region between SH2 and Kinase domains and this interaction cause the protein in bent "inactive" state by COOH terminal phosphotyrosine and SH2 domain[7].

Tec family members composed of a unique NH3 terminal domain, SH3 domain, SH2 domain and kinase domain except myristoylation signals or the COOH terminal tyrosine instead of these they contain long NH3 terminal unique domain which is consists of Pleckstrin homology (PH) domain and Tec homology (TH) domain. PH domain play an essential role in physically tethering Tec protein to the cell membrane by binding certain types of phospholipids and convert in to phosphatidylinositol 3-kinase (PI3-kinase) so act as PI3-K activity dependant manner. Cells can regulate the activity of Tec kinases through the control of PI3-K[8].

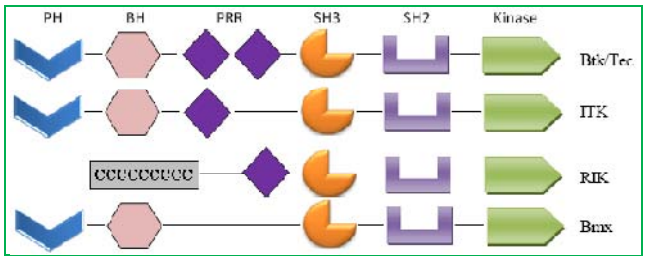

Figure 1: Domain structure of Tec kinase.

In addition to the PH domain, a second domain is Tec homology domain (TH domain) which consist of Btk motif in the NH3 terminal half and the proline rich region in the COOH terminal half. TXK/RIK lacks the Btk motif because they are derived from the same ancestor[9].

Tec family kinase contain catalytic C terminal kinase domain, two Src homology domains(SH2 and SH3) and two proline rich regions while ITK and RIK contain only one PRR. RIK does not contain Btk homology domain (BH) or an N-terminal plekstrin homology instead of these they contain string of N-terminal cysteine repeats[10].

PH Domain

Binding module for phospholipids

PH domain binds with number of phospholipids by phospholipase C-γ and form a phosphatidylinositol-4, 5-bisphosphate [PI (4, 5) P2] at high affinities in vitro. The Btk PH domain associate with phosphatidylinositol-3,4,5-triphosphate [PI(3,4,5)P3] over PI(4,5)P2 or phosphatidylinositol-4-phosphate[PI(4)P] but PH domain of Tec has a higher binding affinity for [PI(3,4,5)P3] than PI(4,5)P2. These result indicate that 3'-phosphoinositides is a binding partner for PH domain of the Tec kinase so Tec members act as downstream to PI3-K. In fact activation of Itk is inhibiting by addition of PI3-K inhibitor, wortmannin.

Binding module for Proteins

Several cellular proteins are linked with the PH domain of Tec family kinase like certain types of Gα subunits of heterotrimeric G proteins are directly bind to Btk, which opens the possibility that heterotrimeric G proteins are able to control Tec activities. The Btk PH domain also bind with the actin and responsible for increase in the filamentous form[11].

TH Domain

TH domain composed of a Btk motif and proline rich region and Btk motif is located COOH-terminally to the PH domain of interferon-γ binding protein and RasGAP in addition to the Tec kinases. TH domain is hypothesized to bind intramolecularly it own SH3 domain, keeping the kinase in an inactive state so involved in the regulation of its own kinase activity.

SH3 Domain

SH3 domain of Tec kinase is responsible for negative regulation of their kinase activity. Internal deletion of the SH3 domain leads to the activation of c- Src and c-Abl and truncation of the SH3 domain results in the activation of the Tec kinase.

SH2 Domain

In Tec kinase activity, small numbers of proteins are involved in SH2 domains. Recently identified novel docking protein, termed BRDG1 which is expressed in myeloid and B-cell. For phosphorylation of BRDG1 and Dok-1 requires both PH an SH2 domain. So BRDG1 and Dok-1 are good candidates for the Tec SH2 binding proteins[12].

LOCALIZATION OF TEC FAMILY KINASE

Membrane localization

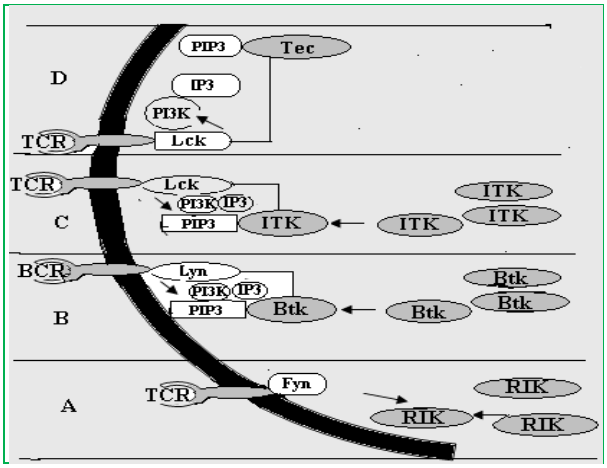

Figure 2: Membrane localization of Tec family kinase

A. The larger isoform of RIK is constitutively to the plasma membrane through palmitoylation of the cysteine string motif at the amino terminus. Up on T cell receptor (TCR) engagement, RIK proteins in the vicinity of the TCR are activated by Fyn through phosphorylation of the RIK kinase domain.

B. Up on BCR engagement, Btk protein activated by Lyn and results activation of PI3K, leading to the production of PIP3. Btk is then recruited to the plasma membrane through interaction of its PH domain with PIP3 and finally Lyn phosphorylates and activates Btk[13,14].

C. Up on TCR engagement, ITK is cytosolic. ITK protein activated by Lck activates the PI3K and results production of PIP3. ITK is recruited to the plasma membrane through interaction of its PH domain with PIP3 and finally Lck phosphorylates and activates the ITK protein.

D. Tec is recruited in to vesicles at the plasma membrane that contain signaling component such as Lck. Tec is then recruited to PIP3 through its PH domain where it can be activated (Lck in T-cell and Lyn in B-cell).

Nucleus localization

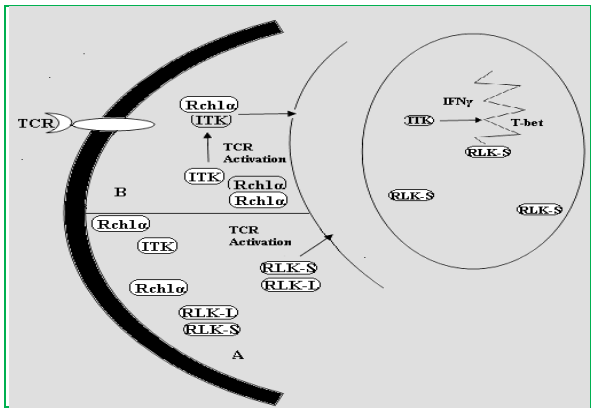

Figure 3: Nucleus Localization of Tec family kinase

A. Up on TCR engagement, the short form of RIK (RLK-S), usually found in complex with the long form (RLK-L), migrates to the nucleus. Once in the nucleus RLK-S binds to the promoter region of the IFN-γ gene.

B. Up on TCR engagement, the SH3 region of ITK interacts with the PRR region of the nucleur transporter Kayopherin alpha (Rch1α). The ITK-Rch1α complex translocates in to the nucleus. In the nucleus, ITK may bind T-bet, a master regulator of IFN-γ transcription, and perhaps phosphorylation it[15].

ACTIVATION OF TEC TYROSINE KINASE

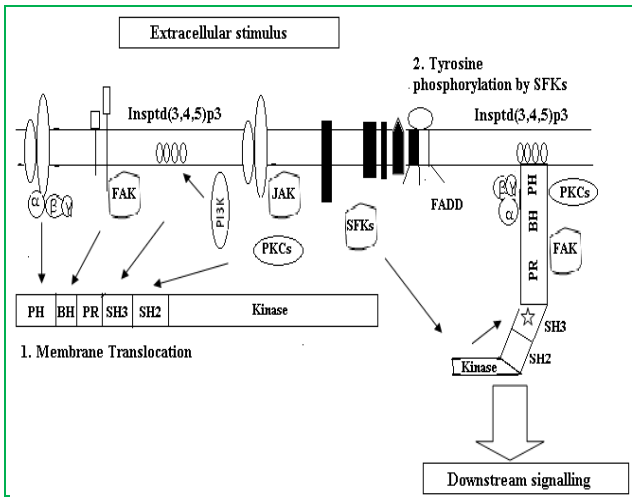

Figure 4: The two step activation of Tec kinase

1. In the first step, the PH domain interacts with the products of PI3K or, alternatively, with other binding partners (such as the FERM domain of FAK, heterotrimeric G protein subunits, PKCs or F-ctin) to translocate to the plasma membrane or specific intracellular microenvironments required for activation.

2. Once at the membrane, Tec kinases are phosphorylates on a tyrosine residue in their catalytic domain by SFKs. Subsequently, a tyrosine residue in the SH3 domain is autophosphorylated, preventing further inhibitory intramolecular interactions.

Recent evidence suggest that the interaction of the PH domain with PtdIns(3,4,5)p3 targets Tec kinases to specific membrane micro domain, referred to as Rafts or glycolipid enriched membranes(GEMs), where signaling molecule convene up on antigen receptor activation. ITK translocate to GEMs up on CD3-TCR stimulation in a PtdIns(3,4,5)p3 and PH domain dependent manner. Similar results have been found for Btk. In Btk and Bmx physically interact with caveolin-1, a primary protein component of caveolae, a glycolipid enriched membrane compartment[16-19].

EXPRESSION & REGULATION TEC FAMILY KINASE

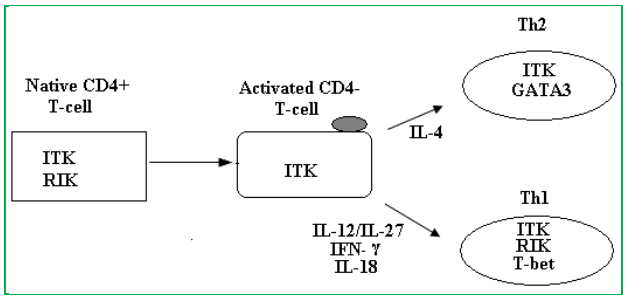

Figure 5: Expression and regulation of Tec kinase in CD4+ T-cell

ITK, RIK and Tec kinases are expressed in T-cell and ITK have predominant role in TCR signaling. ITK is found in mature T-cell and thymocytes and is found at maximum levels in the mature adult thymus. Similar ITK, RIK is expressed in thymocytes and mature resting T-cells; however, RIK mRNA levels are 3-10 folds lower than the levels of ITK mRNA in resting T-cells. Furthermore, unlike ITK, RIK is dramatically down regulated at both the mRNA and proteins level up on TCR stimulation. The Tec kinase is expressed at much lower levels in resting T-cells, with mRNA levels 100 fold lower than that of ITK.

Tec kinase levels are also regulated during T helper cell differentiation. When native CD4+ cell differentiate in to T helper cell(Th) cells, ITK levels increase 2-3 fold in Th2 cells, which express the master transcription factor GATA3, versus Th1 cells, which express master transcription factor T-bet, consistent with the known role of ITK in Th2 responses. Similar to ITK, Tec is expressed at two fold higher levels in Th2 cells than in Th1 cells, however functional significance of this differential expression is not known. In contrast to ITK and Tec, RIK is down regulated following native CD4+ cell activation, and is re-expressed in Th1 cells but not Th2 cells; these result suggest that a specific role for RIK in Th1 responses.

ITK and RIK are both expressed in native CD+4 T cells; ITK is expressed at higher levels. Upon activation ITK is up regulated while RIK is strongly down regulated. Th2 differentiation, mediated by IL-4, causes ablation of RIK expression while ITK levels remain high (2-3 fold higher than basal levels). Tec expression is also up regulated 2 fold on Th2 cells when compared to Th1 cells. These cells also express the Th2 master transcription factor GATA3. In contrast Th1 differentiation, mediated by IL-12/IL-27, IFNγ and IL-18, results in up regulation of RIK while ITK goes back to being expressed at basal levels. These cells also express the Th1 master transcription factor T-bet[20-23].

UPSTREAM REGULATORS OF TEC KINASES

Lymphocytes surface Antigens

Surface antigens are responsible for tyrosine phosphorylation and activation of Tec kinases in lymphocytes. In T-cell CD3 and CD28 leads to activation of Tec, ITK and TXK while in B-cell CD38 and CD72 leads to activation of Tec and Btk through the B cell antigen receptor. It is not clear how engagement of this surface antigen can trigger the activity of Tec kinases[24].

Cytokines receptors

Tec kinases are expressed in non lymphocytes tissues and involved in intracellular signaling mechanism of cytokines receptors. For example, Tec can be activated by stimulation of SCF, IL-3, IL-6, granulocytes colony stimulating factor (G-CSF), erythropoietin (EPO) and Btk can be activated by stimulation of IL-5 and IL-6 receptors. Therefore Tec PTK acts as members of the cytokine receptor super family. Tec and Btk are bind to the gp130 component of the Il-6 receptor; Tec PTKs may therefore also become dimerized and activated when receptors are stimulated through the ligand binding[25].

Heterotrimeric G-protein-coupled receptors (GPCR)

A variety of GPCR stimuli can activate the Tec family proteins like stimulation of thrombin and thromboxane A2 leads to activation of Tec and Btk respectively. The isolation of G-protein specific PI3-K consisting of the p101 regulatory subunit and p110g catalytic subunit. Heterotrimeric G-protein activated via GPCR then stimulates the lipid kinase activity of p101/p110g.

Integrins

In human platelets, stimulation of surface glycoprotein IIb-IIIa molecule with fibrinogen induces the activation of Tec; whish is further enhanced by the co-stimulation with thrombin[26, 27].

DOWNSTREAM REGULATORS OF TEC KINASES

PLC-γ2 and calcium mobilization

PLC-γ2 is good candidate effectors for intrinsic role in calcium flux in B-cells. There are number of studies indicate that an increase in intracellular (Ca2+) is the critical step for B-cell development. In human B-cells from XLA patients do not induce calcium flux in response to BCR engagement. Ectopic expression of wild type Btk, Tec and Itk restores (Ca2+) mobilization in these cells indicating presence of Tec kinase- PLC-γ2-calcium flux signaling mechanism in vivo.

BRDG1, a novel scaffolding protein

BRDG1, a small protein consists of 295 amino acid residues and contain PRR and one PH domain. BRDG1 is tyrosine phosphorylates when co-expressed in 293 cells with Tec. However Btk, Itk and Bmx are not phosphorylates BRDG1 under the same conditions, suggesting that the Tec family kinases have distinct specificities toward their targets.

TF II-I/BAP-135

TF II-I expressed multifunctional transcriptional factor. TF II-I/BAP-135 linked with the PH domain of Btk and cause tyrosine phosphorylates in vivo. Importantly, co-expression of Btk with TF II-I/BAP-135 induces the activation as well as nuclear import of the latter. TF II-I

can bind to promoter region including the initiator (Inr) elements which is present in VpreB, TdT and λ5. TF II-I is also shown to drive the expression of C-fos proto-oncogene. These finding open the possibility that Tec kinases directly regulate transcriptional factor, as in case of JAK/STAT.

Control of PI3-K

Tec kinase regulated by PI3-K, Tec seems to utilize PI3-K as its effectors also. Interestingly, Tec phosphorylates and activates PIK in 293 cells and these effect depends up on physical interaction between the phosphotyrosine of Tec and the COOH-terminal SH2 domain of PIK which is regulatory subunits of PI3-K[28].

IN VIVO ROLES OF TEC FAMILY KINASES

Induction of Bcl-xl

B-cell activation through the surface IgM molecule induces the transcription of Bcl-xLgene, coding for a potent anti-apoptotic factor. In Xid B cells, however, IgM stimulation fails to activate the Bcl-xL gene, and instead induces apoptosis. More importantly, forced expression of Bcl-xL gene rescues the immune defect in Xid mice. It is therefore likely that transcriptional regulation of the Bcl-xL gene may be a element in the pathogenesis of xid.

Mitogenic signals in T-cells

Mice lacking functional Itk shows partial block in T-cell development and these reduction is enhanced when mice had a mutation in the Fyn gene. TCR stimulation of peripheral T-cells obtained from Itk mice resulted in an impaired mitogenic responses.

Tec kinases as a RhoA regulator

The small G-protein RhoA, a member of the Ras superfamily, plays an essential role in the regulation of actin organization. Tec and Bmx are shown to enhance GPCR driven RhoA activation in fibroblasts. Mutation of Tec and Bmx suppressed RhoA activity and over expression of Tec cause formation of filamentous actin in cells. Since internal deletion of the TH domain makes Tec unable to control RhoA, Tec seems to send out a positive signal toward RhoA through its TH domain.

Regulation of apoptosis

It remains unclear whether Tec kinases function as pro or anti apoptotic factor in vivo. The latter possibility is supported by the finding that Btk activity is required to induce Bcl-xL messaging in B-cells and that Btk suppress the Fas-mediated apoptotic signal via the disruption of the FAS-FADD interaction in chicken B-cells.

In contrast, Btk may be indispensable to the radiation mediated apoptosis mechanism in B-cells. Chicken B-lymphoma cells, DT-40; undergo apoptosis in response to radiation. Targeted mutation of the Btk gene, however, makes these cells refractory to radiation, a resistance which is not achieved by disruption of the Lyn or Syk genes. In addition, mast cell prepared from Xid or Btk mice are resistant to the apoptosis triggered by cytokines deprivation. It is also shown that activates JNK in a Ras dependant manner. These lines of evidence support a pro apoptotic role for Btk. It is possible that Tec kinases have a dual function in apoptosis, with the fate of Tec driven apoptosis signaling being context sensitive and type dependant[29-31].

Control of c-fos transcription

Expression of c-fos and c-myc proto-oncogene abrogates the growth factor requirement in some cells; transcriptional regulation of these two genes appears to be directly linked to the proliferative signaling mechanism. Expression of Tec induces transcriptional activation of the c-fos protooncogene.Furtheremore, expression of a dominant interfering mutant of Tec suppressed the cytokines driven activation of c-fos promoter. These findings suggest that Tec kinases are involved in the regulation of c-fos transcription[32].

DISEASES ASSOCIATED WITH TEC TYROSINE KINASES

1) Behcet's disease

Behcet's disease is characterized by recurrent attack of oral and gential ulcerations, erythema nodosum, papulopustular skin eruptions, arthritis, uveitis and cerebritis. It has been found that excessive Th1 cell function is involved in the pathogenesis of BD. Txk acts as a Th1 cell specific transcription factor. Thus, The Th1 cytokine production and Txk expression of T-lymphocytes in patients with BD. Peripheral blood lymphocytes produced excessive th1 assiciated cytokines including IFNγ and interleukin-12 in patient with BD. Circulating CD3+ and purified CD4+ T cells expressed excessive Txk protein.

Treatment

Immunomodulator

- Cycloshorin A is a calcineurin inhibitor and cause inhibition of T lymphocytes activation and recruitment Alkylating Agents
- Chlorambucil: This drug interferes with DNA replication and cause decreased B and T cell functions.
- Cyclophosphamide: It is fast acting alkylating agent and mechanism of action is similar with chlorambucil.
- Colchicine: It is an anti-inflammatory drug and causes the inhibitin of microtubule functions. It is used in treatment of active mucocutaneous and joint manifestations of BD without ocular or major organ involvement.

Other Treatment

Thalidomide, INF-α, FK-506, Infliximab, Etanercept, Pentoxifylline, Methotrexate and Corticosteroids are used in treatment of BD patients[33-35].

2) X-Linked agammaglobulinemia (XLA)

XLA caused by mutation of the human Btk gene. In XLA, B lymphocytes and plasma cells are decreased whereas T lymphocytes subsets show in relative increase. The defect is caused by an arrest in B-cell differentiation, distinguishing XLA from other Ig deficiencies.

3) X-linked immunodeficiency (XID)

XID is caused by a single point mutation in the pleckstrin homology domain of murine Btk. Mice bearing mutation in Btk gene have been generated replacing different parts of gene.

Treatment

- The quinine epoxide terreic acid blocked Btk Ph domain interaction
- Also terreic acid and leflunomide metabolite analogs inhibited the enzymatic activity of the Tec family kinase Btk.
- ITK represents a novel potential target for anti-inflammatory therapy in a variety of indications such as psoriasis and allergic asthma[36-38].

CONCLUSION

In intracellular mitogenic signaling mechanism, Protein tyrosine kinase (PTKs) play essential role in human. Several cellular proteins are linked with the PH domain of Tec family kinase like certain types of Gα subunits of heterotrimeric G proteins are directly bind to Btk, which opens the possibility that heterotrimeric G proteins are able to control Tec activities. TH domain composed of a Btk motif and proline rich region and Btk motif is located COOH-terminally to the PH domain of interferon-γ binding protein and RasGAP in addition to the Tec kinases. TH domain is hypothesized to bind intramolecularly it own SH3 domain, keeping the kinase in an inactive state so involved in the regulation of its own kinase activity. SH3 domain of Tec kinase is responsible for negative regulation of their kinase activity. Internal deletion of the SH3 domain leads to the activation of c-Src and c-Abl and truncation of the SH3 domain results in the activation of the Tec kinase. In Tec kinase activity, small numbers of proteins are involved in SH2 domains. Recently identified novel docking protein, termed BRDG1 which is expressed in myeloid and B-cell. For phosphorylation of BRDG1 and Dok-1 requires both PH an SH2 domain. So BRDG1 and Dok-1 are good candidates for the Tec SH2 binding proteins. In contrast, Btk may be indispensable to the radiation mediated apoptosis mechanism in B-cells. Chicken B-lymphoma cells, DT-40; undergo apoptosis in response to radiation. Targeted mutation of the Btk gene, however, makes these cells refractory to radiation, a resistance which is not achieved by disruption of the Lyn or Syk genes. In addition, mast cell prepared from Xid or Btk mice are resistant to the apoptosis triggered by cytokines deprivation. It is also shown that activates JNK in a Ras dependant manner. These lines of evidence support a pro apoptotic role for Btk. It is possible that Tec kinases have a dual function in apoptosis, with the fate of Tec driven apoptosis signaling being context sensitive and type dependant.

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