A computational analysis of E2A gene in B & T-Cells Development

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Article

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Abstract

The E2A (TCF3) gene reveals a dominant role during lymphocyte and CNS growth. E2A is an object of the E proteins family of TFs. E proteins encoded by bHLH TFs are a key moderator of B & T cells development. Precisely, sequencing of E proteins and antagonists reveals lymphoid development. The B & T cells lineage commitment suggested E2A, HEB, E2-2, ID2/ID3, and other bHLH TFs are necessary at a proximate phase of cellular maturation. E protein controls the responsibility of various factors and antigen receptor-associated genes that promote Ig and TCR rearrangement coordinate cellular growth and survival via TCR signalling. In this research, I applied a computational technique for the genome-wide examination of bHLH TFs in two different organisms. This application can adapt purpose to gain current knowledge of particular TFs in the genome. My observation suggested E proteins, tissue-specific bHLH domain, and antagonists in two organisms. In light of E2A and other components elicit classical molecular mechanisms that reckon B & T- cells development. Therefore, I documented the results of E2A also illustrated the functional mechanism involved in E protein, ID2/ID3, and tissue-specific bHLH TFs in the *mammal*. In some conditions, the combined functions of E2A, E2-2, HEB, ID1-ID3, and other molecular interactions lead to tumour suppressor activity in tumour biology.

Highlights

- E2A and antagonist ID genes correlated in B & T cells development.
- E2A, ID2, RB, and MYC genes serve as cell cycle regulation.
- E2A and HEB genes lead to the development of CNS.
- E2A, SCL, and TAL1 genes regulate blood vessel development.
- E2A and other TFs leads to the improvement of B and T-ALL.

Introduction

The immune process builds on the B & T cells and myeloid lineage cells (macrophages, NK cells, granulocytes, and DCs). These defensive cells originated from the HSCs initially regulated in the thymus also bone marrow. Maturation of cell lineage appears in lymphatic systems *i.e.* bone marrow, thymus, lymph nodes, tonsils, spleen, and mucous membrane in organisms. The initiation of tissues or organs suggested the propagation of immune response require a phase of cell fate decision established on the equilibrium between diverse proteins plays a significant role during organisms development. Renewal of origin depends on HSC that are powerful and efficient to produce erythroid, myeloid, dendritic, and lymphoid cell lineages. Lymphocyte maturation appears through the CLP that control lineage potential. CLP originates between three variant cells: (a) B cells, (b) T cells and (c) NK cells [1–5]. The lineage commitment and growth of B & T lymphocytes reveal different stages defined by the rearrangement of antigen receptor-associated genes. The gene expression pattern during lymphocyte maturation control by groups of TFs known as the bHLH TFs. Specifically, TCF3 (E2A or E12/E47) play a dominant role during lymphocyte and CNS development. The viability of lymphocytes derives from HSCs via coordinate

functions of numerous factors. The gain or loss of cell surfaces depends on intracellular protein responses to the growth and survival of organisms. Combine functions of the E protein (Class A), tissue-specific (myogenic) bHLH proteins (Class B), and antagonists (ID2/ID3) suggested lymphoid development. TCF3 component of the E proteins family of bHLH TFs recognizes by broad expression pattern and ability to bind DNA. The E2A functions either as homodimers or heterodimers through the function of tissue-specific bHLH proteins (MyoD, NeuroD, MASH, TAL, and MYOG). However, E12 & E47 have distinct biochemical properties like E47 of homodimers bind with high affinity to DNA. The inhibitory residue of E12 controls homodimers from high-stability DNA binding. E2A proteins fold to E-box motifs found in tissue-specific enhancers such as insulin, Ig intronic, 3' enhancers, and muscle-specific creatine kinase [6–15]. E proteins govern the mobility of heterogeneous factors & antigen receptor-associated genes that promote Ig and TCR rearrangement coordinate cellular growth and survival. The bHLH polypeptides of E proteins build on their efficiency to bind with high stability to a palindromic DNA sequence is CANNTG (E box) [2–4]. E box sequence motifs elevate the promoter and enhancer side of the B & T lineage-specific genes. These genes contain enhancers in Ig, TCR α & β loci, promoters of mb-1, λ5, pre-T α, and CD4 are enhancer and silencer components [16–21]. Therefore, Class A execute as the leading regulator of the B & T lymphocyte progression. The B & T-cell lineages commitment suggested E proteins are essential at subsequent stages of maturation. E proteins family (E2A, HEB, and E2-2) share a positive conserved domain called bHLH contain two amphipathic α helices divided by a loop structure. This domain conveys dimerization potentiality between different bHLH TFs [12]. Precisely, the amino-terminal of bHLH is a conserved residue that allows domain dimers to fold to DNA. Yet to bHLH residue, the *mammalian* E proteins share two conserved transcriptional catalytic residues known as (a) AD1 and (b) loop-helix (LH) domains [22–24]. AD1 domain forms an acidic helical residue present in retrograde regulation protein 3 (RTG3 or Rtg3p). RTG3 have R-Box binding site to produce a heterodimeric bHLH/leucine zipper transcriptional complex. The nuclear derivative of RTG3 initiates by rapamycin, a specific inhibiter of rapamycin kinesis [25]. LH residue contains a loop located in a putative amphipathic helical structure conserved among all E proteins. The domain suggests the target molecules with E proteins interact and sustain throughout evolution [26]. A removal of activation residue suggests deletions or structural mutations severely affect the transcriptional capabilities of E proteins [22, 24]. The E2A from E proteins appears by splicing exon encoded for the bHLH domain [4, 27]. But E2-2 and HEB are encoded separately in the E proteins [3, 28]. However, ubiquitous E proteins cannot express clearly, but secure E protein complexes are limited to specific cells [13, 20, 29–31]. In some conditions, the balance of E protein activity appears through the loop of ID1-ID4 proteins [32]. ID family (ID1-ID4) of TFs have to lack initial domains and cannot fold to DNA [33]. Inhibitor differentiation (ID) is powerful for heterodimerization with E protein and virtually conducts as a dominant-negative bHLH domain. E proteins inhibitor depends on ID proteins, a non-DNA binding partner of all E proteins. The *mammalian* ID1-ID4 proteins examine earlier in the genome [33–39]. Generally, functional mechanisms of ID2/ID3 are vital during B & T lymphocytes development [40, 41]. Since the ID1-ID4 acts as a dominant-negative bHLH domain. So fractions of E proteins to ID proteins ultimately govern the symmetry of novel proteins. Those studies promote that bHLH TFs are the unique regulator of organism development. In this work, I would like to address the molecular immunologic mechanisms associated with the E2A gene during B & T

lymphocytes development. In contrast, E proteins, ID2/ID3, and other bHLH TFs evoke tumour suppressor strategy in cancer biology.

Results

Structural analysis: The primary structure determines the composition of nucleotides and peptides. The target structure arranges by 1965 nucleotides and 654 peptides with 54 peptides tied to DNA (**Table 1**). A three dimensional (3D) structure stated that the 54 polypeptides make a bHLH residue recognized by two alpha-helix linked through a loop. The variability of the loop allows dimerization through folding and filling in the case of other helices. Those amphipathic alpha-helices have separated by a linker region of length (**Fig. 1a**). The Ramachandran diagram (φ, ψ plot) describe the polypeptides localised in parallel and anti-parallel beta sheets (**Fig. 1b**).

Genome-wide analysis: The genome-wide analysis of both organisms by the HMMER algorithm obtained 72, 59 of the bHLH domain in *Homo sapiens* and *Mus musculus*, respectively (**Table 2 and Table 4**). Standalone BLAST2 output represents 95, 72 homologs of inhibitor differentiation genes in *Homo sapiens* and *Mus musculus*, respectively (**Table 2**). The gene ontology annotation confirmed sequence accuracy 6, 11 of E2A, 7, 7 of HEB, and 32, 23 of E2-2 in Homo sapiens and Mus musculus, respectively (Table 3 and 5). Classification of the bHLH domain suggested the E proteins (E2A, HEB, and E2-2), tissue-specific bHLH proteins (MyoD, NeuroD, MASH, TAL, and MYOG), and antagonist (ID1, ID2, ID3, and ID4) (**Table 4**).

Domain, motifs and phylogeny analysis: The highest hits of E2A (target gene) listed from both organisms for sequence aligning, MSA results demonstrated conserved bHLH domain. The high consensus (90%) confirmed the extended bHLH residue (**Fig. 2**) and their specific motifs (**Fig. 3**). Further observation of the HEB, E2-2 and ID2/ID3 (negative regulator) domains concluded that the E proteins and their antagonist conserved through evolution. The experiment of the phylogenetic tree suggested the molecular evolutionary relationship of the E proteins (E2A, HEB, and E2-2) and antagonist (ID2/ID3) in-between *Homo sapiens* and *Mus musculus* (**Fig. 4**).

Chromosome location, gene network, gene expression, and pathways analysis: A chromosome location study confirmed that the E2A located band 19p13.3 Started at 1,609,290 bp and, end 1,652,615 bp in humans (Fig. 5). The gene network study determined that the E2A (TCF3) interacts with other molecules such as TCF4, TAL1, MYOD1, MYOG, NEUROD1, MYF6, CREBBP, EP30, LDB1, and LMO2. Those molecular interactions govern the outcome of the E2A gene in particular cells (**Fig. 6**). The disease state study in humans suggested the E2A gene expressed in the neoplasm of lymphoid, hematopoietic tissue, lymphoblastic leukaemia, and acute lymphoid leukaemia (**Fig. 7 and Table 6**). The pathways study exposed that the E2A gene regulates stem cells. Also, maintain the strategy of cells through other molecular signals (**Fig. 8**). Therefore, the TF's data analysis concluded the bHLH domains, E proteins, tissue-specific proteins, and antagonists. The target gene analysis documented the composition of

nucleotides, peptides, structure, domain, motifs, phylogeny, chromosome location, gene network & expression, and pathway in isolated organisms.

Discussion

The maturation of B & T cells depends on activations of lineage-specific genes that propose antigen receptor rearrangements to coordinate the proliferation and survival of organisms. An examination of novel targets of histocompatibility complex in the genome suggested the E proteins reveal cell viability and development. A computational genomics study suggested E2A and other TFs promotes lymphocyte and CNS development. The B lymphocyte growth depends on several gene expression programs and environmental threads. But, gene functions included Ig associated elements of BCR such as Igα, Igβ, VpreB, and λ5. A variation of recombination machinery like RAG1 and RAG2 was also reported earlier [42, 43]. The study of TFs suggested E2A, EBF, and PAX5 regulate a glimpse of B lineage-specific factors [44–47]. Also, B-cell initiated genes like CD19, mb-1, germline IgH transcript play a significant role during development. E2A, PAX5, and EBF sustain the function of genes that promote B lymphocyte growth [21, 48–52]. E2A-deficient suggested barrier in B lineage growth at cycle before the threshold of IgH DJ rearrangement. Early B lineage-specific transcriptions of Igα, RAG1, Iμ, and PAX5 have lack E2A mutants in cells that have not affected myeloid maturation. A phenotype characteristic suggested the expression of the ID family, an inhibitor of E protein movement [53]. These interruptions in B cell progression also their severity builds on the impression level of targets associated genes. ID3 generates an analogous function for E protein in lymphopoiesis [54]. In E proteins, E2-2/HEB plays a preface in B lymphocyte maturation. HEB/E2-2 generate B lymphocytes and contains a few pro-B cells in the organ. The heterozygous for two E proteins promote pro-B cells more than the heterozygous for the remaining E proteins [55]. So, the renewal of E2A allows B lymphocyte growth to various degrees. The responses of E12/E47 enhance B lineage maturation. Furthermore, HEB initiates into an E2A locus to recover B lineage growth [56, 57]. Therefore, a degree of E protein moderator of B cells growth. Also, absences of the EBF factor in the B cells barrier are similar to E2A-deficient. E2A/EBF interacts to enhance B lineage maturation revealing the B cell phenotype as heterozygous. However, the rate of VpreB in heterozygous similar to pro-B lymphocytes indicates synergy with E2A/EBF is not a degree of expression but at the balance of cellular growth and survival [58]. In addition, EBF/E2A promotes B lineage growth, a unique regulator of PAX5 within B cells commitment. PAX5-deficient arrest in pro-B cell state after IgH DJ rearrangement. Thus, the defect of PAX5 drive to a barrier in B cells maturation is similar to E2A/EBF deficiency. Also, pro-B lineage cells suggested PAX5-deficient manifests of non-B lineages genes like GATA-1, pre-Tα, and macrophage stimulating factors. Therefore, PAX5 leads to an oath of B cell lineage via the function of genes coordinated with alternative hematopoietic lineages [47, 59, 60]. Since the E2A defect suggested a lack of B lymphocytes, also other transcriptional strategies propose the targets of E2A initiation in B lineage commitment. The mobility of E47 in NIH3T3 cells help the adoption of Ig and B cell-associated factors like TDT and RAG1 [61]. Additionally, E12 in macrophage cells (70Z/3) hold a rearrangement of Igk and IgH associated genes but lack IgM. Those mechanisms are limited to activating B lineage-associated genes like RAG1, λ5, EBF, and PAX5. The EBF in macrophage cells (70Z/3)

suggested the activity of E2A-induced genes of λ5 and PAX5. Those data illustrated E2A govern the targets of PAX5 through EBF. Consistent with the mechanisms suggested that the promoters of PAX5 hold functional EBF binding sites [49]. Those data also propose E2A/EBF synergize to initiate target associated genes. The genesis of E47/EBF in mast cells demonstrated F3/BA stimulate transcription of VpreB also λ5 genes [62]. The pioneer of λ5 suggested E47 and EBF binding sites through the transcription λ5 gene. These data propose E2A and EBF reveal lineage commitment and promote B lineage to raise the function of linage specific genes correlated with the cellular process [63]. The transition from pro-B to pre-B cell position basis on surface expressions that functionally rearrange the IgH chain. Link of IgH chains with substitute light chains in synchronism with signalling components of Igα even Igβ constitutes pre-BCR. Pre-BCR signalling in a transient burst of proliferation and allelic inhibition of IgH chain allowed by the initiation of IgL chain associated gene rearrangement [64–66]. B cells define the IgH chain and activity of the RAG1/RAG2 barrier at the pro-B cell state [67–69]. Likely, B cell growth may be insufficient for λ5, an element of the delegate light chain that fails to rise effectively to the pre-B lymphocyte position [70, 71]. Signalling in pro-B cells negotiate through Igα, Igβ, or activated form of RAS is efficient to enhance the growth of the pre-B cell stage [72–74]. Targets of pre-BCR remain controversial, but they need to include E proteins. Moreover, E2A proteins require during IL-7-dependent stretch for the viability of pro-B cells [75]. During cell survival, E2A proteins closely engage with function also a rearrangement of IgL and IgH chain associated genes. Yet, it is necessary to discuss the RAG1/RAG2 control by E2A [51, 59]. The E2A can enhance IgH/IgL chain-linked gene rearrangement in various cell categories. E47 in pre-T cell effect preface of IgH D to J rearrangement associated with Iμ germline transcripts [76]. Furthermore, E47 to RAG1/RAG2 in embryonic cell lines promotes IgH DJ and Igk VJ rearrangements. Rearrangements of Igk locus predominantly conduct Vk1 family segments, which contain a conserved E box in their promoter regions. Ig rearrangements in the origin of B cells have separate V segments and coding joints. These studies propose that E2A reveals a key component in Igk and IgH recombination [77]. Those rearrangements sequential and functional regulators act with E2A to enhance permissive rearrangement of IgL and IgH associated genes. Invariance, EBF to enhance the IgH DJ joining, but not Vk-J joining. Additionally, E protein differentially regulates in pro-B versus pre-B cells. Also, the analogous degree of E protein in pro-B and pre-B cells governs whether E protein regulates by signals of pre-BCR similar to TCR-initiated signalling [78]. Antigen engagement ingrown B cell receptors initiate B cell function characterized by cell cycle entry and adjustment of surface markers. The effective B cells receive co-stimulatory T cell-derived signals that differentiate low-affinity plasma cells or migrate to shape germinal centres. They tolerate affinity and immunoglobulin isotype switching through high-affinity antibody-secreting effector cells and MBS [79–82]. In the organ system, E2A present an optimal but detect ratio in naive B cells. In contrast, E2A function is high in B lymphocytes and appears in the germinal centres. Inactivation of B cells process via co-stimulation with T lymphocyte, antigen, and different mitogenic impulses by a ratio of E2A. Thus, the preface of E2A is a landmark of B lymphocyte maturation [83, 84]. Indifference, antagonist ID3 rapidly induces in BCR engagement suggested cell cycle process. Also, ID3-deficient demonstrated a proliferation in reaction to anti-IgM stimulus. The dimension of ID3 enters before E2A transcription. ID3 regulates antigen-induced differentiation remains controversial, but it is plausible that ID3 functions regulate by the dynamism of E proteins [83, 85, 86]. In

a stage of the pro-B cell, lack of E2A in peripheral suggested B cells does not restrain proliferation and viability [83]. However, B cells do not sustain isotype switching to appropriate stimuli during the omission of E2A function. Likely, the activity of ID1 in B cells supported the isotype inhabiting with IgA surface. The lack of E2A activities is a barrier to switching at a domain of genomic recombination since the switch residue of the germline is affected by the shortness of chromatin availability. Rather, E2A require elements of switch recombinase machinery [83, 84]. During T-cells maturation, the growth of T lymphocytes differentiates by rearrangement of TCR loci and activity of CD4 also CD8 co-receptors. T cell source in the thymus is present within CD4/CD8 double-negative cells. These immune cells distinguish CD44 + and CD25- reveal mature NK and T lineage cells. So, the T lymphocyte lineage coordinates with CD25 by genetic rearrangements at TCR γ, TCR δ, and TCR β loci. TCR β associated gene assumes the responsibility of a pre-TCR depth involved with pre-Tα, TCR β chain, and CD3 by a group of signalling molecules. Signal mediates by the pre-TCR complex during growth progression concern as a β selection. The above transitional mechanisms characterize by gene rearrangement, initiation of cellular expansion, and growth of CD4/CD8 double-positive cells. The double-positive cells remove from the cell cycle also begins TCR α rearrangement. The α β TCR assume DP cells to MHC-initiate + ve or -ve selection. Therefore, a DP cell regulates CD4/CD8 function at SP cells growth of T lineage lymphocytes [87–90]. NK and T lineage cells develop from a bipotent T/NK precursor cell. A recent study demonstrated the nature of bHLH proteins in NK and T lineage commitment. So, ID2 deficiency exposes a barrier in LGL at the T/NK precursor cell, but α β T cell growth is natural. E2A-deficient shown appreciative phenotypes differentiate by the barrier in the T cell growth but normal LGL. Similarly, the ID3 antagonist of E2A in precursor T/NK or progenitor T cells barrier T lineage growth also do not LGL maturation. Those studies reveal the nature of E2A/ID2 likely regulates NK versus T cell lineage decision. A dominance of CD44 + and CD25- (DN1) cells not committed to T cell lineage and expresses a low degree of E47. The transition of CD44 + even CD25+ (DN2) closely correlates with a bias towards T cell growth [31, 91–96]. Interestingly, the response of E47 in γ δ and α β T lineage lymphocytes examine earlier. Also, E47 induces at the DN2 cells state. In addition, γ δ T lymphocytes from α β T lineage act at a high ratio of E47. The E47 remain high during DN cells maturation upon pre-TCR mediate signalling via the DNA-binding domain. With a compression of double negative cells, DP cells express the rate of E47 during the process from DP to SP cells. So, the gradient E47 is existent during thymocyte maturation. E47 ratio is elevated in double-negative cells and optimum in SP cells [97]. Constant with a specimen of E47 in thymocytes revealed a reduction of E2A function in both α β and γ δ T lymphocyte lineages. During E2A-deficient, not only are γ δ T lymphocyte elements decreased also mortal regulation of TCR γ and δ recombination is affected. E2A requires repressing fetal-initiate γ and δ rearrangements in thymocytes through rearrangements of appropriate V segments. Moreover, E2A/HEB juxtaposition with RAG1/RAG2 can induce γ δ TCR rearrangements in the embryo [98–100]. Thymocyte maturation blocks through one double negative to two double negative cells stages. The double negative cells transition for α β T cell growth builds through a rearrangement of the TCR β locus. Additionally, the act of RAG recombination by E2A suggests the E protein through a dominant-negative appearance of HEB/ID1 in V β to DJ β rearrangements. These data propose that the E protein response is fundamental for efficient progression toward T cells lineage and V (D) J recombination during T lymphocyte maturation [31, 101, 102]. Proper

rearrangement of pre-Tα, TCR β chain/locus and CD3 subunits made a pre-TCR complex. Complex molecular signalling is fundamental for thymocytes and maturation DN to DP cells stages by β selection. In contrast, the HEB reveal the response of pre-Tα and HEB-deficient of SCL/LMO. The pre-T lymphocyte with ID3 suggests repression of the pre-Tα and analogous block. Also, E2A activity regulates β selection. Genomic studies rewarded the E47 deficiency enhances DN cells to the DP cell stage during the absence of the TCR β chain. The pre-TCR signalling promotes progression by repress of E2A. Glacial with E47 function high in DN cells growth. However, pre-TCR-mediates signalling suggested E47 of DNA binding response downregulated. In combination, ID3 increase upon pre-TCR-mediated signalling in double-negative cells by a pathway basis on the ERK/MAPK cascade. These data suggested the molecular immunologic evidence of E protein by pre-TCR signalling to promote β selection [96, 97, 103, 104]. Once the DN cells pass β sorting, CD8 regulates through ISP cells by the DP cells state. Also, HEB-deficient explores ISP cells to a barrier in the DP state. HEB activity during the above transition remains clarified by the CD4 [20, 105]. In the DP cells, thymocytes mediate TCR α rearrangement. During α β TCR initiation, DP cells connect with peptide-MHC complexes to sustain assortment. DP cells receive appropriate signals by TCR through + ve selection. In contrast, the cells express a TCR with high stability for self-peptide-MHC complexes exploring a -ve selection. Failure to receive a TCR mediates signal outcome death [106–108]. E2A-deficient decreases the ratio of DP cells and elevates the rate of SP cells toward CD8 SP cells. The negative rate of DP cells is a part to decrease survival. Massive apoptosis in the thymocytes process via ID1 by E2A/HEB inhibitors. In-variation, functions of MHC class I and class II mediate + ve selection in E2A. In particular, E47-deficient of H-Y TCR attacks the rate of CD8 SP cells in the thymus and peripheral. The stimulation of sorting to CD8 SP cells appear in heterozygous for E47. Thus, the set of CD8 lineages emerges subtly to E protein. The E47 deficiency barrier in TCR β rearrangement not only progress to the DP state also the growth of CD8 SP cells detect. Interestingly, the lack of CD4 SP cells reveals a loss of E2A to govern CD8 SP cells, whereas extra signals enter for the maturation of CD4 lineage. However, it requires deriving the result of + ve sorting in T lymphocytes. These data propose the preface of E2A in thymocytes [31, 97, 101, 109]. Also, ID3 interacts with E2A and explore a thymic phenotype. But, the insufficiency of E2A/ID3 exposes a thymic phenotype deficiency. The thymic cellularity of ID3-deficient decreases the value of CD4/CD8 SP cells in the thymus and spleen. The AND even H-Y TCR suggested MHC class I/II-restricted positive selection that inhibits during ID3-deficient. In particular, CD4 + ve selection of AND TCR block by the absence of ID3. Moreover, the ID3 on + ve sorting is latent to T lymphocytes [41, 109]. Also, the preface of ID3 during the -ve selection process appears. Thymocytes from H-Y TCR recognize a specific antigen. The shortage of ID3 in thymic cellularity considers DP thymocytes and increases the rate of CD4 SP cells in the spleen. In contrast, super-antigen appears natural through ID3 in the MHC class II and class I. The -ve selection in H-Y TCR suggested ID3-deficient is not congenital to T cell lineage [41]. Thymocytes express a dominant-negative formation of MAPKK1 from the DN cells to DP cells phase in the thymic organ. Besides, lack of RAS activity or effects of MEK1/ERK1 exposes defective thymocyte maturation at the DP cells to SP cells transition is blocked by ID3-deficient. The immunologic suggested E proteins appear to function at these checkpoints. The postulation of TCR-mediated signals promotes development through the E protein of DNA binding. Those signals mediate by pre-TCR and α β TCR act to E2A/HEB activity. In addition, the ID3 replication to CD3

initiated signals appears at both DN also DP cells stages [41, 97, 110–113]. It is mandatory to determine asymmetrical levels of E47/ID3 in future. Furthermore, a dominant-negative state of RAS does not comprise ID3 in reaction to TCR cross-linking. Inhibition of the C-RAF molecule blocks the origination of ID3 in a dose-based manner. Signalling molecules indicates that ID3 govern by the ERK/MAPK cascade through the EGR-1 factor [113]. More investigation is indeed to observe bias toward CD8 lineage during lack of E2A conceive a preface of E proteins in CD4 against CD8 lineage response. Thus, it is conceivable that strong signals made by the ERK/MAP kinase pathway lead to improve levels of ID3 for CD4 lineage commitment, whereas a weak signal affects CD8 maturation. It is interesting to govern the allied degree of E2A, HEB, and ID3 to examine their ratios during cell fate [41, 113, 114]. In estimation to RAS-ERK/MAP kinase pathway, inhibitor differentiation (ID) expression regulates by the component of the TGFβ family. In contrast, B lymphocyte progenitors (BLP) of TGFβ induce cell cycle growth through transient initiation of ID3. The ectopic function of ID3 is sufficient for growth. But ID3-deficient of BLPs response decrease to TGFβ signalling. In DP cells, the machinery of ID3 initiation of TGFβ seems to involve by process of SMAD and not the RAS-ERK module [75, 115]. Also, TGFβ influence cell cycle regulation through signalling molecules like cyclin-dependent kinase inhibitors p21Cip, p27Kip, and p15INK4a, and inhibition of C-MYC [116–119]. Neumour's study suggested cytokine inhibits lymphocyte growth, survival, and differentiation via the response of E protein inhibitors. So, a TGF-β related bone morphogenic protein 4 (BMP-4) can induce antagonist ID2 and ID3 in embryonic cells (For example, BMP4 have to activate ID2/ID3). The above mechanisms indicate the E protein response is a feature of TGF-β related proteins. In addition to E2A in lymphocytes, TGF-β1 modulates the activity of several transcription factors. Thus, signalling utilizes to govern E protein function by expression of inhibitor differentiation (ID). In addition, in the B cell line, the TGF-β1 and WEHI 231 generate a decreased response in AP-1 mediated DNA-binding and initiate IκBα function to inhibit the response of NF-κB. TGF-β1 causes a collapse in C-MYC associated cells' foundation on the signal of NF-κB. The NF-κB initiated complex is likely a target of TGF-β1 in primary BLPs. However, the mobility of the TGF-β1 response needs further investigation. TGF-β1 inhibits GATA-3 function in T helper (Th) cells and inhibits TH2 cell growth. Therefore, rapid inhibitions of E2A activity by the process of TGF-β1 control lymphocyte differentiation, growth, and survival [120–124]. Recent data propose the preface of C-MYC control ID2. An enforcement function of N-MYC or C-MYC induces by ID2 response. It logically assumes that the MYC initiated ID2 leads to the control of RB that drive cellular proliferation and cell cycle regulation [125]. It is plausible that an expanded rate of ID2 levels promotes cellular transformation through the E protein activity. Also, recent data implicated the NOTCH-mediated signalling in a decision between B & T lineage determination. In some conditions, lack of NOTCH1 signals blocks at progenitor T cells stage. Conversely, the fundamental form of NOTCH shares many phenotypes E2A-deficient such as B cell maturation block before the threshold of Ig gene rearrangements, T cell lymphomas exhibits with similar kinetics, and malformation in α β and γ δ cell lineages. These observations led to E2A activity control by the NOTCH signalling pathway. Also, an initiated formation of NOTCH represses E2A function in temporal transfection assays. Further studies will require determining the E2A and NOTCH act parallel in a pathway [126–129]. In cancer biology, E2A implicates cellular proliferation and apoptosis. Nemours data reveal the high or low volume of E2A activity promotes rapid cell death. So, the lymphocytes can persist within a ratio of E2A. The deficiency of

E2A develops T cell lymphoma. But, ectopic functions of antagonist ID1/ID2 promote lymphomagenesis [31, 101]. Renewal of E2A function in cells attained from E2A-deficient lymphoma governs apoptosis. Likewise, the ectopic function of E47 in T-ALL suggested a barrier in the cellular process and PCD. These are data-driven to the defence of the E2A gene as a tumour suppressor. Also, the deactivation of E2A governs the progress of T-ALL [130, 131]. Furthermore, the genetic deficiency associated with T-ALL build on the TAL1 and TAL2 of TFs. The TAL1 and TAL2 made heterodimers with E2A in myeloid and erythroid cells [132, 133]. Both genes activate also expressed in the thymus upon chromosomal translocation leads to the development of T-ALL. The TAL1/TAL2 gene products form heterodimers with E47, a bHLH domain potentially transactivator. These data indicate that the E47 homodimers cannot activate in the response of TAL1 or TAL2. Therefore, the possibility of E2A inactivation contributes to the growth of T-ALL. Indifference in T-ALL, the LYL1 encodes bHLH TFs is not expressed in the thymus but transcriptionally activates depending on translocation to the TCR β locus. LYL1 is linked with E2A to form a heterodimer that binds to the E47 homodimer. Thus, LYL1 functions as a dominant-negative mutant to prevent the E2A-responsive genes. Those studies suggested the E2A gene products in T-ALL that contribute to the growth of lymphomas [134, 135]. Furthermore, SCL/TAL1 is robust for blood cell development [136, 137]. SCL is elevated in multipotent erythroid progenitors and differentiates in all lineages. SCL build heterodimers via E protein and oligomeric complex. Both are activators or repressors of E proteins associated targets in the cellular process [138–140]. Also, SCL interacts with LMO1/LMO2 to generate T-ALL. The encoding LMO1/LMO2 targeted chromosomal translocations in T-ALL. The SCL cooperate with LMO1 to enhance a partial T-cell differentiation barrier in the pre-leukemic phase due to low pTα expression, a vital and novel target of E2A or HEB in the thymus [141–146]. Interestingly, E2A control lethality even survives any sex and develops T-cell leukaemia. In combination, the ID1 antagonist of the E2A response appears in the cells and develops leukaemia. These observations suggested the response of E2A for T-cell variation. Besides, E2A and TAL1 exhibit expression patterns during the deficiency of SCL activity at the stage of B-cell growth. The dimension of SCL appears through SIL-SCL during the omission of the E2A allele. The essentiality of bHLH domain in B-cells maturation at commitment stages of pro-B to pre-B cells state. The switch of IgM + cells reveals E2A during the cellular process and the growth of B lymphocytes [48]. E2A play a significant role in childhood pro-B/pre-B cell leukaemia by chromosomal translocations. The anti-proliferative activity of E2A in B-ALL correlated with chromosome translocation of t (1; 19) and t (17; 19) disrupts the E2A allele that accord to leukemogenesis fusion proteins [48]. The chromosome translocation t (1; 19) of 50 portions of E2A integrates into the homeodomain-containing region of the PBX1 gene [147]. This translocation event suggested the response of a chimeric E2A-PBX fusion protein. In the pro-B cell, leukaemia contains a chromosome translocation t (17; 19) demonstrated the E2A gene dissolve to HLF, a gene encoded by bZIP protein [148]. The exact machinery in translocations that cause leukaemia is not explicit yet. It establishes that the targets of E2A to variable loci by DNA-binding domain correlated with cellular growth also survival and leads to cellular regeneration. However, these translocations successfully control the ratio of E2A in the genome. Yet, it is necessary to prove the reduction of E2A functions for the transformation of B cells progenitors through E2A in the T cells. Various signalling molecules like LCK (p56Lck), TPL2 (COT), MAP2K1 (MEK1), and RAS implicated the lymphoma [147–151]. The signal of LCK in mature thymocytes reveals the rapid

growth of tumours. So, oncogenic TPL2 is a serine kinase that can phosphorylate MEK1 [152, 153]. Interestingly, the formation of RAS and inhibitor differentiation (ID) detect in cancers. It is sensible of the function of inhibitor differentiation (ID) in T cells lymphoma. It is necessary to determine malignancies that occupy RAS become transformed induction of inhibitor differentiation expression [154–156]. Therefore, a unique target insight into the E proteins, ID proteins, and other proteins lead to cellular proliferation and survival.

Materials And Methods

Target Sequence and Database

The query sequence retrieves from the different specific databases (UniProt, KEGG, GenBank, EMBL, DDBJ and NCBI) and performs web-based application SMART for observation of the particular residue in the suspected sequence (query sequence). SWISS-MODEL performs for the prediction of three-dimensional protein structures. It is a bioinformatics web-server for remodelling the structure of proteins. This method generates molecular structure and utilizes it in many practical applications. The SWISS-MODEL is an updated database of remodelling of organism proteome for medical research.

Genome

Two organisms' genome sequences download from various exclusive databases (Ensemble and NCBI).

Standalone Tools

The HMMER algorithm executed by MSA of the target residue as a profile search. HMMER is a statistical algorithm built by MSA of the suspected region for profile search. Is implemented probabilistic model is generally known as the profile HMM. Standalone BLAST2 executed for homologs gene in two different organisms.

Gene Annotation

The BLAST2GO initialized for GO annotation. BLAST2GO is a computational and bioinformatics application for high-throughput GO annotation of particular sequences. The functional property of genes rectified via GO (Gene Ontology) annotation is a popular tool for practical work.

Domain

For observation of the conserved residue in the target sequence, we perform the MSA method to calculate unique tests of the homologs also streak them up, so we can observe the identity, differences and similarities. MSA of highest hits sequences analysis conducted through web-based application MultAlin for examination of sustain domain.

Motifs

MEME suite application performs for the resolution of sequence motifs is a bioinformatics web-based tool for analysis and discovery of the specific motifs.

Phylogeny

For experimentation with the molecular evolutionary relationship of the particular gene in both organisms, we can perform MEGA-X for constructing a phylogenetic tree using Neighbor-Joining Methods.

Gene expression

The gene expression analysis can carry out by GENEVESTIGATOR. GENEVESTIGATOR is an excessive-performance search engine for gene expression of different organisms. That application performs to determine and validate novel targets.

Chromosome location

The chromosome location retrieves using a web-based application is well-known as a gene card. The gene card database provides information on all known and predicted genes. This database is currently available for biomedical research like predictions of genes, encoded proteins and associated diseases.

Gene networks

The genetic matrix (gene network) is a group of molecules that regulates and interacts with one another in the cells to control the expression volume of mRNA or proteins. Many proteins obey to activate genes are TFs that bind to the pioneer area and initiate the function of other proteins called regulatory cascades. We can retrieve the STRING database for the prediction of protein-protein interaction. STRING database contains various resources like experimental data and computational prediction of proteins and nucleic acids.

Pathways

The pathways analysis (PA) is generally known as functional enrichment analysis. PA is a widely accessible application for biological research in the domain of Molecular Biology, Life Science, Biotechnology, and Bioinformatics. PA application helps an examination of the biological preface of candidate genes to design and develop therapies. The KEGG database is accessible to retrieve and intellect the high-level function and utilities of biological molecules such as gene and proteins signal in a cellular process.

Abbreviation

CLP**:** Common lymphoid progenitor

TF’s: Transcription Factors

CNS: Central Nervous System

PNS: Peripheral Nervous System

p53: Tumor Protein P53

TCF3: Transcription factor 3 (E2A immunoglobulin enhancer-binding factors E12/E47)

DNA: Deoxyribonucleic acid

BAX: Bcl-2-associated X protein

Bcl-2: B-cell lymphoma 2

BLAST: Basic Local Alignment Search Tools

HMM: Hidden Markov Model

MAG: myelin-associated glycoprotein

GO: Gene Ontology

MSA: Multiple Sequence Alignment

CDKIs: Cyclin-dependent kinase inhibitor (p15, p16, p18, p19, p21, p27, and p57)

UB: Ubiquitin

CDC16: Cell division cycle 16

CDC23: Cell division cycle 23

CDC27: Cell division cycle 27

D-box: Destruction-box

FGFR1: Fibroblast growth factor receptor-1

MMP2: Metalloproteinase 2

TSP-1: thrombospondin-1

VEGF: vascular endothelial growth factor

BMP: Basic metabolic panel

BCL-XL: B-cell lymphoma-extra large

ATP: Adenosine triphosphate

TNF: Tumor necrosis factor

IL-6: Interleukin 6

IL-3: Interleukin 3

APC/C: anaphase promoting complex/cyclosome

APC6: anaphase-promoting complex 6

APC8: anaphase-promoting complex 8

APC3: anaphase-promoting complex 3

PAI: Plasminogen activator inhibitor

CSR: Class switch recombination

TCR: T cell receptor

LPS: Lipopolysaccharides

HSCs: Hematopoietic stem cells

GM-CSF: Granulocyte-macrophage colony-stimulating factor

GFI1: Growth factor independent 1

TLRs: Tool like receptors

NS: Nervous System

TECs: Tumor endothelial cells

NSCs: Neural stem cells

TGF-β1: transforming growth factor-beta 1

KEGG: Kyoto Encyclopedia of Genes and Genomes

UniProt: Universal Protein Resource

NCBI: National Center for Biotechnology Information

EMBL: European Molecular Biology Laboratory

DDBJ: DNA Data Bank of Japan

SMART: Simple Modular Architecture Research Tool

STRING: Search Tool for the Retrieval of Interacting Genes/Proteins

mRNA: Messenger RNA

RNA: Ribonucleic acid

NGM: *Neighbor-Joining Methods*

MEGA: Molecular Evolutionary Genetics Analysis

OMPG: Oligodendrocytemyelin glycoprotein

Declarations

The work furnished in this paper is original and communicated by the correspondent addressed in the manuscript. The author disclosed that the documents are not concerned elsewhere and have not been received for evaluation by other journals.

Ethical approval:

The study contains an *in-silico* analysis of the *mammalian* genome examination and validation of the particular gene in different organisms.

Consent for Publication:

Applicable

Availability of data and materials:

The data and materials are available on reasonable request. The corresponding author is ready to submit the data and materials by reasonable request or demand.

Competing of interests:

The author declared that the work has no conflict of interest.

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Author Contributions:

This research paper contains a single author. The author proposed the idea, experimented, analyzed data and prepared the manuscript.

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Tables

Table 1: Target Sequence (Query Sequence)

>E2A

Atgaaccagccgcagaggatggcgcctgtgggcacagacaaggagctcagtgacctcctggacttcagcatgatgttcccgct
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(a) Nucleotide

>E2A

MNQPQRMAPVGTDKELSDLLDFSMMFPLPVTNGKGRPASLAGAQFGGSGLEDRPSSGSW
GSGDQSSSSFDPSRTFSEGTHFTESHSSLSSSTFLGPGLGGKSGERGAYASFGRDAGVGGLT
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SSVYPPSSGEDYGRDATAYPSAKTPSSTYPAPFYVADGSLHPSAELWSPPGQAGFGPMLGG

GSSPLPLPPGSGPVGSSGSSSTFGGLHQHERMGYQLHGAEVNGGLPSASSFSSAPGATYGG

VSSHTPPVSGADSLLGSRGTTAGSSGDALGKALASIYSPDHSSNNFSSSPSTPVGSPQGLAG

TSQWPRAGAPGALSPSYDGGLHGLQSKIEDHLDEAIHVLRSHAVGTAGDMHT

LLPGHGALASGFTGPMSLGGRHAGLVGGSHPEDGLAGSTSLMHNHAALPSQPGTLPDLS

RPPDSYSGLGRAGATAAASEIKREEKEDEENTSAADHSEEEKKELKAPRARTSPDEDEDDL

LPPEQKAEREKERRVANNARERLRVRDINEAFKELGRMCQLHLNSEKPQTKLLILHQAVSV

ILNLEQQVRERNLNPKAACLKRREEEKVSGVVGDPQMVLSAPHPGLSEAHNPAGHM

(b) Peptide

Table 2: Summary of the (a) bHLH domains (b) Homologs, and (c) E2A

Organisms	HMMER	BLAST2	BLAST2GO
Homo sapiens	72	95	6
Mus musculus	59	72	11
Total	**131**	**110**	**17**

Table 3: Summary of the E proteins

Gene	*Homo sapiens*	*Mus musculus*
E2A (TCF3)	6	11
HEB (TCF12)	7	7
E2-2 (TCF4)	32	23
Total	**45**	**41**

Table 4: Classification of the (a) E proteins (b) Tissue-specific bHLH proteins, and (c) Antagonist bHLH TF's

Gene	Classification of bHLH TF's
E2A (TCF3)	E Proteins (Class A)
HEB (TCF12)	E Proteins (Class A)
E2-2 (TCF4)	E Proteins (Class A)
MyoD	Tissue-specific bHLH proteins (Class B)
NeuroD	Tissue-specific bHLH proteins (Class B)
MASH	Tissue-specific bHLH proteins (Class B)
TAL	Tissue-specific bHLH proteins (Class B)
MYOG	Tissue-specific bHLH proteins (Class B)
ID1	Negative regulator (Antagonist)
ID2	Negative regulator (Antagonist)
ID3	Negative regulator (Antagonist)
ID4	Negative regulator (Antagonist)

Table 5: Summary of the Gene Ontology Annotation

(a) Homo sapiens

Gene Id	Gene	Protein
ENSP00000262965.5	E2A	transcription factor E2-alpha isoform
ENSP00000480564.2	E2A	transcription factor E2-alpha isoform
ENSP00000468487.1	E2A	transcription factor E2-alpha isoform
ENSP00000396363.3	E2A	transcription factor E2-alpha isoform
ENSP00000344375.6	E2A	transcription factor E2-alpha isoform
ENSP00000378813.3	E2A	transcription factor E2-alpha isoform

(b) Mus musculus

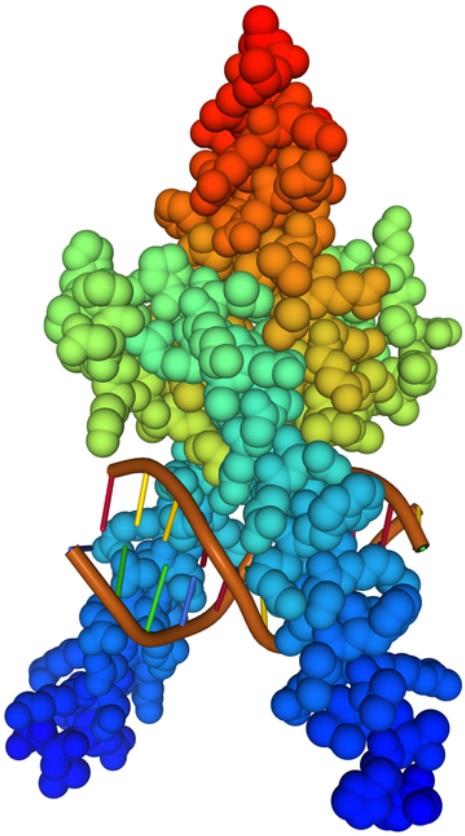
Gene Id	Gene	Protein
ENSMUSP00000100979.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100983.4	E2A	transcription factor E2-alpha isoform
ENSMUSP00000020377.7	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100976.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000020379.7	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100977.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100981.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100982.4	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100980.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000100978.2	E2A	transcription factor E2-alpha isoform
ENSMUSP00000121172.2	E2A	transcription factor E2-alpha isoform

Table 6: E2A gene associated with Human Cancer

Gene	Organisms	Cancer
E2A	*Homo sapiens*	B-ALL
E2A	*Homo sapiens*	T-ALL

Figures

A



B

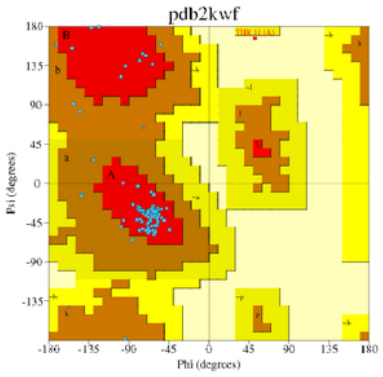


Figure 1

(a) 3D Structure of E2A, (b) Ramachandran Plot

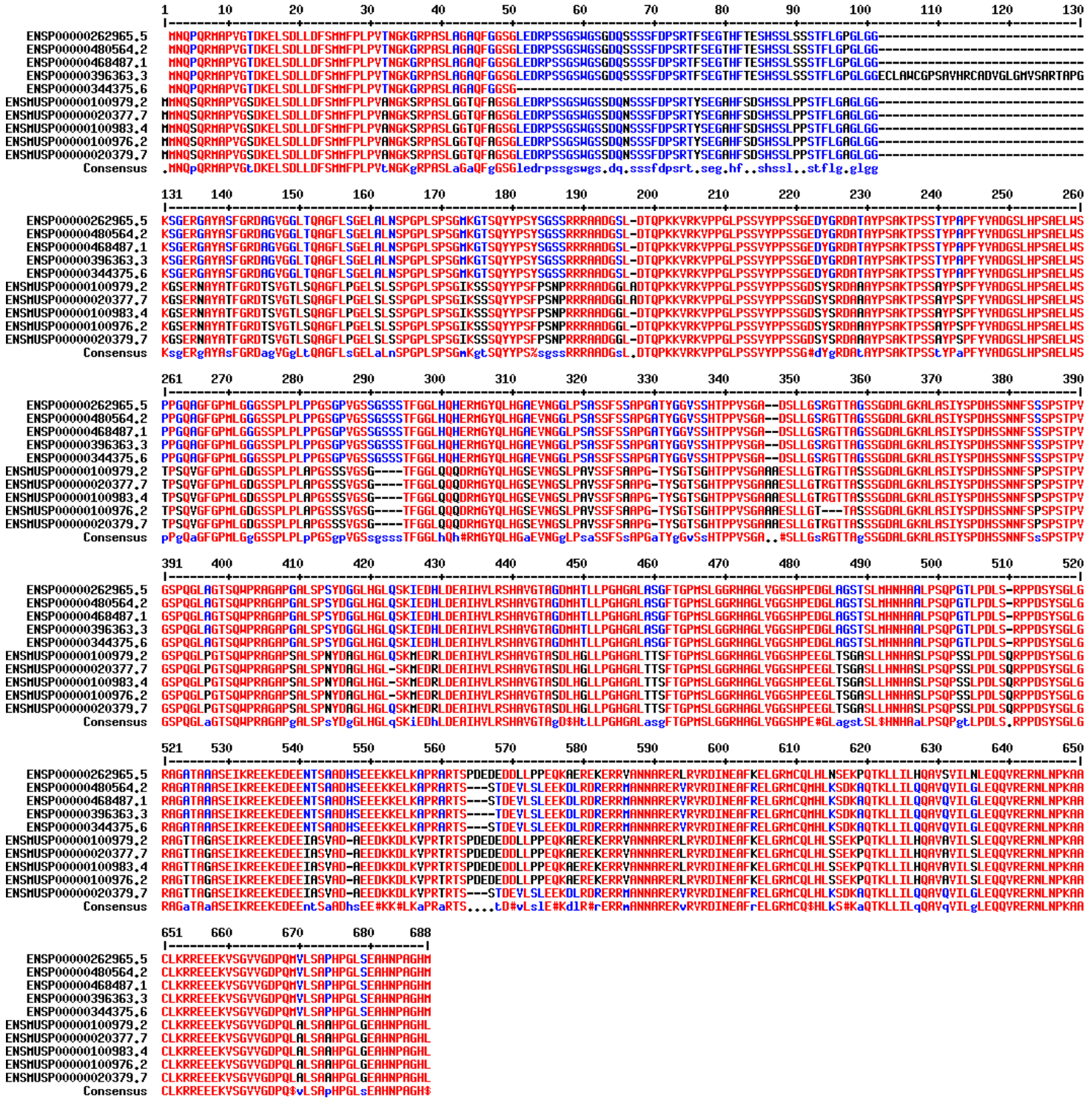


Figure 2

Conserved bHLH domain between two Organisms

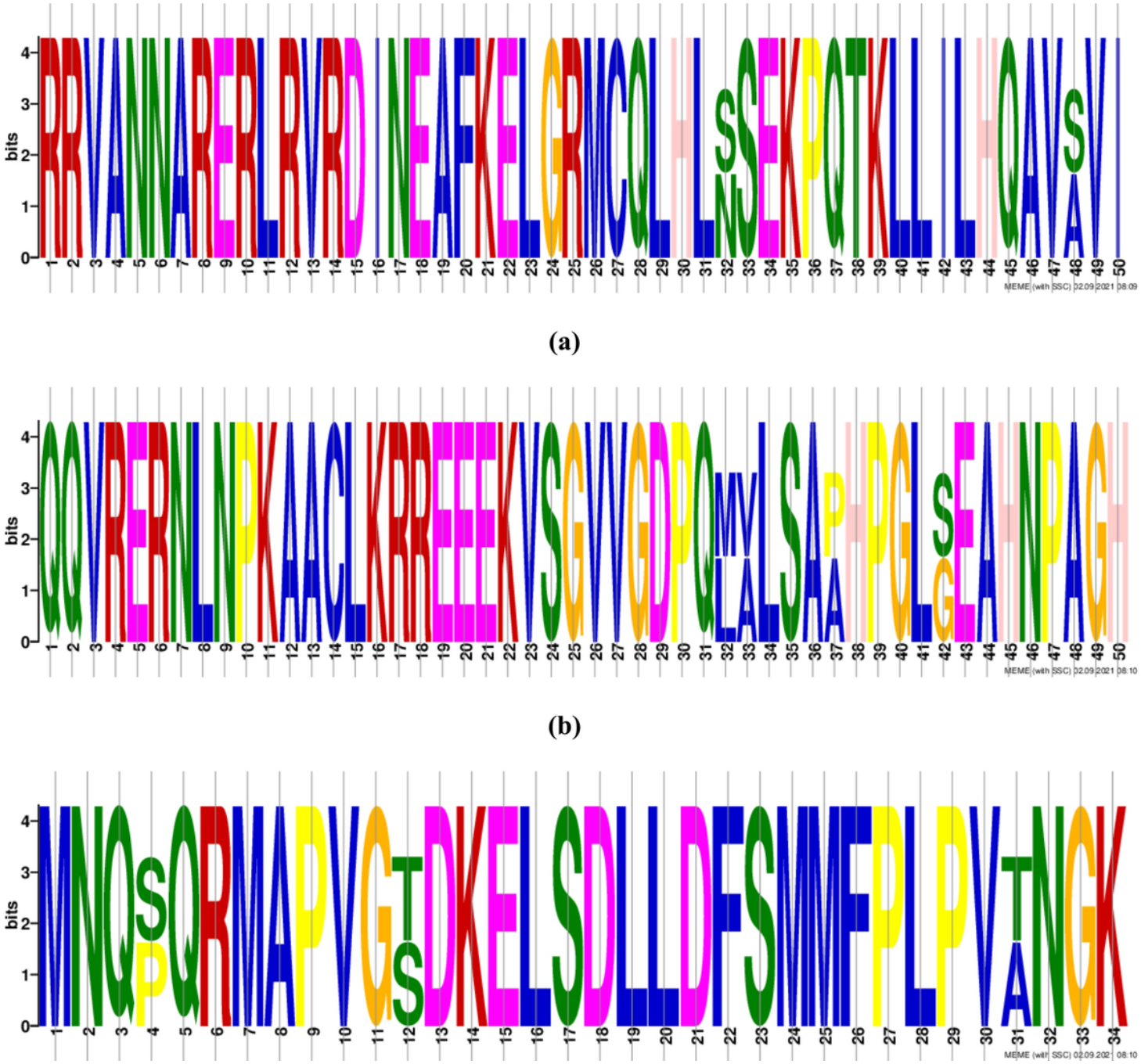


Figure 3

Sequence motifs of E2A (E-box)

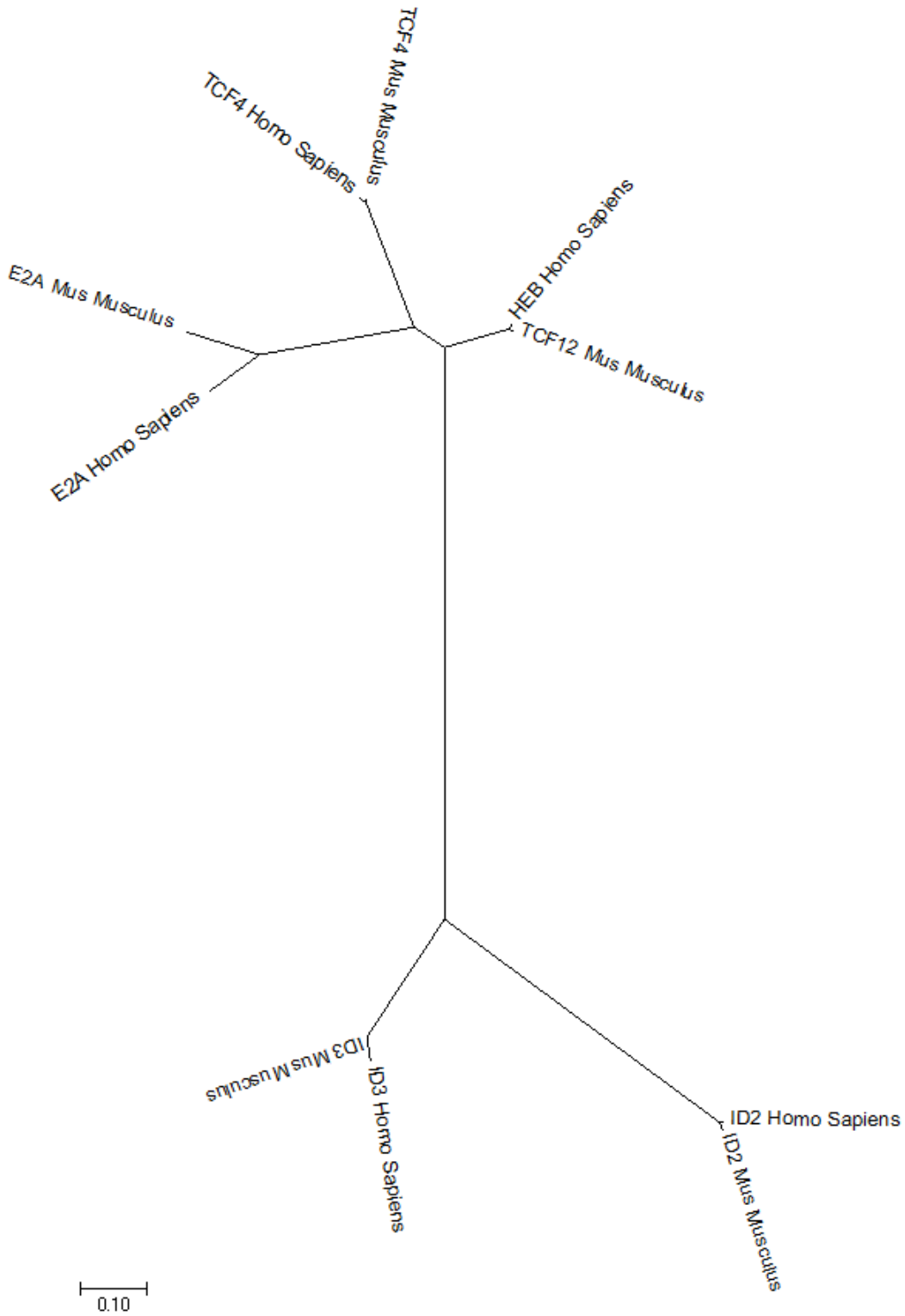
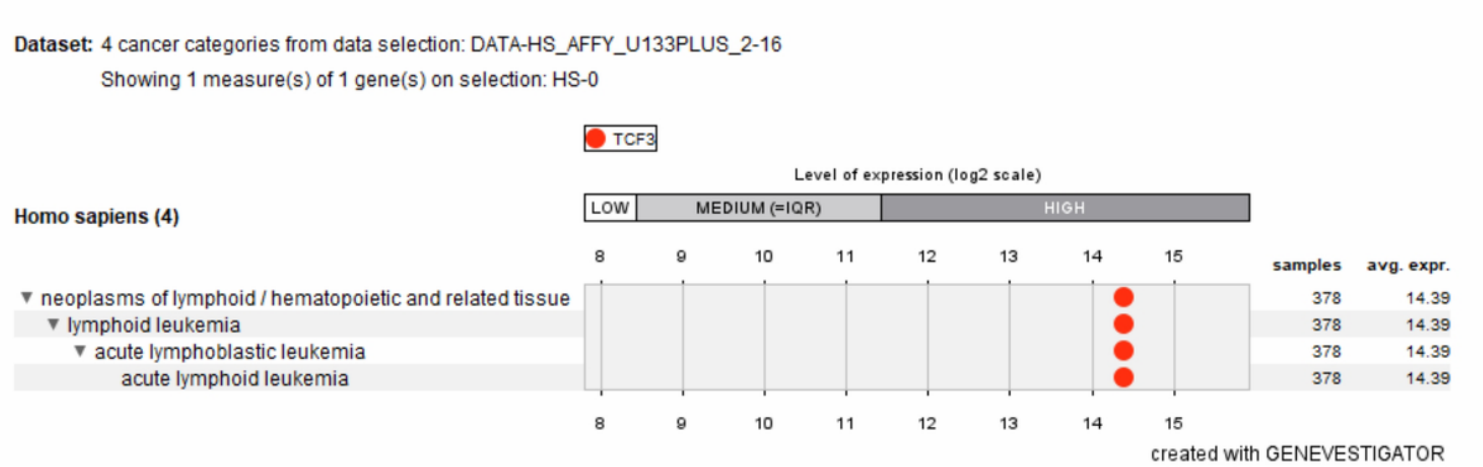


Figure 4

Molecular Evolutionary Link between E proteins and Antagonist



(a)

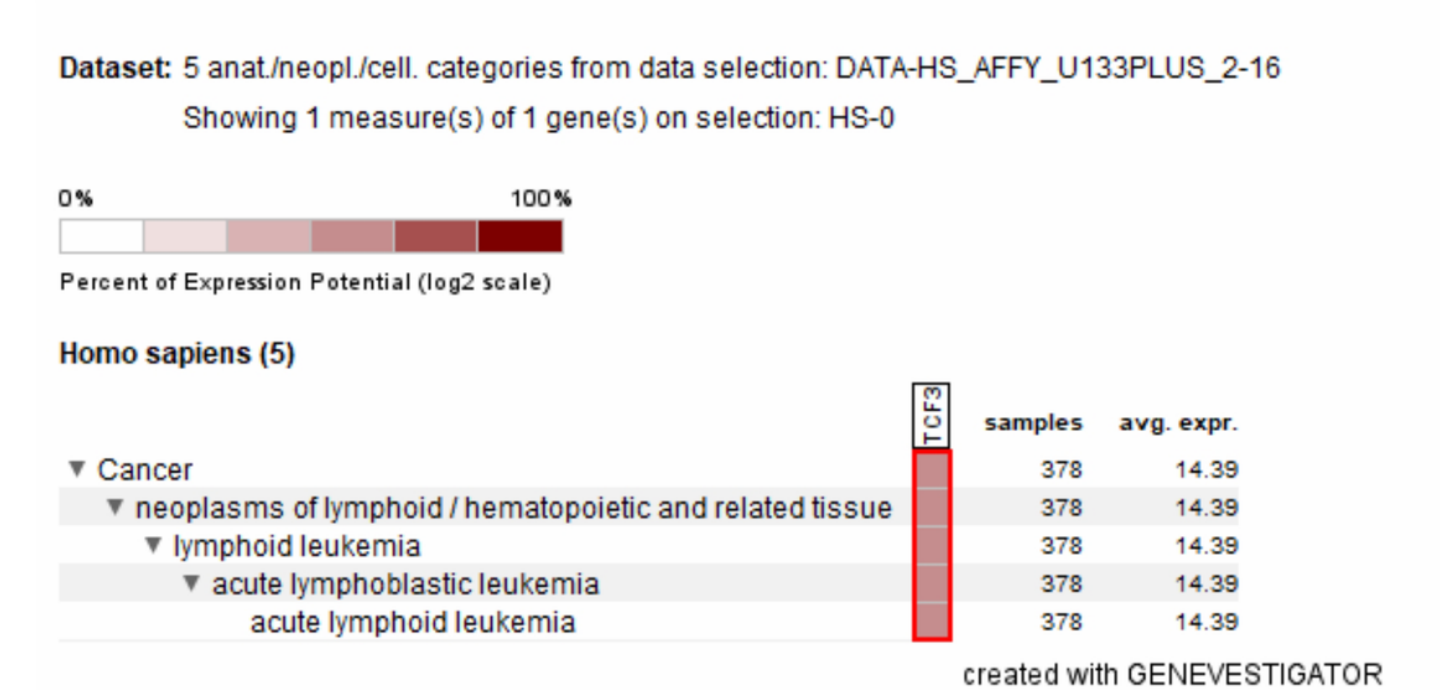


Figure 5

Expression analysis of E2A in Human

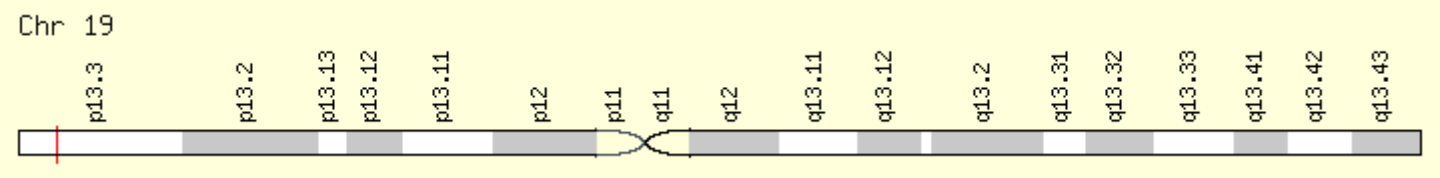


Figure 6

E2A located at Chromosome 19

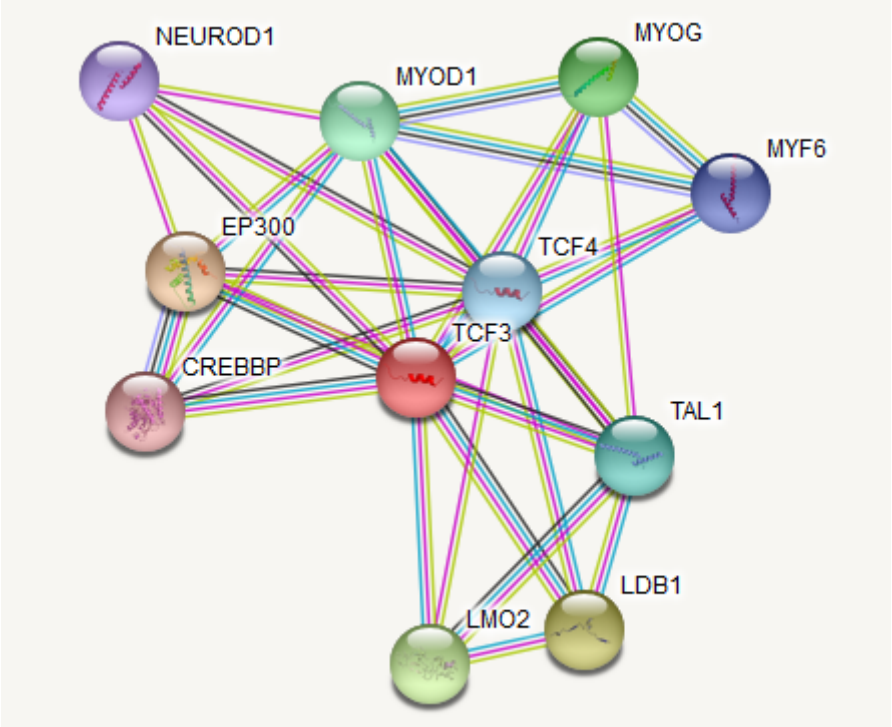


Figure 7

E2A interacts with other TF's

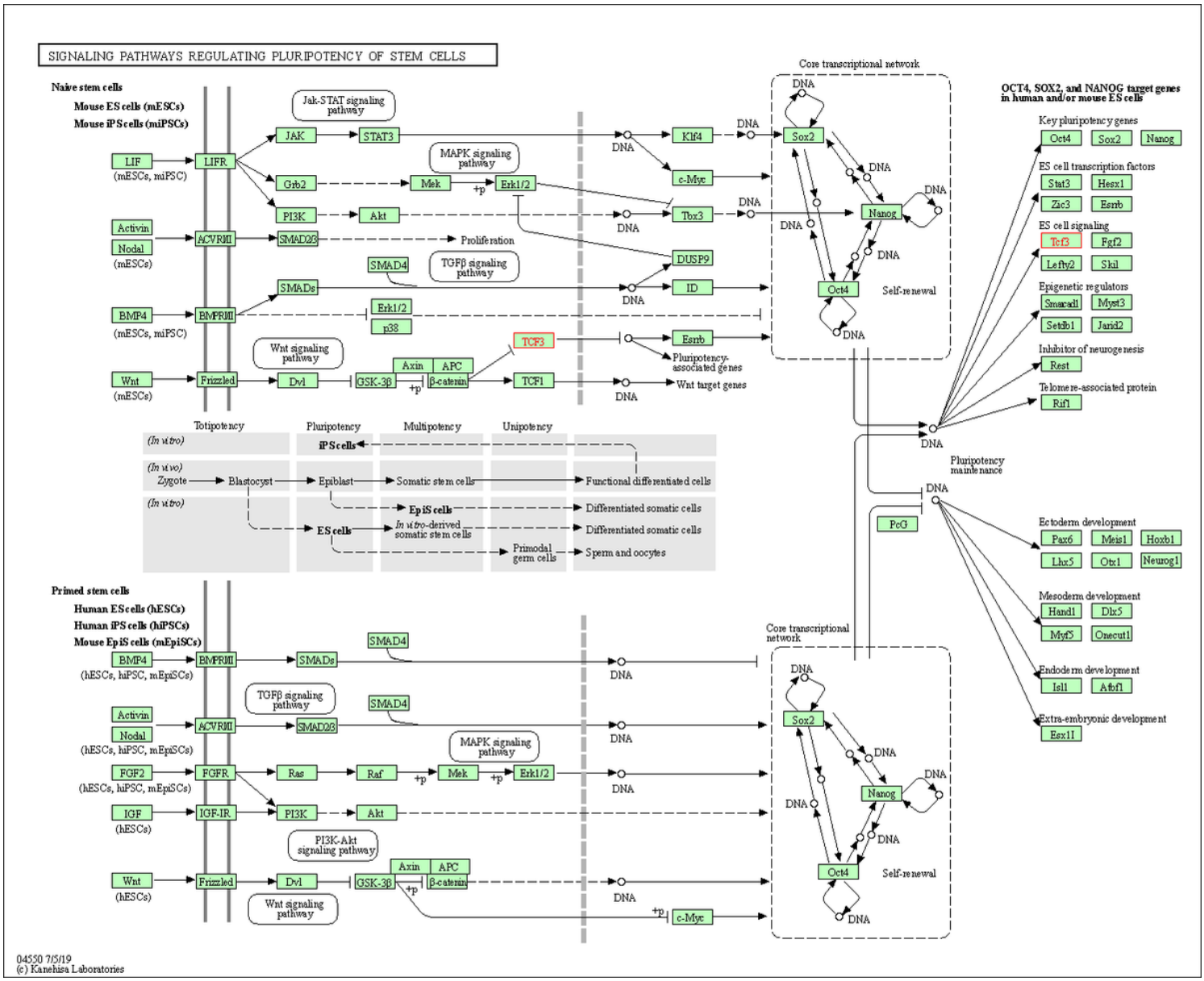


Figure 8

E2A Signalling Pathways Regulating Pluripotency of Steam Cells