E2f8 transcription factors

Abstract

E2Fs is a common and important family of transcription factors. E2F transcription factors have been widely studied in many organizations, it has many regulating function related to cellular proliferation differentiation, DNA repair, cell cycle and cell apoptosis. E2F8 is recent identification member of E2F family, it has high degree of similarity with E2F7 on structure and function. E2F8 have a duplicated DNA-binding domain(DBD) and control gene expression in a DP-independent manner. E2F8 in balance E2Fs family transcription regulatory networks have a vital role. E2F8 as transcription factors have close relationship with a variety of physiological functions and disease, which may bring new breakthrough point for the treatment of certain diseases. Here, we review E2F8 latest research data and the progress in various kinds of related physiological function.

Keywords: E2F8, DP, DBD

Introduction

Transcription factor E2F familyhas many regulating function related to cellular proliferation differentiation, DNA repair, cell cycle and cell apoptosis [1-4]. The study of E2F family began in the 1980 s, E2F1 is one of the most thorough of research [5]. The transcriptional activities of the E2Fs are related to the members of pRB family (pRB, p107 and p130) and this inhibition is dependent on the combination of these proteins and thereby inhibiting E2F activity. In the G1 to S period of the cell cycle, the cyclin – dependent kinases (CDKs) phosphorylate Rb resulting in the dissociation of E2F from Rb-containing complexes and making E2F out of inhibition [2]. Studies have

shown that E2Fs evolution in plants and animals is very conservative but not in yeast [2]. Has now been found E2F family members have eight (E2F1-8) [6]. Further layer of complexity in the regulation of E2F function has been afforded by alternative splicing of some family members and generate isoforms [1]. Christensen, Jet al searching GenBank using the E2F7 sequence as query, they noticed the existence of several human and murine expressed sequence tags and database accessions showing highly similarity to E2F7. They have designated the cloned transcripts asE2F8 [1]. According to different structure and function, the E2Fs usually can be divided into two groups (activators and repressors), four subgroups [1, 2, 7]. E2F1–6 are characterized by the presence of two conserved domains necessary for sequence specific DNA binding in the N-terminally and dimerization with DP1 or DP2 proteins, respectively, whereas the two most recently identified family members, E2F7 and E2F8, bind to DNAin a DP-independent manner[4].

E2F1–3a are considered to be transcriptional activators and, when overexpressed, can drive quiescent cells into S-phase. It was demonstrated that E2F1-3 triple knock-out cells are defective for S-phase entry [1]. In contrast, E2F3b, E2F4 and E2F5 occupy E2F-regulated promoters in the G0/G1 phase of the cell cycle and interact with all three pRB family members, which repress transcription by recruitment of chromatin remodeling complexes, histone- and DNA-modifying enzymes such HDAC and DNA methyltransferases [1]. E2F1–5 possess conserved transactivation and pocket protein-binding domains at the C terminus that are absent in E2F6. E2F 6 did not take pRB, P107 or P130 regulation. Instead, E2F6

represses transcription through interactions with the Polycomb group of proteins as well as Mga and Max [1-3]. E2F7 harbours a tandem repeat of E2F DNA-binding domains, and the absence of DP-dimerization, retinoblastoma-binding, and transcriptional activation domains, E2F7 interacts with DNA independently of DP proteins[2]. Recently discovered a new E2F family members, E2F8. E2F8 shows a high degree of resemblance to E2F7 and shares the unique structure of E2F7 by having two distinct domains exhibiting a high degree of similarity to the DNA-binding domain of the E2F family [8]. Ectopic expression of E2F8 inhibits cellular proliferation.

The structure and properties of E2F8

NM 024680 and XM149937 were identified of E2F8 at the earliest. They encoding Homo sapiens FLJ23311 protein and the Mus musculus RIKEN cDNA 4432406C08gene, respectively. NM 024680 and NM 024680 contained highly homologous ORFs capable of encoding proteins of 867 and 860 amino acids (identity 82. 2%) with calculated molecular weights of 94 272 and 93 382 Da, respectively[1]. E2F8 shows a high degree of resemblance to E2F7. Alignment of human E2F8 and the human E2F7 showed an overall identity of 31. 9%, with the highest conservation around the unique repeats of the two E2F-like DNA-binding domains found in E2F7 [1]. The genomic organization of E2F8 is similar to E2F7 suggesting that they originate from a common ancestral gene. The human and murine E2F8 genes are located on chromosome11p15. 1 and short arm of chromosome 7, respectively. Both the human and murine E2F8 genes are consist of 13 exons separated by 12 introns with the start ATGs located in the second exons [1, 2]. mE2F8mRNA has a 300-bp long 5î€)-UTR and a 587-bp long 3î€)-UTR. There are two

consensus polyadenylation signals, AATAAA and ATTAAA, that are 327 and 238 bp upstream of the poly(A) tail, respectively[2]. The primary structure of E2F8 contained two E2F DNA-binding domain at positions 112–182 and 260–357; each of these regions included the canonical RRXYD motif that interacts directly with DNA [9]. The entire E2F8 protein was required for full activity, but the majority of the signaling activity appeared to reside in the first 200 residues [9]. Together with the sequence similarity, the genomic structure strongly supports that the human and murine E2F8 genes are true orthologues [1]. (Maiti, B. Li, J) found that E2F8 is highly expressed in the liver, skin, thymus, and testis but not in the brain, muscle, and stomach [2].

E2F8 Overexpression Blocks Cellular Proliferation

E2Fsareto be critical players in orchestrating the control ofcellular proliferation. The roles for each family member in controlling Cellular Proliferation, cell cycletransitions and apoptosis are different. The expression of E2F7 and E2F8 during the cell cycle are different from that of other E2Fs, with peak levels found later in the cell cycle during S-G2. A decrease in E2F activity is generally associated with a reduction inthe proliferation capacity of cells but not in them [3]. Moreover, their overexpression in fibroblasts can, unlike that of other E2Fs, repress E2F-target gene expression and block cell proliferation.

E2F7 and E2F78 is Essential for CellSurvival and Embryonic Development

The regulation of E2F activity during the cell cycle is thought to be critical for cellular homeostasis. A amount of genetic currency has been invested to finely control E2F activity in cells, including by direct binding of the Rb tumor

suppressor, by transcription, by post-transcriptional mechanisms involving miRNAs, and by post-translational mechanisms involving protein degradation, phosphorylation and acetylation[3]. E2f7 and E2f8 represent a unique repressive arm of the E2F transcriptional network that is critical for embryonic development and cell survival[10]. Genetic ablation of E2f7 and E2f8 demonstrates that at least one allele of E2f7 or E2f8 is required for embryonic development and viability [3]. Examine proliferation and apoptosis in E2f7 $^{-/-}$ E2f8 $^{-/-}$ mice embryos show a significant fraction of DKO embryos died by E10. 5, proliferation and apoptosis were measured in E9. 5 embryos[3]. E2F7 and E2F8 could form homo-dimers and hetero-dimers, the preferred state of dimerization is E2F7: E2F7 > E2F7: E2F8 > E2F8: E2F8 [3] . Both homo- and hetero-dimers of E2F7 and E2F8 could occupy E2F binding sites on E2F-target promoters, including E2f1. E2F7 and E2F8 represent a critical regulatory arm of the E2F network that controls apoptosis through the E2F1-p53 axis[10]. At the same time deletion of E2f7 and E2f8 resulted in a spectrum of embryonic defects impacting the vasculature and cell survival [3].

E2F8 proteins and DNA damage response

E2F7 and E2F8 are induced in cells treated with DNA-damaging agents, which coincide with binding to the promoters of certain target genes, such as E2F1.[8] E2F7 and E2F8 are required for the cell-cycle effects that occur in response to DNA damage. When U2OS cells were treated with etoposide, there was a specific induction of E2F7 and E2F8 ; p53 and E2F1 were, as expected, induced under these conditions. A similar response was apparent in various other cell types, including MCF7, HeLa, T98G, HCT15 and HCT116

tumour cells and mouse embryonic fibroblasts, as a consequence of treating with different DNA-damaging agents, such as etoposide and bleomycin[8]. E2F7 and

E2F8 to modulate E2F1 activity response to DNA damage .

E2F8 promote angiogenesisand lymphangiogenesis

Simultaneous deletion of E2F7/8 in zebrafish and mice leads to severe vascular defects during embryonic development, E2F7/8 are essential for proper formation of blood vessels[11]. E2f7/8 regulate VegfA dependent angiogenesis in zebrafish[12] . E2F7/8 form a transcriptional complex with the hypoxia inducible factor 1 (HIF1) to stimulate VEGFA promoter activity. E2F7/8 and the HIF1-VEGFA pathway providing a molecular mechanism by which E2F7/8 control angiogenesis[11]. E2F7/8 bind to the N-terminal 80 amino acids of HIF1α, amino acids 53 while RB1 binds to amino acids 530–694[13] . E2f8 as novel in vivo transcriptional regulators of Ccbe1 and Flt4, both essential genes for venous sprouting andlymphangiogenesis[12].

E2F8 proteins and cell cycle control

Together with pocket proteins, the E2F family controls transcription of a variety of growth and cell-cycle related genes in the different phases of the cell cycle [1]. E2F8 are functionally involved in cell cycle control, particularly in DNA replication during the G1-to-S transition[4]. Cell-cycle progression is driven by mitogenic growth signals, which result in the synthesis and accumulation of D-type cyclins. For HeLaS3 cells, the relative level of E2F8 peaked at the time of release, early S-phase, which coincided with, two

CyclinE1. As the cells progressed through S-phase, E2F8 transcript levels dropped and finally increased again when the cells had gone through mitosis and started re-entering S-phase[1].

E2F8 influence to polyploidization

Shusil K. Pandit, et al, To determine E2F expression levels in postnatal liver development, they collected murine livers during the first 9 weeks after birth and analysed the messenger RNA and protein levels by quantitative PCR (qPCR) and western blot analysis, respectively. The mRNA levels ofE2f7 and E2f8 were low in 1-week-old livers and were strongly inducedat 3–5 weeks. Importantly, the induction of these atypicalE2Fs coincided with the onset of hepatocyte polyploidization [14]. This physiological binucleation process was markedly reduced in E2f8−/− livers at 3 and 4 weeks of age. Combined deletion of E2f7 and E2f8 in hepatocytes resulted in stronger inhibition of binucleation when compared with E2f8−/− livers. E2f7−/− livers showed a minor decrease in binucleation at 4 weeks. These genes involved in DNA replication, mitosis and cytokinesis are regulated by the atypical E2F repressors, in particular E2F8, as well as by the classical E2F1 activator. A deficiency in E2f8 led to an increase in the expression level of E2F target genes promoting cytokinesis and thereby preventing polyploidization [14]. The ploidy of E2f7−/−and E2f8−/− TGCs never exceeded 64C, whereas Wild type TGCs with genomes > 1000C were readily detected. E2F8 in facilitating TGC endocycles by repressingkey molecular events required for mitosis and karyokinesis [15].

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