Am J Cancer Res 2013;3(4):339-346
www.ajcr.us /ISSN:2156-6976/ajcr0000217

Review Article

Nuclear transcription factor Y and its roles in cellular processes related to human disease

Luong Linh Ly, Hideki Yoshida, Masamitsu Yamaguchi

Department of Applied Biology, Insect Biomedical Research Center, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto, 606-8585, Japan

Received July 16, 2013; Accepted August 3, 2013; Epub August 14, 2013; Published August 30, 2013

Abstract: Nuclear transcription factor Y (NF-Y) is an example of a transcriptional regulation factor in eukaryotes consisting of three different subunits, NF-YA, NF-YB and NF-YC, which are all necessary for formation of NF-Y complexes and binding to CCAAT boxes in promoters of its target genes. Highly conserved between human and *Drosophila*, NF-Y regulates transcription of various genes related to the cell cycle and various human diseases. *Drosophila* models have been widely used as tools for studying genetics and developmental biology and more recently for analyzing the functions of human disease genes, including those responsible for developmental and neurological disorders, cancer, cardiovascular disease and metabolic and storage diseases, as well as genes required for function of the visual, auditory and immune systems. In this review, *in vivo* findings from *Drosophila* models relevant to the roles of NF-Y in various human diseases are summarized. Recent studies have demonstrated novel contributions of dNF-Y to apoptosis and apoptosis-induced proliferation, and in photoreceptor cell differentiation during the development of the *Drosophila* compound eye.

Keywords: Transcription factors, NF-Y, NF-YB, apoptosis, *Drosophila* model

Introduction

Transcription factors are well characterized as proteins that bind to specific short DNA sequences in control regions of genes and thereby regulate their transcription, either positively or negatively [1]. They contain one or more DNA-binding domains that attach to specific sequences of DNA, while other regions are responsible for stimulatory or inhibitory effects on transcription [2]. Transcription factors play vital roles in many important cellular processes and consequently changes in these factors can lead to human diseases which can be categorized into three major groups: developmental disorders, disorders of hormone responses and cancer [3]. Nuclear transcription factor Y (NF-Y) is one of the transcriptional regulation factors that bind to the CAAT box in promoters of various genes in eukaryotes [4]. Currently NF-Y is emerging as a regulatory factor for many genes overexpressed in several different kinds of cancer [5]. In this review, we summarize information on NF-Y target genes, focusing on the *Drosophila* homologue to provide clues to understanding human diseases.

CCAAT box

The CCAAT box is one of the most common cis-acting elements found in the promoter and enhancer regions of a large number of genes in eukaryotes [4]. As detailed in a very recent review, it is believed to be enriched in promoters of large sets of genes overexpressed in several different kinds of cancers such as in the breast, colon, thyroid and prostate, as well as in leukemia [5]. Many DNA binding proteins interact with this sequence but only NF-Y has been shown to absolutely require all five nucleotides [6]. It is also reported that the frequency of CCAAT boxes appears to be relatively high in TATA-less promoters, particularly in the reverse ATTGG orientation [6]. In TATA-containing promoters, the CCAAT box is preferentially located in the -80/-100 region (mean position -89) with respect to the transcription initiation site (+1) and is not found nearer to the transcription initiation site than -50. In TATA-less promoters, it

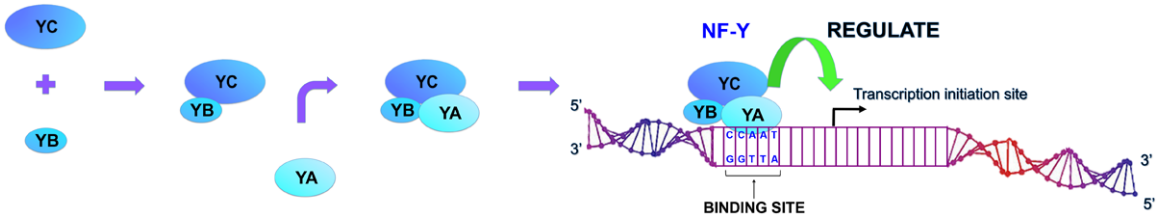

Figure 1. NF-Y complex formation. NF-Y consists of three different subunits, NF-YA, NF-YB and NF-YC, which are all necessary for formation of NF-Y complexes and binding to CCAAT boxes to activate transcription. The arrow with bar indicates transcription initiation site.

is usually located closer to the transcription initiation site (at -66 on average) and is sometimes present in close proximity [6]. Analysis of CCAAT boxes in 502 unrelated promoters indicated that NF-Y is the major, if not the sole, CCAAT box recognizing protein and that it might serve different roles in TATA-containing and TATA-less promoters [6].

Subunit structure of NF-Y

NF-Y consists of three different subunits, NF-YA, NF-YB and NF-YC, which are all necessary for formation of NF-Y complexes and binding to CCAAT boxes [7]. These subunits are encoded by independent genes. NF-YA contains a DNA binding domain, while both NF-YB and NF-YC contain histone-fold motifs (HFMs). First, NF-YB and NF-YC interact to form heterodimers through their HFMs [7] (**Figure 1**). The NF-YB/NF-YC heterodimer then interacts with NF-YA to form the heterotrimeric NF-Y transcription factor (**Figure 1**). The absence of any of the NF-Y subunits results in loss of binding of the NF-Y complex to DNA [8] and NF-Y-directed transcription [7]. However, there is evidence that Mes4 instead of NF-YC can also form complexes with NF-YA and NF-YB to regulate NF-Y target genes in *Drosophila* mesoderm [9].

NF-Y and its target genes

NF-Y (also called CBF, a-CP1 and CP1) was first recognized as a protein binding to the *major histocompatibility complex* (MHC) class II conserved Y box [10]. Subsequently, many studies identified target genes of NF-Y and roles in various biological pathways [7, 11]. Reviewing publications over nearly three decades, we can divide the target genes of NF-Y into two major groups: cell cycle-related genes and human disease-related genes, including examples important for hematopoietic disorders and cancer.

NF-Y and cell cycle related genes

In the first group, NF-Y controls the expression of several key regulators of the cell cycle such as *topoisomerase II alpha* (*topo IIα*), *cdc2, cyclins* and *cdc25C* genes [12-14]. For example, *topo IIα* activated during the late S and G2/M phases of the cell cycle carries several NF-Y binding sites in its promoter. The mouse *topo IIα* is reported to require NF-Y to bind to and activate its promoter by disrupting the surrounding nucleosomal structure during the cell cycle [12].

Cyclin-dependent kinases (CDKs) also play an important role in the eukaryotic cell cycle progression. The *Cdc2* (*CDK1*) gene is expressed during the late G1/S phase and is required for the G2 to M phase transition in higher eukaryotes. The adenovirus E1A protein mediates optimal transactivation of the human *cdc2* gene promoter by inducing the expression and assembly of a heteromeric complex consisting of the 110-kDa protein and NF-Y which then interacts with the two CCAAT motifs of the *cdc2* promoter [13]. It is also reported that NF-Y mediates transcriptional inhibition of mitotic *cyclins* and the *cdc25C* genes during p53-dependent G2 arrest induced by DNA damage. These observations suggest a transcriptional regulatory role of NF-Y in the G2 checkpoint after DNA damage [14]. Moreover, NF-Y is reported to be required for widespread activation of G2/M and anti-apoptotic genes [15]. Knockdown of NF-YB impairs G2/M progression, induces apoptosis and is sufficient to functionally activate p53, in the absence of DNA damage [15]. Impairment of Bax/Bcl-2 and Bax/Bcl-X(L) ratios contributes to failure to maintain a physiologic level of CCAAT-dependent transcription of anti-apoptotic genes. Fine balancing the NF-Y-p53 duo appears to be

important for cell survival by maintaining transcription of anti-apoptotic genes and preventing p53 activation that triggers the apoptotic cascade [15].

NF-Y and human disease related genes

NF-Y can regulate transcription of several genes that are related to human diseases such as *gamma-globin*, *Hoxb4*, *MHC class II*, *transforming growth factor beta type II receptor* and the *SRY*-related HMG-*box* (*Sox*) family [16-22]. Laminin-1 that is related to muscular dystrophy is a major component of embryonic basement membranes and consists of α1, β1, and γ1 chains. Expression of the *laminin-1* gene is induced in mouse F9 embryonic carcinoma cells upon differentiation into parietal endoderm cells. A study in Japan in 2004 showed that a combination of the actions of the ubiquitous factors, Sp1/Sp3 and NF-Y, and the parietal endoderm-specific factors, SOX7 and SOX17 controls the transcription of the mouse *laminin α1* gene during the differentiation of F9 cells [23]. In the following sections NF-Y target genes related to hematopoietic disorders and cancer are described.

Hematopoietic disorder diseases and the role of NF-Y

NF-Y recruits both transcription activator and repressor to modulate tissue- and developmental stage-specific expression of human *gamma (γ)-globin* gene [16]. The *γ-globin* genes (HBG1 and HBG2) are normally expressed in the fetal liver, spleen and bone marrow. Two gamma chains together with two alpha chains constitute fetal hemoglobin, which is normally replaced by adult hemoglobin at birth. In some β-thalassemias and related conditions, however, γ chain production continues to adulthood. The two types of γ chains differ at residue 136 where glycine is found in the G-γ product (HBG2) but alanine in the A-γ product (HBG1). The former is predominant at birth.

The human embryonic, fetal and adult β-*like globin* genes provide a paradigm for tissue- and developmental stage-specific gene regulation. The fetal *γ-globin* gene is expressed in fetal erythroid cells but is repressed in their adult counterparts. NF-Y recruits to neighboring DNA motifs the developmentally regulated, erythroid transcription activator GATA-2 and general repressor BCL11A, which in turn recruit erythroid repressor GATA-1 and general repressor COUP-TFII to form respectively the NF-Y/GATA-2 and the BCL11A/COUP-TFII/GATA-1 transcription repressor hubs. Both the activator and the repressor hubs are present in both the active and the repressed *γ-globin* promoter complexes in fetal and adult erythroid cells. Through changes in their levels and respective interactions with the co-activators and co-repressors during erythroid development, the activator and the repressor hubs modulate erythroid- and developmental stage-specific transcription of the *γ-globin* gene [16]. In this process, NF-Y plays a major role.

In another study, spatially specific expression of *Hoxb4* was found to be dependent on NF-Y [17]. *Hoxb4* is a member of the Antennapedia (Antp) homeobox family encoding a nuclear protein with a homeobox DNA-binding domain. Intracellular or ectopic expression of this protein expands hematopoietic stem and progenitor cells *in vivo* and *in vitro*, making it a potential candidate for therapeutic stem cell expansion in leukemia therapy. Since NF-Y and the transcriptional repressor protein YY1 mediate opposing transcriptional effects by reorganizing the local chromatin environment, the relative levels of NF-Y and YY1 binding could represent a mechanism for balancing activation and repression of *Hoxb4* through the same site [17].

NF-Y also plays a role in regulation of the *MHC* gene. MHC is a cell surface molecule that mediates interactions of leukocytes, determining compatibility of donors for organ transplant as well as one's susceptibility to autoimmune disease via cross-reacting immunization. In humans, MHC is also called human leukocyte antigen. It is reported that MHC class II promoters require cooperative binding between the transcription factors, Regulatory Factor X (RFX) and NF-Y [18].

Cancer related genes and the role of NF-Y

NF-Y is known to be involved in regulation of the *transforming growth factor β type II receptor* (*TβRII*) gene, a tumor suppressor gene. Trichostatin A (TSA) induces TβRII promoter activity and acetylation of Sp1 by recruitment of PCAF/p300 to a Sp1/NF-Y complex within the promoter. *TβRII* itself can be transcription-

ally silenced by histone deacetylases (HDACs) and it has been reported that TSA treatment of pancreatic cancer cells leads to transcriptional activation of the TβRII promoter through modulation of components of a Sp1/NF-Y/p300/PCAF/HDAC-1 multiprotein complex. Moreover, the interaction of NF-Y with the Sp1-associated complex may further explain why this specific Sp1 site mediates transcriptional responsiveness to TSA [19]. HDAC4 is known to be recruited on promoters repressed dependent on NF-Y and a relationship between p53 and HDAC4 recruitment following DNA damage has also been noted [20]. Furthermore, there is evidence that recruitment of HDAC1 to the TBP-2 promoter is mediated by a protein complex consisting of the RET finger protein (RFP; also called TRIM27) and NF-Y, which regulates the sensitivity of cancer cells to oxidative stress [21].

Sox proteins are expressed at many stages of mouse development and in a variety of tissues. The transcription factor *Sox-2* is first expressed throughout the inner cell mass during embryogenesis and subsequently becomes localized to the primitive ectoderm, developing central nervous system and the lens. Sox-2 is also highly expressed in F9 embryonic carcinoma cells, but becomes undetectable following differentiation of these cells, suggesting potential roles in cancer development. A consensus inverted CCAAT box motif is present in the *Sox-2* promoter which can bind to NF-Y [22]. Mutagenesis of this site significantly reduces the expression of *Sox-2* promoter/reporter constructs.

Drosophila model for analyzing the function of human disease genes

Because of many advantages *Drosophila* models have been widely used as a tool for studying genetics and developmental biology as well as in searching for novel biomarkers for human diseases by genetic screening and for high throughput screening of drugs for therapy of human diseases. The relatively rapid life cycle of ten days and the fact that thousand of individuals can be assessed at the same time makes it possible to do large scale genetic and physical screening. In future these advantages should aid the analysis of complex multigenic disorders [24]. In addition, 77% of human disease genes in the Online Mendelian Inheritance in human database match *Drosophila* sequences [25]. Therefore, *Drosophila* is emerging as one of the most effective tools for analyzing the function of human disease genes, including those responsible for developmental and neurological disorders, cancer, cardiovascular disease, metabolic and storage diseases, and examples required for function of the visual, auditory and immune systems. Some of these are described below [24].

Sporadic and familial forms of amyotrophic lateral sclerosis (ALS) may feature mutations in the fused in sarcoma/translated in liposarcoma gene (FUS/TLS, FUS) [26]. FUS is an RNA-binding protein that is normally localized in the nucleus, but is mis-localized to the cytoplasm in ALS, and forms cytoplasmic inclusions in ALS-affected areas. Neuron-specific knockdown of Cabeza (Caz), a *Drosophila* homologue of FUS, resulted in degeneration of motoneurons and locomotive disability in the absence of abnormal cytoplasmic Caz aggregates, indicating that the established *Drosophila* model is suitable for screening of genes and chemicals that might modify pathogenic processes that lead to the degeneration of motoneurons in ALS [26].

Syntrophins are components of the dystrophin glycoprotein complex (DGC), which is related to muscular dystrophies. *Drosophila* Syntrophin-1 (Syn1) and Syntrophin-2 (Syn2) are counterparts of human α1/β1/β2-syntrophins and γ1/γ2-syntrophins, respectively. A combination of *Syn1* knockdown and $Syn2^{37}$ mutation dramatically shortened life span, synergistically reduced locomotion ability and synergistically enhanced overgrowth of neuromuscular junctions in N-ethylmaleimide sensitive factor 2 mutants. Therefore it can be concluded that Syn1 and Syn2 are required for locomotion and are involved in regulation of synaptic morphology [27].

Disorganization and aggregation of proteins containing expanded polyglutamine (polyQ) repeats, or ectopic expression of α-synuclein, underlie neurodegenerative conditions including Alzheimer's, Parkinson, Huntington, Creutzfeldt diseases. Small heat-shock proteins such as αB-crystallin act as chaperones to prevent protein aggregation and thus play key roles in the prevention of such protein disorganization diseases [28]. In *Drosophila*

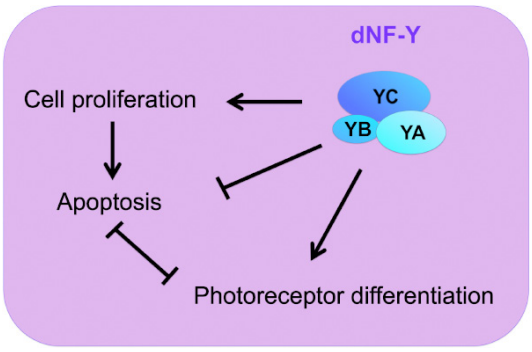

Figure 2. Roles of dNF-Y during *Drosophila* eye development. dNF-Y plays dual roles in apoptosis, which is followed by apoptosis-induced proliferation, and in photoreceptor cell differentiation during development of the *Drosophila* compound eye.

model, it is reported that αB-crystallin not only suppresses both the compound eye degeneration induced by polyQ and the α-synuclein-induced rough eye phenotype but also inhibits aggregation of polyQ [28].

Cancer research is now a major activity all over the world and *Drosophila* models have also been used for studying cancer related genes. The p53 protein which functions as a tumor suppressor and contributing to prevention of cancer requires *Drosophila* NF-Y for its transcriptional regulation [29]. The Hippo tumor suppressor pathway in *Drosophila* represses expression of DIAP1 and Cyclin E via inactivation of the transcription co-activator Yorkie, resulting in cell cycle arrest and induction of apoptosis [30]. The *warts* (*wts*) gene is well known as a core kinase in this pathway. In *Drosophila*, the DRE/DREF transcriptional regulatory pathway is reported to be necessary for *wts* gene promoter activity, indicating a novel link between the DRE/DREF and the Hippo pathways [30].

Studies on *in vivo* roles of NF-Y in *Drosophila* models

Drosophila NF-Y (dNF-Y) and human NF-Y demonstrate high conservation, with 82% identity within the DNA-binding domain in NF-YA, 65% identity within the HFMs in NF-YB and 72% identity within the HFMs in NF-YC [8]. Therefore *Drosophila* provides a useful model in studying *in vivo* roles of NF-Y that are not fully understood with mammalian systems. Current studies with *Drosophila* are demonstrating novel roles of NF-Y in eye development and apoptosis.

Photoreceptor differentiation and the role of dNF-Y

The adult *Drosophila* compound eye consists of nearly 800 ommatidia. Each ommatidial unit is surrounded by a hexagonal lattice of 12 interommatidial cells which include bristles, secondary and tertiary pigment cells [31] and contains eight photoreceptor cells, four cone cells, and two primary pigment cells. The photoreceptors (R cells) are divided into three different types depending on their genetic and morphological function: the outer R1-R6 lie in a ring surrounding two central receptors; R7, the distal, or outer, central cell; and R8, the proximal, or inner, central cell. R cells have been found to be generated sequentially: R8 is generated first, with movement posterior from the MF, then cells are added pair wise (R2 and R5, R3 and R4, and R1 and R6), R7 being the last photoreceptor to be added to the precluster [32]. Several enhancer trap lines expressing a nucleus-localized form of *E. coli* β-galactosidase under control of the specific enhancer-promoter located near the P-element can be used to determine the identities of individual photoreceptors. Eye disc-specific knockdown of dNF-YA or dNF-YB induced an abnormal eye morphology (rough eye phenotype) in adults. Detailed analyses with these knockdown flies and the enhancer trap lines demonstrated that NF-Y is involved in differentiation of R7 photoreceptor cells in *Drosophila* [33] (**Figure 2**).

It is reported that the *Drosophila* signal transduction pathway *sevenless* (*Sev*) regulates the R7 differentiation [34] and in *sev* mutants the R7 photoreceptor is missing from each ommatidium [35]. *Sev* is a receptor tyrosine kinase whose activation induces intracellular changes in presumptive R7 cells to adopt an R7 rather than a cone cell fate [36]. Recently, dNF-Y has been reported to be involved in *sev* gene transcription and therefore regulate *sev* gene expression during *Drosophila* R7 photoreceptor development [33, 37].

Apoptosis and the role of dNF-Y

Apoptosis (programmed cell death) is an essential process in any kind of cell in all animals which is used to remove damaged or irregularly

proliferating cells so that they do not disturb normal development [38]. Lack of strict regulation of diminution or lack of apoptosis often results in tumor formation and/or autoimmune diseases, whereas excess of cell death is associated with neurodegenerative diseases [39]. The Bcl-2 family proteins are key regulators of apoptosis in mammals. There are three subfamilies: the proapoptotic multidomain proteins exemplified by Bax, Bak, and Bok, the proapoptotic BH3-only proteins such as Bad, Noxa, Puma, and Bim, and the antiapoptotic multidomain proteins that include *Bcl*-2, *Bcl-XL*, and *Bcl*-w [40]. *Debcl* was the first *Bcl*-2 homologue identified in *Drosophila*, with a structure reported to be similar to Bax-like proapoptotic Bcl-2 family members and functions in a caspase-dependent manner [41].

In our recent study, we found that dNF-YB plays dual roles in apoptosis, which is followed by apoptosis-induced proliferation, and in photoreceptor cell differentiation during development of the *Drosophila* compound eye (**Figure 2**). Moreover, we identified four potential CCAAT boxes in the 5'-flanking region of the *debcl* gene and demonstrated that all of them are required for debcl promoter activity in *Drosophila* cultured cells. Our data also indicate that dNF-Y regulates *debcl* gene expression [33]. We further confirmed dNF-YB and dNF-YA binding to the genomic region of *debcl* containing four CCAAT boxes and that dNF-YB and dNF-YA positively regulate *debcl* gene expression at the transcriptional level. These findings taken together suggest that dNF-YA indeed forms functional complexes with dNF-YB and dNF-Y is a key regulator of *debcl* gene expression in *Drosophila* [33]. In this way, *Drosophila* model has been successfully used to analyze *in vivo* functions of NF-Y. Further analysis with the *Drosophila* model, for example with extensive genetic screens, should provide further insights in studying the gene regulatory network in which NF-Y plays major roles.

Acknowledgements

We thank Dr Moore for comments on the English in the manuscript. This study was partially supported by a scholarship and grants from the KIT, and Grants-in-Aid for Scientific Research (A), (C).

Address correspondence to: Dr. Masamitsu Yamaguchi, Department of Applied Biology, Insect Biomedical Research Center, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan. Tel: +81 75 724 7781; Fax: +81 75 724 7799; E-mail: myamaguc@kit.ac.jp

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