Minireview

In search of a function for the TIS21/PC3/BTG1/TOB family

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Abstract The Btg family of anti-proliferative gene products includes Pc3/Tis21/Btg2, Btg1, Tob, Tob2, Ana/Btg3, Pc3k and others. These proteins are characterized by similarities in their amino-terminal region: the Btg1 homology domain. However, the pleiotropic nature of these family proteins has been observed and no common physiological function among family members was suggested from the history of their identification. Recent progress in the search for Btg family functions has come from the analysis of cell regulation and of cell differentiation. It is now emerging that every member of this family has a potential to regulate cell growth. We would like to propose here to use a nomenclature APRO as a new term for the family.

Key words: Btg1; Btg2; Btg3; Tob; Tob2; Pc3; Pc3b; Pc3k; Tis21; Fog3; Amphitob; Ana; B9-10; B9-15; Cell cycle; p53; Rb; Anti-proliferative activity

1. Introduction

The control of the cell cycle plays an essential role in cell growth and in the activation of important cellular processes. A large number of signaling molecules are involved in mediating extracellular signals to the control of cell cycle. Among them, it is well known that retinoblastoma protein (Rb) and p53 are key regulators of the cell cycle progression or cell apoptosis. Increasing evidence indicates that loss of function of these tumor suppressor genes represent a major route to tumor development. However, characterization of other physiologically important anti-proliferative genes such as cyclin-dependent kinase inhibitors was also achieved.

In 1991, the *Pc3* gene and *Tis21* gene were reported as immediate early genes induced in rat PC12 cell line during neuronal differentiation by nerve growth factor (NGF), and in mouse 3T3 cell line by the tumor promoter tetradecanoyl phorbol acetate, respectively [1,2]. In the following year, molecular characterization of a chromosomal translocation observed in a lymphoid malignancy resulted in the *Btg1* cloning [3], a distinct but close homologous gene to the *Pc3*/*Tis21*. Furthermore, a third member (termed *Tob*) of this gene family was identified as a binding molecule to ErbB2, a receptor tyrosine kinase [4]. Although the respective approaches to discover the genes/molecules were different, a biological common feature of these gene products was their ability to inhibit cell proliferation. From that time on, other novel related genes were also isolated over the past years using different cloning strategies [5–10]. Since no homology to known functional motifs is evident in their protein sequences of them, it appears likely that these molecules belong to a novel functional class of cell cycle regulators. In this review we will focus on the family members and discuss the parallels and differences among them.

Before entering the main subject, we should put terms of the family in order, for a smooth understanding of the context. More than 20 members of this family have been found from several species by a lot of laboratories. However, six distinct proteins of the family have been identified in human cells at present. Some of the designations are now a little bit apart from the original concept of the name and might be confusing. Accordingly, we would propose and use a united term, which is now being introduced to the nomenclature committee (UK), hereafter in this article. The name of APRO is derived from the consensus function of the gene family as 'anti-proliferative'. The six human APRO family proteins might be subgrouped into three classes as shown in Fig. 1. Each two members have close amino acid sequence similarities.

2. Structure, expression and localization

Many proteins contain motifs or regions that may be considered as building blocks, representing structural elements or functional domains. Based of the presence of this structural element concept, it is easily imagined that APRO proteins may constitute a certain family. The APRO homology domain can be divided in two short, relatively more conserved elements, box A and box B, separated by a spacer sequence of non-conserved amino acids. This molecular organization is reminiscent of pocket proteins such as Rb and Bcl2, which are involved in certain signal transductions through protein–protein interaction [6]. Both APRO5 and APRO6 contain a predicted nuclear localization signal in this region. *APRO* gene family often contains some copies of ATTTA motif that is known as the most common determinant of the RNA stability in mammalian cells. It should be noted that mRNA degradation is influenced by many exogenous factors such as TPA and calcium ionophores. APRO proteins seem to be very labile. It has been shown that *APRO1* and *APRO2* are expressed early during the G0/G1 transition phase of the cell

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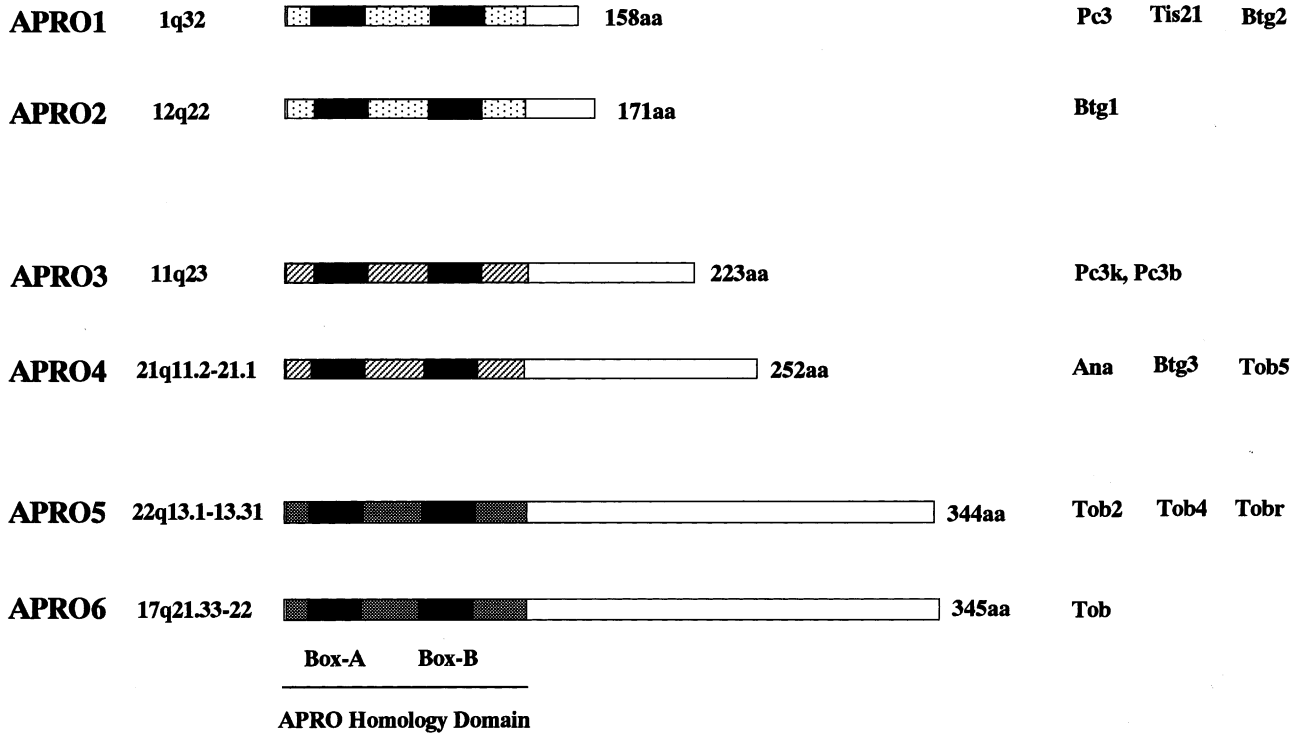

Fig. 1. Comparison of the schematic structure of the predicted APRO protein family members. The human chromosomal mappings of the genes are also shown. Numbering of the APRO is arranged in order of protein length of the respective gene product. The original names used in the published paper or in the gene bank account are shown on the right.

cycle [3,11]. This expression decreases quickly as the cells progress through the cell cycle.

These proteins are involved in cell growth control in various cells such as T lymphocytes, fibroblasts, epithelial cells and neuronal cells. These functional specificity and selectivity of the different members of the family might be achieved by the interaction with different cellular targets. For example, APRO1 and APRO2 interact with PRMT1 (protein arginine methyltransferase of type 1), an arginine *N*-methyltransferase that plays an important role in their anti-proliferative function, and modulate its activity positively [12,13,50]; APRO1, APRO2 and APRO5 can also interact with Caf1 (a homolog of the yeast Caf1/Pop2 that is a component of the CCR4 complex), which regulates the expression of a number of genes involved in cell cycle regulation and progression [14]; APRO6 can associate with the ErbB2 growth factor receptor; and a recent report shows that APRO6 interacts with Smad proteins. These interactions will be discussed further in Section 4.

The APRO homology proteins have been found in organisms from nematodes to humans with phylogenetically well-conserved homology [15] (Fig. 2). In particular, on the basis of the designations as proposed above, six of the structurally defined human APROs are mentioned in Figs. 1, 2 and 3. Searching human genome sequences, it seems likely that no more member of the APRO family exists in human genome. The ordinal number of APRO is then numbered due to the length of predicted protein. According to the claim of the referenced paper, APROs could be annotated briefly as follows.

2.1. *APRO1 (Pc3, Tis21, Btg2)*

It was initially described as an immediate early gene induced by tumor promoters and growth factors in PC12 and Swiss 3T3 cells [1,2,16]. *Pc3*, *Tis21* and *Btg2* are cognate genes from rat, mouse and human, respectively. It was then proved that *APRO1* and *APRO4* were of the primary responsive genes super-induced by TPA [17], and that the expression is also regulated by redox changes [17]. The mRNA is 2.6 kb long. *APRO1* is endowed with anti-proliferative activity and shares significant sequence homology to *APRO2*. In stable NIH3T3 clones expressing *APRO1*, the transition from G1 to S phase was impaired [18]. This gene is expressed in a variety of cell and tissue types and encodes a remarkably labile protein [19–21]. It is noteworthy that *APRO1* expression is up-regulated by p53 after DNA damage induced by genotoxic agents, suggesting that APRO1 function may be relevant to cell cycle control and cellular response to DNA damage [11].

2.2. *APRO2 (Btg1)*

APRO2 is also essentially expressed in quiescent cells and in differentiated cells, whereas it is down-regulated as the cells enter the growth cycle. This gene was first identified as a translocation gene in a case of B cell chronic lymphocytic leukemia [3,22]. The mRNA is 1.8 kb long. AP-1-like sequence is located in the promoter region of *APRO2* gene to react to AP-1 activity [23]. By the gene transfection experiment, it was shown that APRO2 negatively regulates cell proliferation. APRO2 displayed a diffuse cytoplasmic localization in confluent cells, whereas a major nuclear localization in proliferative cells in some condition, suggesting that some pathway could drive the translocation of APRO2 into the nucleus [23]. It was shown that *Xenopus APRO2* was expressed in the prospective mesoderm and overexpres-

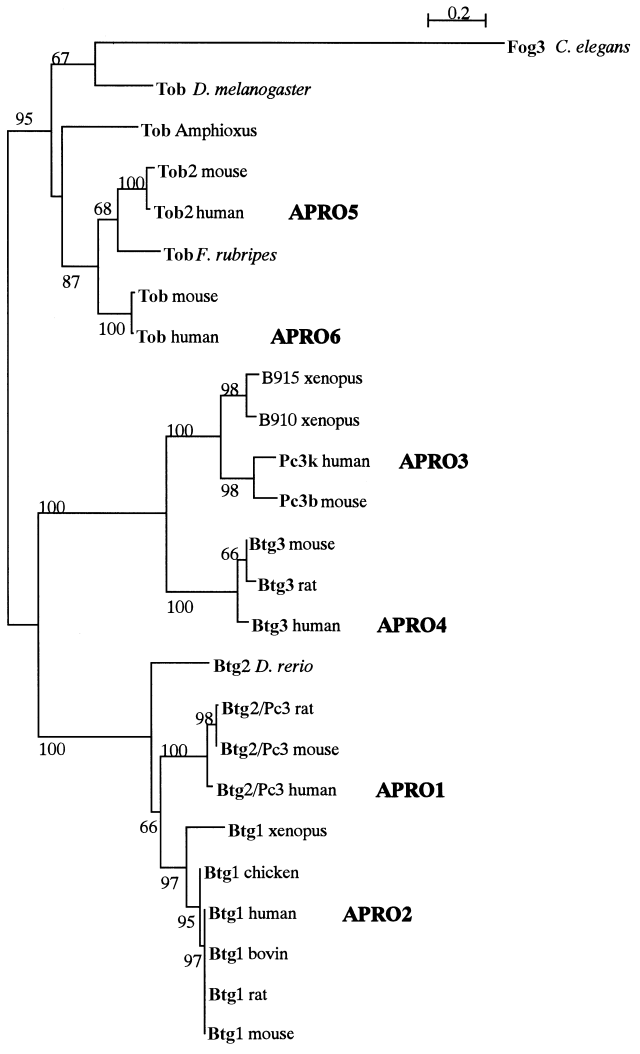

Fig. 2. Phylogenetic relationship in the APRO family. An evolutionary tree with the significantly correlated sequences based on the alignment of the APRO conserved region (101 residues) was calculated with the nearest-neighbor-joining algorithm (distance PAM). The evolutionary distance is shown by length of the horizontal line segments. The gene name/species/accession number/alternative name are follows: Btg2/Pc3 human U72649 (Btg2); Btg2/Pc3 mouse M64292 (Tis21); Btg2/Pc3 rat M60921 (Pc3); Btg2 *Danio rerio* AB036784; Btg1 human X61123; Btg1 bovine AF014008; Btg1 chicken X64146; Btg1 *Xenopus* AJ009283; Btg1 mouse Z16410; Btg1 rat L26268; Btg3 human D64110; Btg3 rat AF087037; Btg3 mouse Z72000 (tob5); Pc3b mouse AJ005120; Pc3k human AJ271351; B910 *Xenopus* X73317; B915 *Xenopus* X73316; Tob *Fugu rubripes* AL017231; Tob human D38305; Tob mouse D78382; Tob2 human AB035207; Tob2 mouse AB041225; Tob *Amphioxus* U95824; Tob *Drosophila melanogaster* AF177464; FOG3 *Caenorhabditis elegans* Z81033 (C03C11.c)

sion of the APRO2 prevented gastulative movements in embryos.

2.3. APRO3 (Pc3k, Pc3b)

Isolation of *APRO3* gene has been reported most recently [9]. This gene is also endowed with marked anti-proliferative activity resulting in G1 arrest. The mRNA is 1.4 kb long. Its expression is high in testis, in oocyte and in the olfactory epithelium at midgestation, suggesting involvement in gametogenesis and neuronal differentiation.

2.4. APRO4 (Btg3, Ana)

It has been reported that the *APRO2* and *APRO4* are highly expressed in neuroepithelium near the lateral ventricle [7]. However, it seems that this expression is ubiquitous with variations between different tissues. The mRNA is 1.5 kb long. The RNA level of *APRO4* peaks at the end of G1 phase of cell cycle [6], and the expression is inducible in cultured cells by redox changes [19]. Immunohistochemical studies have described APRO4 as a cytoplasmic protein [7]. Although APRO4 also physically interacts with Caf1, APRO4 does not interact with PRMT1 [24]. In a certain condition, APRO4 might associate with BANP, a novel nuclear protein [24].

2.5. APRO5 (Tob2, Tobr)

APRO5 was isolated as a related sequence to *APRO6* gene by means of a RT-PCR-mediated procedure [8]. The mRNA is 4.1 kb long and ubiquitously expressed in adult tissues (relatively high in skeletal muscle and in oocytes). The gene is mapped to human chromosome 22q13.1–q13.31. APRO5 seems to function as an association molecule to Caf1, and exogenous expression of *APRO5* inhibits G1 progression of the cells [8].

2.6. APRO6 (Tob, Tob1)

APRO6 gene was initially identified by screening an expression library to seek for an interaction molecule with ErbB2, a receptor tyrosine kinase [4]. The *APRO6* gene is ubiquitously expressed and the mRNA is 2.3 kb long. Recently, it has been proved that APRO6 is associated with Smads to control osteoblast-growth [25]. It was also shown that the mice lacking the *APRO6* gene frequently developed osteopetrotic phenotype [25]. Furthermore, APRO6 seems to be phosphorylated and regulated by Rsk1, a protein kinase functioning downstream MAPK [26].

3. Implication of APRO family genes in biological processes

Several arguments suggest that these genes have mainly a role in the negative control of the cell cycle. First of all, there is a correlation between their level of expression and the different phases of the cell cycle. In various models, *APRO1* and *APRO2* are strongly expressed in the phases G0/G1 of quiescence of the cell cycle [3,11,23,27,28]. *APRO4* is detected rather in G1/S phase [6]. Besides, the addition of prostaglandin E2 inhibits the proliferation of macrophages and enhances APRO2 expression [29]. It was also shown that variations of expression of the *APRO* genes accompanied different events linked to the cell differentiation. Several experiments have established a link between APRO1 and neurogenesis. It was described that APRO1 was expressed during the phase G1 of the cell cycle in neuroepithelial cells which were going to generate a neuron after their next mitosis [27,30,31]. It is necessary to note that the gene *APRO1* was initially isolated as being induced by the NGF in PC12 cells and that *APRO3* is strongly expressed in the olfactory epithelium [1,9]. The APRO2 role was studied during gametogenesis where it reaches a maximal expression in spermatids [32]. *APRO5* is strongly expressed in ovocytes [8]. Confirming the hypothesis of a role of the APRO family during the sexual differentiation, FOG3, the only representative of the family in *Caenorhabditis elegans*, was involved in the sexual determinism of this organism [33]. Another study showed a modification of *APRO2*

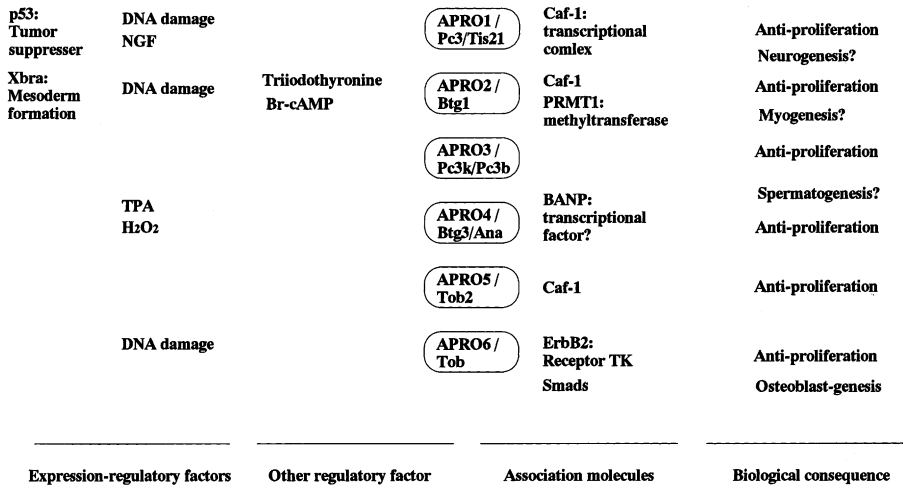

Fig. 3. The outlined involvement of APROs in the biological and biochemical processes.

expression during myogenesis with an increase of its expression during the phase of differentiation of myoblasts into myotubes [23,34]. Finally, xBTG1 (*Xenopus*) and Amphitob (*Amphioxus*) play a role in the control of the embryonic development of these animals [5,35]. On the other hand, several experiments showed that the forced expression of these genes (*APRO1, APRO2, APRO3, APRO4, APRO5, APRO6*) was more or less anti-proliferative [3,4,7–9,18,35,36]. Furthermore, CAF1, a transcription factor partner of APRO proteins presents also this characteristic [37]. It is interesting to note that CAF1, perhaps in association with APRO1, would regulate negatively the expression of cyclin D1 ([38], our unpublished data). Conversely, APRO1 deleted cells do not stop proliferating when they are subjected to conditions such as control cells would arrest [11]. Besides, in different models, a link seems to exist between the *APRO* gene expression level and the proliferation. A study showed that the expression of *APRO2* was higher in androgen-dependent prostate cancer cell line than in cell line independent from hormones which are more invasive [39]. APRO1 would be associated too to a lesser aggressiveness of the tumors which express it [40]. Finally, a loss of *APRO1* expression was correlated with the development of tumors into SV40 T transgenic mice [41]. *APRO* genes are also induced in various situations of stress being able to lead to a cell cycle arrest or even to the apoptosis: *APRO2* in macrophages loaded with lipids [36], *APRO1* and *APRO4* by an oxidative stress [17], *APRO1*, *APRO2* and *APRO6* by a genotoxic stress [42], *APRO1* by a membrane depolarization, an acute pancreatitis, a kidney ischemia, a neonatal hypoxia or an electroconvulsive shock [1,43–46]. Finally, APRO1 was shown to be involved in biochemical pathways leading to apoptosis [47,48]. It is noteworthy that the expression of *APRO1* is regulated by the tumor suppressor gene p53 [11,41]. So, the induction of p53 activity consecutive to a stress leads to *APRO1* upregulation what would finally induce the cell cycle arrest. Recently, it has been shown that *APRO6* gene-deficient mice have a greater bone mass resulting from increased number of osteoblasts, suggesting that APRO6 is a physiological regulator of proper osteoblast proliferation [25]. As expression of *APRO5* (a close homolog of *APRO6*) was very low in osteoblasts, the phenotype of the *APRO6*-deficient mice seemed be conspicuous in the bone without redundant effect. So far, *APRO* genes seem to be involved in the negative control of the cell cycle in particular during cell differentiation and this frame allowed at least to give a possible explanation for these various observations. In the next paragraph, we are going to try to understand the biochemical nature of these phenomena.

4. Downstream effectors

APRO1 expression is regulated by p53, and its inactivation in embryonic stem cells leads to the disruption of DNA damage-induced cell cycle arrest [11]. These observations raise the question whether APRO1 may promote p53-induced cell cycle arrest similar to p21Cip1. The involved molecular mechanisms have again little known. However, the demonstration of a link with cyclin D1 allows a better understanding of the biochemical pathways [38]. Indeed, several works had shown that the overexpression of members of the *APROs* (*APRO1*, *APRO5* or *APRO6*) family was accompanied by Rb hypophosphorylation [8,18]. Rb under its hypophosphorylated form sequesters factors of transcription, E2F in particular, and in this way prevents the transcription activation of genes necessary to the pursuit of the cell cycle. These Rb phosphorylations are catalyzed by CDK/cyclin complex of variable composition depending on the phases of the cell cycle. To understand if the Rb hypophosphorylation observed following *APRO1*, overexpression was attributable to the particular deficiency of a CDK/cyclin complex, cyclins were expressed in cells along with APRO1; only the cyclin D1 was able to counteract the APRO1 mediated cell cycle arrest [38]. APRO1 exhibits a transcriptional inhibition on the cyclin D1 promoter that leads to the observed decreased kinase activity of the CDK4/cyclin D1 complex. These findings indicate that APRO1 acts as a transcriptional regulator of cyclin D1 and then impairs G1-S transition by inhibiting Rb function in the consequence of a reduction of cyclin D1. Furthermore, this impairment could be finally mediated by CAF1, what would explain the anti-proliferative effect of several members of the APRO family (our unpublished results of the analysis of CAF−/− cells). It should be noted that CAF1 has recently been shown to belong to a deadenylase complex [60]. So, regulation of RNA stability could also be implicated in cell

cycle control. A physical interaction of APRO1 with CDK1, as well as with CDK4 was also observed [38]. As a functional consequence, one can imagine that *APRO1* overexpression modifies the activity of the CDK4/cyclin E complex, which were critical for a G1-S transition in cell cycle, as observed by Lim and co-workers in their cellular model [49]. Another important observation allowing a better understanding of these mechanisms is that APRO1 and APRO2 interact with PRMT1 and control its activity [50]. 90% Of this activity of type 1 is due to PRMT1. Furthermore, PRMT1 expression has a fundamental role since PRMT1−/− mice are not viable and die in utero [51,52]. Methylation of proteins is a post-translation modification of a presently unknown role but that could be involved in the transduction of anti-proliferative signals [53]. Indeed, it was shown that an inhibition of this methylation prevented the differentiation of PC12 cells under the influence of NGF [54]. Furthermore, an increase of the cellular methyltransferase activity was observed simultaneously to the induction of the expression of *APRO1* and *APRO2* by genotoxic treatments [42]. PRMT1 also interacts with IFNAR1 (intracytoplasmic chain of the interferon receptor) [55]. This observation brings a supplementary element in PRMT1 implication in the negative control of the cell cycle because cells where PRMT1 activity was invalidated by antisense oligomers, do not stop to proliferate under the influence of the interferon contrary to control cells [55]. Recently, it has been demonstrated that this inhibition arose from impaired STAT1 function in the absence of arginine methylation [61]. Discovery of PRMT1 targets and of the consequence of the methylation on their activity is now the goal to achieve. One of the most interesting results at present is that PRMT1 is a co-factor belonging to a transcription complex including among others the nuclear receptors of hormone [56,57]. Thus, the methyltransferase activity regulated by APRO1 and APRO2 could be consequently integrated at this level.

Another element which can explain the role of APRO1 and APRO2 in the control of the cell cycle and of the differentiation is their association with HOXB9 [58]. APRO1 and APRO2 enhance HOXB9-dependent transcription. HOXB9 is thought to regulate the transcription of NCAM. This latter is involved in the neurogenesis and its overexpression is anti-proliferative. APRO1 and APRO2 are supposed to enhance finally its expression and this could explain some effects elicited by APRO1 and APRO2 [58]. The expression of xBTG1 (*Xenopus*) is regulated by xBRA (*Xenopus* homolog of Brachyuary) and Pintallavis. The authors show that xBTG1 overexpression in whole embryos impairs the gastrulation and would be anti-proliferative [35]. APRO6 was initially isolated as an interaction molecule to ErbB2 kinase, however, the significance of the binding needs to be clarified further. Recently, APRO6 has been shown to act as a negative regulator of Smad signaling in osteoblasts. They showed that APRO6 associated with receptor-regulated Smad1, Smad5, Smad8 and co-localized with these Smads in the nuclear bodies after bone morphogenetic protein (BMP) stimulation. These data clearly suggest that APRO6 is a novel inhibitor of BMP/Smad signaling. These observations link APROs to an already known and studied pathway. So, it should allow us to establish its function more exactly in order to understand cell cycle regulation by APROs.

5. Perspective

A better understanding of the APROs involved in the regulation of cell growth is now emerging. It seems likely that the main points for the control are in the cell cycle, however, the process to the resultant phenomenon with cell cycle inhibition mostly during cellular differentiation seems to include some different effector pathways. This could also explain the apparent overlapping and sometimes differing functions of APROs. Now, we have a simple question. What is the common cellular process mediated through APRO homology domain in response to various stimulation? In other words, given that the APRO protein family is characterized by the presence of two conserved boxes (APRO homology domain) in their amino terminus, what is the most important physiological and biochemical function by the APRO domain? It may be plausible that interaction of the APRO family with Caf1 may affect a variety of transcriptional machineries involved in cell proliferation [59]. Furthermore, it should be noted that APRO proteins could play a role in RNA regulation: Caf1 has recently been shown to be involved in a deadenylase complex and PRMT1-mediated arginine methylation is thought to interfere with RNA/protein association. Various powerful experimental approaches could guide further exploration of the involved proteins and pathways in order to define more precisely if they constitute the elements of a novel signaling pathways.

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