Surfing on prothymosin α proliferation and anti-apoptotic properties

Minireview

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Prothymosin α is an extremely abundant nuclear oncoprotein-transcription factor essential for cell cycle progression and proliferation that has been recently suggested as an anti-apoptotic factor. Similarly to other oncoproteins, prothymosin α is overexpressed in a variety of cancer tissues and cell lines. The present review highlights on the proliferation and anti-apoptotic properties of prothymosin α and its possible role in cancer development.

Key words: prothymosin α, transcription factor, proliferation, apoptosis, cancer

Prothymosin α (ProTα) is a 12.5 kDa acidic nuclear protein, first isolated from rat thymus as the putative precursor of thymosin α1, and initially considered as a thymic immunoregulatory hormone [1, 2, 3]. In humans, ProTα is encoded by a gene family of six members. One of them contains introns, exons and classic regulatory signals, while the remaining five are intronless [4]. ProTα gene is upregulated by c-myc [5–8], E2F-1 [8] and human papilloma virus type 16 E6 oncogene [9], and downregulated by p53 tumor suppressor protein [10]. The wide distribution among mammalian tissues as well as the high conservation during evolution indicate an essential biological role of the protein [11, 12]. Previous studies performed during the last two decades have demonstrated a plethora of intracellular and extracellular functions of ProTα [13]. Today is widely accepted that the fundamental effects of the protein are closely related to cell proliferation and cell death (apoptosis). The present review highlights on the proliferation and anti-apoptotic properties of ProTα and its possible involvement in cancer development.

Prothymosin α and proliferation

Previous studies have demonstrated the crucial intracellular role of ProTα in cell cycle progression, proliferation and differentiation. ProTα is considered a chromatin-remodeling protein that modulates the interaction of histone H1 with chromatin [14]. The association of ProTα with the oncoprotein SET has been implicated in chromatin decondensation [15]. In the interphase nucleus the protein exhibits a punctuated nuclear distribution associated with transcription sites (PML and CstF64 proteins), while during mitosis ProTα is colocalized with alpha-tubulin in the mitotic spindle [16, 17]. ProTα mRNA expression is induced at the end of S and G2/M phases of cell cycle, in parallel with cyclin B levels [3]. ProTα transcripts are induced by growth stimulation of resting lymphocytes, NIH3T3 fibroblasts [4], thymocytes, and hepatocytes during liver regeneration [18]. ProTα mRNA expression is increased during the early post-implantation stages of mouse embryogenesis. ProTα gene is expressed exclusively in ectodermal and mesodermal structures, but not in endodermal regions [19]. Overexpression of ProTα has been shown to accelerate proliferation and retard differentiation in HL-60 cells [20]. Knockdown of ProTα synthesis by antisense oligonucleotides leads to cell division arrest [21].

ProTα has been linked to various transcriptional activation events that mediate critical stages of cell proliferation. The protein interacts with the CREB-binding protein, a versatile transcription co-activator, and stimulates AP1- and NF-κB-dependent transcription [22]. NF-κB activation is a well known transcription factor that mediates cellular transformation and induces tumorigenesis [23]. Epstein-Barr virus nuclear antigen 3C and ProTα interact with the p300

transcriptional coactivator and cooperate in the regulation of transcription [24]. ProTα selectively enhances estrogen receptor (ER) transcriptional activity and increases cell proliferation, while is itself upregulated by the estrogen-ER complex [25–27]. Furthermore, ProTα transcriptional activation by estradiol E2 has been implicated in the differentiation of human neuroblastoma SK-ER3 cells [28]. The tyrosine-phosphorylated signal transducer and activator of transcription-3 (STAT3) has been implicated in the induction of cell cycle progression and cellular transformation and prevention of apoptosis [29, 30]. ProTα interacts with STAT3 leading to STAT-3 translocation from the cytoplasm to the nucleus [10]. The phosphorylated STAT3 enter the nucleus and working coordinately with other transcriptional co-activators or transcription factors lead to increased transcriptional initiation. Activation of STAT3 signalling is accompanied by upregulation of target genes implicated in cell proliferation (cyclin D1, c-myc) [8, 30, 31].

ProTα has been suggested as an oncoprotein inducing transformation in rodent fibroblasts [32]. Similarly to other oncoproteins-transcription factors, ProTα is overexpressed in a variety of cancer tissues and cell lines, including colon [12, 33], hepatocellular [34], breast [35, 36], lung [33], ovarian [37], and thyroid cancer [38], as well as in human neuroblastoma [39] suggesting an essential role in tumorigenesis. Downregulation of ProTα gene with coincidental overexpression of connective tissue growth factor attenuates cell growth in human oral squamous cell carcinoma [40]. The inhibition of progression of prostatic intra-epithelial neoplasia to carcinoma by isoflavones has been attributed among the others to downregulation of ProTα expression [41]. Estradiol E2 upregulates ProTα mRNA and protein expression. Inhibition of nuclear ProTα expression in breast cancer cells using antisense methodology resulted in the inhibition of estradiol E2-induced breast cancer cell proliferation [42].

Prothymosin α and apoptosis

The most important transcription factors that are related to apoptosis can be divided into the following groups: (a) transcription factors that induce apoptosis such as E2F-1 [43], c-myc [44], p53 [45], c-Jun [46], and AFX [47]; (b) transcription factors that prevent apoptosis such as STAT3 [48], STAT5 [49], and ProTα [50]. NF-κB can be either pro-apoptotic or anti-apoptotic, depending on the timing of the modulating NF-κB activity relative to the death stimulus [51, 52].

ProTα has been recently associated with programmed cell death. Inhibition of ProTα synthesis and expression by antisense oligonucleotides and RNA interference, respectively, sensitizes cells to apoptosis [50, 53]. Ectopic production of human ProTα and its mutants with nuclear or nuclear-cytoplasmic localization confers increased resistance of HeLa cells toward the tumor necrosis factor-induced apoptosis [54]. WANG et al have shown that ProTα gene is upregulated in the early stages of retinoic acid-induced apoptosis in T-cell lymphoma cells [55].

The protein has been suggested as an anti-apoptotic factor that negatively regulates caspase-9 activation by inhibition of apoptosome formation (Apaf-1/cytochrome c complex) [50]. The mitochondrial pathway is thought to be the principal target of survival signaling pathways, which act by stabilizing mitochondrial function and integrity and suppressing release of cytochrome c. Once cytochrome c has been released from the mitochondrion, it orchestrates assembly of an intracellular apoptosome complex that recruits caspase 9 via the adaptor protein Apaf-1 [56]. Apaf-1 is the molecular core of the apoptosome, a multiproteic complex mediating the so-called mitochondrial pathway of cell death. Apaf-1 is considered an essential downstream molecule of p53 to induce apoptosis, functioning as a tumor suppressor. Apaf-1 deficient, c-myc expressing cells are resistant to p53-depended apoptosis, indicating the interrelationship between Apaf-1 and p53 [57]. p53-induced apoptosis is mediated mainly through the Bcl-2/Bax pathway via activation of bax gene [58]. ProTα expression is downregulated by p53 [59], a fact possibly critical in the p53-dependent pathway of apoptosis. Bcl-2 survival factor negatively modulates the formation of the apoptosome by blocking the release of cytochrome c from mitochondria [60]. We have recently showed a direct correlation between ProTα and Bcl-2 immunoexpression patterns in thyroid carcinomas, and thus ProTα may promote cell survival through the Bcl-2 anti-apoptotic pathway [38]. An alternative anti-apoptotic program involving ProTα has been recently reported to be mediated by the RNA-binding protein HuR, a critical regulator of the post-transcriptional fate of target transcripts. In HeLa cells, treatment with the apoptotic stimulus triggered the mobilization of ProTα mRNA to the cytoplasm and onto heavier polysomes, where its association with the RNA-binding protein HuR increased dramatically. The anti-apoptotic action of HuR was shown to be vitally dependent on ProTα expression, since use of oligomers that blocked ProTα translation abrogated the protective effect of HuR [61].

Different activation pathways of NF-κB may cause the expression of proteins that induce apoptosis (Fas, c-myc, p53) or inhibit apoptosis (TRAF2, IAP proteins, Bcl-2-like proteins) [62]. ProTα through the CREB-binding protein stimulates the NF-κB-dependent transcription [22], and therefore may participate in the NF-kB anti-apoptotic pathway. In addition, the association of ProTα with the anti-apoptotic protein STAT3 may be involved in a different anti-apoptotic program implicating the transcriptional activation of the Bcl-xl protein [10, 29].

In apoptotic HeLa cells, caspase-3 cleaves ProTα at one major carboxyl terminal [DDVD (99)] and several suboptimal sites. The major caspase cleavage disrupts the nuclear localization signal of ProTα leading to a profound alteration in subcellular localization of the truncated protein

which becomes deficient in phosphate [54, 63, 64]. During apoptosis the negatively charged truncated ProTα interact with the positively charged cytochrome c. In the complexes formed, ProTα inhibits cytochrome c oxidation and abolish its operation as electron carrier between the outer and inner mitochondrial membranes [65]. These data suggest that disabling of ProTα is a significant part of apoptosis.

ProTα has been considered as one of the molecules mediating the physiological switch between apoptosis and autophagic cell death in terminally differentiated cells such as neurons. Overexpression of ProTα with or without other caspase inhibitors has been reported to induce autophagic cell death possibly in association with cytochrome c release secondary to endogenous stress [66]. Additionally, ProTα has been recently demonstrated to exhibit a protecting role against oxidative stress by releasing the Nrj2 transcription factor from the Nrf2-Keap1 inhibitory complex [67].

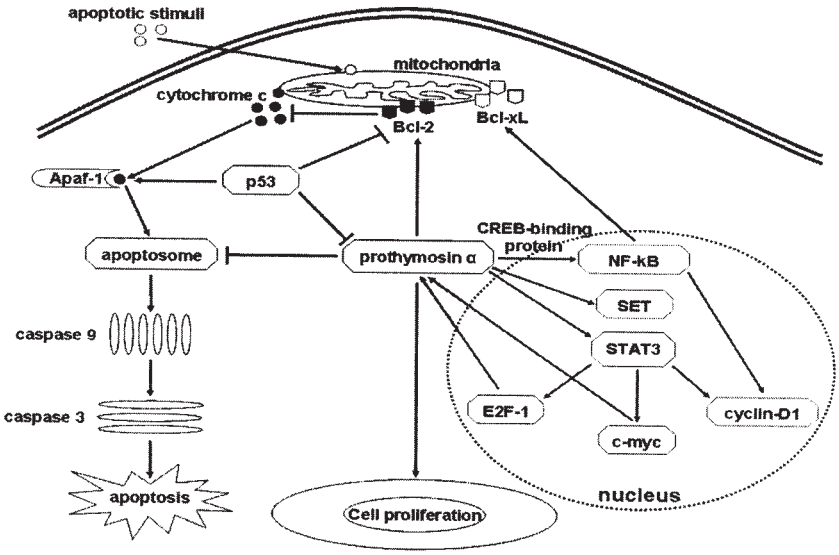

Figure 1. Selective model for prothymosin α target genes implicated in cell death and survival pathways.

Conclusion

ProTα seems to exhibit a strategic role in continuous cell growth and cancer development. The available evidence clearly indicates that ProTα acts pleiotropically in various transcriptional activation events that mediate critical stages of cell proliferation and apoptosis (Fig. 1). However, many questions remain to be answered: (a) a full picture of ProTα-target genes; (b) a better understanding of ProTα-dependent pathways that lead to cellular transformation and tumorigenesis; (c) the mechanisms of how ProTα through association with other factors increase transcriptional initiation; and (d) a more comprehensive definition of pathways leading to cell survival by inhibiting apoptosis.

Further studies are necessary to establish ProTα as a molecular marker for early detection of certain types of cancers as well as a prognostic index for determining tumor aggressiveness and the response to various treatments. The essential participation of ProTα in the proliferation and apoptotic processes is opening up new prospects regarding the detection of new molecular targets for the development of future cancer therapy.

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