HHS Public Access

Author manuscript

. Author manuscript; available in PMC 2016 May 10.

Published in final edited form as:

. 2015 December 20; 31(12): 1261–1266. doi:10.13865/j.cnki.cjbmb.2015.12.06.

Mechanism and Function of Angiogenin in Prostate Cancer

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Abstract

Angiogenin (ANG), the fifth member of the vertebrate-specific ribonuclease (RNase) A superfamily, is a secreted angiogenic ribonuclease strongly up-regulated in human prostate cancers. ANG is translocated to the nucleus in both prostate cancer epithelial cells and endothelial cells to exert its role in prostate cancer progression by mediating tumor angiogenesis, cancer cell survival and proliferation through rRNA biogenesis. ANG-stimulated rRNA is required not only for prostate intraepithelial neoplasia (PIN) formation, but also for androgen-independent growth of prostate cancer cells. Targeting ANG by various antagonists that inhibit its nuclear translocation, function and/or activity has proven to inhibit prostate cancer growth in animal models. Furthermore, the role of ANG in androgen independence has been firmly established, suggesting a strong rationale for therapeutically targeting ANG in the treatment of castration resistant prostate cancer.

Keywords

angiogenin; prostate cancer; angiogenesis; cell proliferation; rRNA biogenesis; castration resistance

1 ANG is a member of the RNASE A Superfamily

RNase A superfamily is believed to be the sole vertebrate specific enzyme family, of which Rnase 5/ANG is a member[1]. They exhibit diverse expression patterns, possess various catalytic activities against specific RNA substrates and have various physiological functions, including degradation of dietary RNAs in the gut, angiogenesis and innate immunity[1–3]. If we take a closer look at the origin and diversification of this superfamily, we can find strong evidence that the members of this family originated from an RNase 5-like gene and expanded in mammals[3,4]. The fact that only RNase 5-like RNases have been reported outside the class mammalia suggests that the ANG/RNase 5 group is probably the most ancient form of this superfamily and that all other members arose during mammalian evolution[3].

There is strong evidence for the hypothesis that the superfamily started as a host-defense mechanism during early vertebrate evolution and that its expansion in mammals led to their current functional diversity[4,5]. The fact that multiple members of this superfamily,

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including RNase 2 (EDN), 3 (ECP), 5 (ANG) and 7 have anti-pathogenic activities fortifies this view[5–8]. More interestingly, gene expression data analysis suggests male reproductive functions for RNases 9 ~ 13, although their sequences suggest the lack of ribonucleolytic activities[3]. Mouse Rnases 9 and 10 are exclusively expressed in the epididymis[9,10], and pig RNase 10 is the most abundant compound secreted in the anterior part of epididymis, where sperm maturation and activation takes place[10]. By using high-density oligonucleotide arrays, Su *et al* has shown human RNase 11 is expressed in the testis at an outstandingly high level, compared to other tissues[11]. Because RNases 9 ~ 13 are evolutionarily closely related, it is possible that they all have specialized functions in the male reproductive organs[3].

Among the 13 paralogs of this superfamily, Rnase 4 is of particular interest in relation to the study of ANG since they share the same promoters and are co-expressed[12,13]. RNase 4 was originally co-isolated with ANG from the HT-29 human colon adenocarcinoma cell-conditioned medium[14] and has 38.7% identity with ANG at the protein level[15]. Interestingly, Rnase 4 is the most conserved gene across the different vertebrate species and has strict substrate specificity towards 3′-side of uridine nucleotides[16,17]. Just like ANG, Rnase 4 shares the same angiogenic, neurogenic and neuroprotective activities[15], however there is strong evidence to suggest a yet unidentified, more specific biological function. The arrangement and regulation of Rnase 4 and ANG suggest that they may have complementary or supplementary biological activities. In honor of the 30 years anniversary of the discovery of ANG, we believe that RNase 4 is worth mentioning since they were isolated at the same time, however for the purposes of this review, we will focus our attention on ANG, especially on its profound role in prostate cancer progression.

2 Prostate cancer: overview and current treatment options

Prostate cancer is the second most common cancer in the US, affecting 1 in 7 men[18]. In 2015, approximately 220 800 men were diagnosed with prostate cancer, and more than 27 540 men died from the disease[19]. The cause of prostate cancer is not known, however there are certain risk factors associated with prostate cancer like age, ethnic background, family medical history and diet[20]. All men are at risk of prostate cancer, but the risk greatly increases with older age. Prostate cancer is rarely found in men younger than 50 years old[19]. Over the last 20 years due to prostate cancer screening tests, more men are being diagnosed with prostate cancer at an early stage, when the cancer is highly curable[21]. However, there have been some conflicting views among major medical associations and societies regarding prostate cancer screening. Even if screening finds a cancer early, it is not clear in all cases that the cancer must be treated[22–25].

Prostate cancer screening mainly involves in prostate specific antigen (PSA) blood test and digital rectal exam (DRE)[26]. PSA is secreted from the epithelial cells of the prostate gland, and when prostate cancer develops PSA level usually goes above 4 ng/mL[27]. No PSA level guarantees the absence of prostate cancer, but as PSA levels increase so does the risk of the disease. Men with PSA levels above 10 ng/mL have 50% chance of having prostate cancer[26]. The PSA test is also a part of staging and can help tell if the cancer is likely to still be confined to the prostate gland. Patients who present with elevated PSA levels or

abnormal DRE findings undergo needle biopsy of the prostate for tissue diagnosis[28]. Whether cancer is suspected based on screening tests or symptoms, the actual diagnosis can only be made with a prostate biopsy. The PSA level and the Gleason grade are then used to determine how aggressive the tumor is and what treatment options are available.

In general, lower-stage cancers are less aggressive and less likely to come back after treatment compared to higher-stage cancers. Stage I and II prostate cancers are referred to as localized prostate cancer, stage III is locally advanced, and stage IV is referred to as advanced or metastatic prostate cancer[28]. There are 3 standard ways to treat localized prostate cancer; active surveillance, which involves PSA testing every 3 months and repeat biopsy once or twice a year, radical prostatectomy and/or radiation therapy, which is sometimes combined with androgen deprivation therapy (ADT)[29]. Androgens fuel the growth of prostate cancer. Treatments that decrease the body's level of androgens reduce the size and slow the growth of prostate cancer[30]. ADT is not recommended for men with small tumors that are unlikely to grow quickly due to serious side effects. Locally advanced stage III prostate cancer is usually treated with this combination of radiation and ADT[31]. A rise in PSA level after radical prostatectomy to greater than 0.2 ng/mL or 3 consecutive PSA increases after radiation therapy are evidence of disease progression[32].

Prostate cancer is advanced if it has spread outside the prostate, beyond the seminal vesicles, into the lymph nodes or to more distant areas, like the bones. Stage IV advanced prostate cancer is usually treated with a combination of treatments, which may include hormone therapy, chemotherapy, immunotherapy, or radiation[33]. Although advanced prostate cancer is not curable, treatment can often help to control the cancer for some duration of time. ADT is usually recommended as the initial treatment for men with metastatic prostate cancer. In cases where disease is quite advanced at the time of initial treatment, ADT is often combined with chemotherapy[33]. ADT may involve surgical or chemical castration and anti-androgen therapy to starve the cancer cells and shrink the prostate. Unfortunately, almost all patients with metastatic disease become resistant to androgen ablation, at this point the cancer is termed 'castration resistant'[34].

There are only a few FDA approved treatment options available for castration resistant prostate cancer that increase survival by 2 ~ 5 months, like the docetaxel and cabazitaxel chemotherapy agents[35,36], abiraterone acetate[37], which is an inhibitor of androgen biosynthesis, enzalutamide that inhibits binding of androgens to the androgen receptor[38], and the cancer vaccine Sipuleucel-T[39]. To create Sipuleucel-T peripheral blood mononuclear cells, including antigen-presenting cells (APCs) are extracted from the patient using leukapheresis and are incubated with prostatic acid phosphatase, an antigen expressed in prostate cancer tissue[39]. The product, which now contains activated APCs is infused back into the patient. This treatment needs to be prepared individually for each patient and prolongs survival by 4 months[39]. More effective treatments for metastatic castration-resistant prostate cancer are urgently needed and ANG presents as a promising molecular target for drug development for the treatment of prostate cancer, especially the castration resistant prostate cancer.

3 ANG is up-regulated in prostate cancer and involved in PIN formation

ANG is up-regulated in human cancers, particularly in prostate cancer, and plays an important role in stimulating cell growth, promoting cell survival and tumor angiogenesis[40–44]. In fact, ANG has been demonstrated to be a permissive factor for other angiogenic factors to induce angiogenesis[45]. ANG protein and mRNA is up-regulated in clinical tissue samples derived from prostatic carcinoma compared to normal prostate tissue. Interestingly, IHC study from a large cohort of radical prostatectomy specimens found that ANG expression increased progressively as prostatic epithelial cells evolve from benign to an invasive phenotype and enhanced expression of ANG is correlated with the occurrence of the disease and with its progression[40,46]. ANG amount in the serum of control patients with no evidence of prostate cancer and patients with prostate cancer was 328 ± 20 ng/mL and 392 ± 17 ng/mL, respectively ($P < 0.01$)[47]. There is also trend toward significantly higher levels of ANG in castration resistant prostate cancer patients compared to untreated patients[48].

Consistently, mouse *Aag* is the most significantly up-regulated gene in AKT-induced PIN in the murine prostate-restricted AKT kinase transgenic (MPAKT) mice[49]. In MAPKT mice, expression of AKT in the ventral prostate results in induction of PIN and up-regulation of ANG in these mice was observed as an early and sustained event[49]. These findings suggest a potential role of ANG both in initial cell proliferation and in cell-survival in AKT-induced PIN. Further evidence for establishing ANG as a causative factor rather than a consequence of PIN formation came from studies demonstrating that *Ang*1 siRNA inhibits PIN formation, despite continuous activation of AKT transgene and activation[50]. Furthermore, knocking down *Ang*1 completely abolished AKT-induced increase in rRNA transcription, suggesting that rRNA transcription in AKT-induced PIN is also mediated by ANG[50].

4 ANG stimulates rRNA transcription in prostate cancer and mediates castration resistance

The biological activities of ANG in regulating prostate cancer cell proliferation and tumor angiogenesis depends on its ability in regulating rRNA transcription[46]. ANG has been shown to undergo nuclear translocation both in endothelial and cancer cells[51]. Upon arriving at the nucleus, ANG accumulates in the nucleolus where ANG binds to the promoter region of rDNA and stimulates rRNA transcription[52]. Thus, ANG acts as a transcription factor to promote rRNA transcription directly. Whether maintaining a normal cell function or in cancer cells, the rate-limiting step in sustaining cell growth is the production of new ribosomes. For cancer cells, ANG-mediated rRNA synthesis is shown to be crucial for sustained cell proliferation and angiogenesis induced by other angiogenic factors that play a role in tumor angiogenesis, including VEGF, bFGF, aFGF, and EGF[45]. Thus, we can conclude that ANG has a dual role in cancer progression by stimulating cancer cell proliferation as well as mediating tumor angiogenesis, both through the mechanism of enhanced rRNA biogenesis.

Interestingly, constitutive nuclear translocation of ANG is observed in androgen-independent cell lines, resulting in a constant rRNA overproduction[53]. Knocking-down

ANG expression in androgen-independent cells decreases rRNA transcription, ribosome biogenesis, cell proliferation and tumorigenecity both *in vitro* and *in vivo*[53]. Critically, *ANG* overexpression in androgen-dependent prostate cancer cells enables castration-resistant growth of otherwise androgen-dependent cells[53]. Thus, ANG-stimulated rRNA transcription is not only an essential component for androgen-dependent growth of prostate cancer but also contributes to the transition of prostate cancer from androgen-dependent to castration-resistant growth status.

Previous studies have firmly demonstrated the effect of androgens in regulating rRNA biogenesis during androgen-dependent cell growth in normal development and disease state of the prostate such as benign prostatic hyperplasia, PIN and prostate cancers[54–56]. In the case of castration resistant prostate cancer, there must be an androgen-independent pathway of rRNA transcription. ANG is a downstream effector that mediates the stimulatory effect of androgen-androgen receptor axis on rRNA transcription[57], which is supported by the fact that androgen receptor does not bind to rDNA directly[58]. It is also conceivable that overexpression of this effector results in overproduction of rRNA and promotes castration-resistant growth of prostate cancer. ANG-mediated rRNA transcription thus fulfills this growth requirement in castration resistant prostate cancer[57].

5 Therapeutically targeting ANG to inhibit prostate cancer growth in mouse models

The anti-cancer activity of ANG antagonists has been well established over the years[43,44,46]. Both inhibition of ANG-induced tumor angiogenesis and inhibition of cancer cell proliferation contribute to this observed anticancer activity of ANG. ANG plays a crucial role in the subcutaneous growth of human prostate tumors in athymic mice, presumably acting at an early stage of tumor development[44]. Currently available ANG antagonists consist of the neutralizing monoclonal antibody (MAb) 26-2F[44], the inhibitors of nuclear localization of ANG neomycin[46] and its nontoxic degradation product neamine[59], siRNA[43], soluble binding proteins, antisense oligonucleotide and enzymatic inhibitors[57]. All of these have been shown to inhibit prostate cancer in various animal models through inhibition of both tumor cell proliferation and angiogenesis. For example, the MAb 26-2F has been shown to prevent the establishment of PC-3, the androgen-independent prostate cancer tumors in about 40% of treated mice ($p<0.0001$)[44]. Additionally, prophylactic systemic administration of MAb 26-2F dramatically reduced (50%) the formation of spontaneous regional metastasis originating from primary growth in the prostate gland[44].

During the study of the mechanism by which ANG is translocated to the nucleus of endothelial cells, neomycin, a phospholipaseC(PLC) inhibitor, was found to block nuclear translocation of ANG[60]. Subsequently, neomycin was found to inhibit ANG-induced endothelial cell proliferation and angiogenesis and it was shown that this effect of neomycin was not due to its antibiotic properties[60]. Treatment with neomycin not only prevented tumor establishment in 50% of mice, but also delayed the appearance of palpable tumors in the other 50% of mice that did grow tumors in PC-3 xenograft experiments[46]. Neamine has

also been shown to inhibit PC-3 tumor establishment in 50% of athymic mice with an overall inhibition of 72.5% in the growth rate[61]. This inhibition was accompanied by a blockade of nuclear translocation of ANG and a decrease in rRNA transcription, consistent with the reports that nuclear function of ANG is related to rRNA transcription and that the neomycin family of aminoglycoside antibiotics blocks nuclear translocation of ANG. Neamine inhibits angiogenesis induced both by ANG and by bFGF and VEGF[59]. In addition, neamine prevents and reverses AKT-induced PIN in MPAKT mice[61]. Given the nontoxic nature of neamine it is a preferred substitute for neomycin as a promising lead agent for further development in the treatment of prostate cancer[57].

Overall, accumulating evidence over the years suggests that ANG plays an important role in prostate cancer progression by stimulating both cancer cell proliferation and tumor angiogenesis. The essential role of ANG in mediating rRNA transcription in both endothelial cells and prostate cancer cells suggest that ANG is a molecular target for prostate cancer drug development. Studies targeting ANG itself as ANG-specific siRNA and antisense that inhibit ANG synthesis, and MAb and binding proteins that neutralize secreted ANG proteins have all been shown to inhibit xenograft growth in athymic mice. However, a disadvantage of this strategy is the relatively high circulating ANG levels (250–350 ng/mL) in plasma, therefore a very high concentration of ANG inhibitors would be needed to neutralize circulating ANG[47–48]. Blockage of nuclear translocation of ANG seems to be a more promising approach and would avoid potential problems caused by high plasma concentration of ANG. To our advantage, the biological function of ANG requires ANG to be physically present in the nucleus, and the nuclear translocation of ANG only occurs in proliferating endothelial cells and cancer cells. Alternatively, the ANG receptor and its signaling pathway could be an interesting and potential target for targeted therapy, however the cell surface receptor of ANG is still under investigation.

Acknowledgments

Supported by National Institute of Health grants (No. R01CA105241, R01NS065237)

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