

Abstract

The placenta and tumors share important characteristics, including a requirement to establish effective angiogenesis. In the case of the placenta, optimal angiogenesis is required to sustain the blood flow required to maintain a successful pregnancy, whereas in tumors establishing new blood supplies is considered a key step in supporting metastases. Therefore the development of novel angiogenesis inhibitors has been an area of active research in oncology. A subset of the molecular processes regulating angiogenesis are well understood in the context of both early placentation and tumorigenesis. In this review we focus on the well-established role of androgen regulation of angiogenesis in cancer and relate these mechanisms to placental angiogenesis. The physiological actions of androgens are mediated by the androgen receptor (AR), a ligand dependent transcription factor. Androgens and the AR are essential for normal male embryonic development, puberty and lifelong health. Defects in androgen signalling are associated with a diverse range of clinical disorders in men and women including disorders of sex development (DSD), polycystic ovary syndrome in women and many cancers. **We summarize the diverse molecular mechanisms of androgen regulation of angiogenesis and infer the potential significance of these pathways to normal and pathogenic placental function.** Finally, we offer potential research applications of androgen-targeting molecules developed to treat cancer as investigative tools to help further delineate the role of androgen signalling in placental function and maternal and offspring health in animal models.

Androgen dependent mechanisms of pro-angiogenic networks in placental and tumor development

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*Highlights

- The placenta and tumors share important characteristics, including a requirement to establish effective angiogenesis.
- We focus on the well-established role of androgen regulation of angiogenesis in cancer and infer potential relevance to placental development and function.

1 **Introduction**

2 It has long been recognized that the placenta and tumors share important characteristics. These
3 include mechanisms related to immune privilege and most notably in the context of this review,
4 a requirement to establish effective neovascularization and angiogenesis. Placental
5 angiogenesis is a tightly regulated process involving complex interactions of pro- and anti-
6 angiogenic factors, which if dysregulated can lead to different pregnancy complications
7 including preeclampsia [1]. Examples of important pro-angiogenic factors in the placenta include
8 vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and fibroblast growth
9 factor (FGF) [2], whereas soluble fms-like tyrosine kinase 1 (sFlt-1) is noted as a key anti-
10 angiogenic factor [3]. A better understanding of placental angiogenesis would be beneficial in
11 understanding pathological conditions such as preeclampsia and intrauterine growth restriction.
12 This review will provide a summary of current understanding of the role of angiogenesis in
13 cancer and placental physiology, with an emphasis on androgen regulation of pro-angiogenesis
14 pathways.

15 Androgens have long been known to play essential roles in male embryonic development and
16 pubertal maturation [4] and are now recognized as having a role in angiogenesis [reviewed in 5].
17 The most abundant physiological androgens in men are testosterone and its more potent
18 derivative 5 α -dihydrotestosterone (DHT) which is produced by steroid-5 α -reductase enzymes
19 [6]. Testosterone can also be converted to the primary estrogen (β -estradiol) by aromatase [7],
20 therefore it is often essential to consider the relative roles of androgen and estrogen signalling.
21 Androgen production is regulated in the hypothalamus, where gonadotrophin hormone-releasing
22 hormone (GnRH) triggers the release of luteinizing hormone (LH) from the pituitary gland [8]. LH
23 in turn acts on the testes where the majority of the testosterone is synthesized. Testosterone is
24 transported to target tissues primarily bound to the sex hormone-binding globulin or to albumin
25 [9, 10]. Secondary androgens, such as androstenedione (AED) and dehydroepiandrosterone

26 (DHEA) are produced primarily by the adrenal glands [8]. As we will discuss in detail later, there
27 is also evidence of androgen synthesis [11] and androgen receptor (AR) expression in the
28 placenta and endometrium [12-14].

29

30 **Androgen receptor signalling**

31 The actions of androgens are mediated primarily by the AR, also referred to as NR3C4 [15]. The
32 AR is a member of the ligand dependent superfamily of nuclear receptor transcription factors
33 which, in the presence of androgens, regulates the transcription of target genes [15]. Nuclear
34 receptors consist of three major domains: the N-terminal region, the DNA-binding domain (DBD)
35 and the C-terminal ligand-binding domain (LBD) [16]. The N-terminal region is variable in both
36 sequence and size and in the AR harbors an agonist independent transcriptional activation
37 function (AF-1) [17]. The highly conserved DBD is situated in the centre of the polypeptide and
38 selectively and preferentially binds to androgen response elements in the regulatory regions of
39 androgen target genes. The DBD and LBD are separated through a variable hinge region that
40 contains DNA minor-groove binding residues [18]. The LBD is the site where both ligands and
41 coregulators bind and where the second transcriptional activation function (AF-2) region is
42 situated. In contrast to AF-1, AF-2 is ligand-dependent and full transcriptional activity can only
43 be accomplished when AF-1 and AF-2 act together [19]. The AR regulates gene expression by
44 recruiting multiple epigenetic coregulators, often through a conserved LxxLL motif, which control
45 transcription via covalent histone modifications (Figure 1) [20]. The role of coregulators in gene
46 activation and how these relate to the modulation of histone lysine acetylation and methylation
47 is an area of active research. Nuclear receptor-coregulator complexes, and by inference the AR-
48 coregulator complex, are believed to be dynamic [21] and involve the recruitment of diverse
49 enzymes which covalently modify the N-terminal tail of histones such as lysine
50 acetyltransferases (KATs), deacetylases (HDACs), lysine methyltransferases (KMTs) and lysine

51 demethylases (KDMs), kinases/phosphatases, poly(ADP)ribosylases and ubiquitin ligases [22].
52 KATs and HDACs have been intensively studied and the general paradigm is that KAT activity
53 increases DNA accessibility, thus activating gene transcription, whereas HDACs are associated
54 with transcriptional repression [23, 24]. It is important to note that certain coregulators, including
55 KDM1A which is also expressed in the placenta [25], can exhibit transcriptional activation and
56 repression properties in a cellular and epigenomic context-dependent manner [26].

57

58 **Androgens and fetal development**

59 During normal embryonic development and sex determination, the 46XY fetus instructs the
60 primitive bipotential gonad to develop into testes [4]. Testicular androgen production and the
61 ability to respond to these androgenic hormones are both then required to enable the XY fetus
62 to complete male sex differentiation [4 and references therein]. Yet, it is estimated that between
63 1 in 20,400 and 1 in 99,100 infants are unable to respond to androgens and present with
64 complete 46 XY sex reversal, termed complete androgen insensitivity [4]. Complete androgen
65 insensitivity syndrome (CAIS) results in 46XY sex reversal and typically presents with pubertal
66 amenorrhea or inguinal swelling in infants [27]. About 90-95% of all CAIS cases show mutations
67 in the AR causing hormone resistance [28]. Partial androgen insensitivity syndrome (PAIS) is
68 more common and the PAIS phenotype is much more complex and diverse [4]. We [29-32] and
69 others [33] have identified and functionally characterized numerous loss of function and intronic
70 mutations in the AR locus in individuals with complete and partial AIS. As we will explore in
71 more detail later, the inability of the CAIS fetus and the fetal placenta component to respond to
72 androgens suggests that pregnancy is sufficiently sustained by the ability of the maternal
73 placental component to respond to androgens.

74

75

76 **Androgens, angiogenesis and cancer**

77 Much of our understanding of androgen regulation of angiogenesis has been obtained in cancer
78 studies. Androgens and androgen signalling are implicated in many human cancer types,
79 including prostate [34, 35], testicular germ cell [36] and bladder [37] cancers. Androgens are
80 also known to have complex roles in breast tumors [38-40]. AR coregulators, including the
81 lysine demethylase KDM1A/LSD1 [37, 41, 42] and p160 coactivators [43-45] have also been
82 implicated in cancer, most notably prostate cancer (PCa). PCa is the most common non-
83 cutaneous cancer affecting men [46]. The treatment options for PCa are often dependent upon
84 the age and general health of the patient, as well as the stage and grade of the cancer.
85 Watchful waiting, active surveillance, radical prostatectomy and radiotherapy remain the most
86 effective initial therapies of localized PCa, however these can be associated with negative
87 impacts on quality of life [47, 48] and post-treatment recurrence remains common [49]. In the
88 case of PCa, treatments which block androgen biosynthesis or signalling, so called androgen
89 deprivation therapies (ADT) are important treatments for advanced PCa (Figure 2). Existing
90 ADTs target AR function by blocking androgen biosynthesis (GnRH analogues), acting as AR
91 selective antagonists (bicalutamide, enzalutamide) or blocking intra-tumoral androgen
92 biosynthesis (abiraterone) [50, 51]. Unfortunately, ADTs are ineffective in the long term for many
93 patients, as incurable hormone refractory PCa tumors which are resistant to ADTs, commonly
94 emerge within ~18 months at which point only palliative treatments are available. For this
95 reason, great effort was invested to develop novel therapies targeting tumor angiogenesis.
96 Indeed >20 years ago, Marshall and Narayan suggested a role for androgens in PCa
97 angiogenesis [52]. Subsequent studies in mouse PCa xenograft models indicated castration
98 decreased angiogenesis with a concomitant decrease in levels of vascular endothelial growth
99 factor A (VEGFA)[53]. More recently, we and others found that androgens and AR-coregulators

100 regulate VEGFA levels (Figure 3) [35, 54, 55]. Consistent with this there is clinical [54] and
101 genetic [56] evidence suggesting a link between VEGFA expression and poorer outcomes in
102 PCa patients. Androgen depletion has been found to significantly induce apoptosis of tumor
103 associated endothelial cells, suggesting a direct effect on angiogenesis, independent of the
104 effect of androgen withdrawal on PCa cell proliferation and/or viability [53]. For these reasons
105 there was much hope for treatments targeting pro-angiogenesis mediators such as VEGFA.
106 However, clinical trials of angiogenesis inhibitors have been disappointing with only modest anti-
107 tumor activity achieved in patients [57], though the use of anti-VEGFA therapy in combination
108 with other agents shows more promise [58, 59].

109

110 **Androgens and angiogenesis in endometrial and placental function**

111 There is robust AR expression in the endometrium [13, 60] and both the AR and
112 dihydrotestosterone are implicated in endometrial cancer. There is also evidence of endometrial
113 and placental androgen biosynthesis [11, 12]. However the expression of AR in the placenta is
114 controversial [14, 60-62]. In normal pregnancy, circulating androgen levels generally increase,
115 compared with non-pregnant female hormone levels. Testosterone has been shown to increase
116 by day 15 after the luteinizing hormone surge with reports of ~1.55 – 1.7 fold average increase
117 from day 15 through to week 33 in comparison to non-pregnant women, changes were not
118 observed prior to day 13 [63, 64]. Androstenedione levels rise from day 14 and increase on
119 average by 1.3 fold from week 5 to 40 in comparison to non-pregnant women [63, 64].
120 Additionally, testosterone decreased uterine blood flow to the placenta [65]. It is interesting to
121 note that the free androgen index fell rapidly from weeks 5-21, plateauing at week 21 and rising
122 marginally at 40 weeks [63]. Interestingly, aberrant placental function has not been described in
123 the pregnancies of CAIS fetuses, suggesting that maternal androgen signalling may be
124 sufficient to mediate any required androgen-regulated angiogenesis during placental

125 development. Excess testosterone during pregnancy can negatively impact placental
126 angiogenesis [66, 67]. For example, androgen levels are higher in pregnant women with
127 polycystic ovary syndrome (PCOS) as compared with normal pregnancy [68]. Free androgen
128 index, testosterone, androstenedione, and dehydroepiandrosterone (DHEA) levels were all
129 increased in PCOS pregnancies compared with normal pregnancies during weeks 22 to 28, but
130 not earlier in pregnancy (weeks 10 – 16) [68]. Despite differing circulating levels of androgens
131 during pregnancy, fetal virilisation was not observed. However this was likely due to fetal
132 virilisation occurring between weeks 8 and 13 of gestation, whilst the increased levels of
133 androgens were observed at week 16 [63, 64, 68]. The placenta also expresses aromatase
134 which rapidly converts androgens to estrogen [68, 69]. This could explain why the fetus is not
135 affected by virilisation in normal pregnancy. No associations have been observed between
136 concentrations of testosterone and the sex of the baby in pregnant vs non-pregnant women
137 [63]. Levels of DHEA, androstenedione or testosterone in normal pregnant women vs pregnant
138 PCOS women were also not dependent on the sex of the baby [68].

139
140 Increased first trimester total testosterone levels in women was also shown to be an
141 independent predictor of gestational diabetes mellitus (GDM) [70]. Increased androgen
142 sensitivity in the human GDM placenta compared to healthy placentas has also been reported
143 [69] as have increased AR mRNA and protein levels of in GDM placentae. In contrast
144 aromatase protein expression was decreased in GDM placentas compared with healthy
145 placentas, which was suggested to lead to reduced conversion of testosterone to estrogen [69].
146 Placentas from women with GDM also showed decreased human placental mRNA and protein
147 expression of *VEGFR2* and *VEGFA* compared to control placentas. Qualitative analysis of
148 immunohistochemical localization reported that although mRNA and protein levels were lower,

149 and immune-staining was weaker, VEGFR2 and VEGFA were expressed in the same cells and
150 localities within the GDM and control placentas [67].

151

152 There is evidence that suggests the mechanisms of angiogenesis are similar in the placenta
153 and prostate cancer. Evidence from early studies on first generation angiogenesis inhibitors
154 such as TNP-470, implicated impaired angiogenesis as a contributing factor in intrauterine
155 growth restriction of the fetus [71]. TNP-470 was shown to have an effect on human PCa cells
156 and a number of tumors in patients [72, 73]. Similarly, the endogenous angiogenesis inhibitor,
157 angiostatin4.5, has also shown activity in tumors [74]. Like TNP-470, angiostatin4.5 also
158 reduces murine placental angiogenesis and with the offspring showing skeletal growth delays
159 [75]. Maliqueo and colleagues have recently provided a comprehensive review of the diverse
160 roles of the sex steroids in the regulation of the uterine-placental vasculature [76]. Yet current
161 understanding of the role of androgen signalling in placental development and particularly its
162 potential role in regulating angiogenesis in the placenta, is incomplete. Androgens are known to
163 stimulate proliferation of human umbilical vein endothelial cells (HUVECs) [77], indicating a role
164 for androgens during pregnancy. Interestingly, this androgen effect on HUVEC function was not
165 sex dependent. There is also evidence from rat models that excess androgen reduces uterine
166 blood flow and increases maternal and adult offspring blood pressure, by a convergence of
167 mechanisms involving angiotensin II, reduced eNOS activity, a consequent reduction in NO
168 production and AR activation of protein kinase C (PKC δ) [78-81]. Furthermore, increased
169 testosterone results in elevated expression of hypoxia related genes including hypoxia inducible
170 factor 1 α (HIF1 α) [80], an established positive regulator of VEGFA [82]. VEGFA is believed to
171 play important roles in the earliest stages of embryonic implantation [83]. Yet the potential role
172 of androgens in regulating VEGFA and angiogenesis in the placenta remains poorly defined. But
173 in a recent ovine study examining the effects of testosterone on the placenta, VEGFA

174 expression was observed to be androgen responsive. Indeed AR and the KDM1A coregulator
175 are recruited to an androgen response element (ARE) in the ovine *VEGFA* locus [25]. On
176 gestational day 90, placental *VEGFA* mRNA, placental VEGFA and AR protein levels increased
177 in testosterone-treated ewes compared with control placentas [25].

178 Beyond androgen regulation of VEGFA in angiogenesis [35, 54], there is also evidence for a role
179 for androgens in regulation of the Slit/Robo pathway [84]. The slits(1-3) are secreted
180 glycoproteins act as ligands for the Robos(1-4) transmembrane receptors. In one recent study,
181 expression of Slit and Robo mRNA was compared in normal and preeclamptic (characterised by
182 impaired angiogenesis and hypoxia) human placental tissue specimens [1]. *Robo1* and *Robo4*
183 were shown to have significantly higher expression in pre-eclamptic as compared to healthy
184 tissue [85]. Additionally, hypoxia was shown to increase expression of Slit 2 in BeWo
185 choriocarcinoma cells and Robo1 and 4 and Slit 3 in human umbilical vein endothelial cells
186 (HUVEC) cells. Robo4 is a vascular specific and its activation by Slit2 has been shown in vitro
187 to inhibit mouse lung endothelial cell migration, tube formation and permeability induced by
188 vascular endothelial growth factor (VEGF)-165 [85]. Conversely, human malignant melanoma
189 cells found to be expressing Slit2 were shown to induce angiogenesis in a xenograft animal
190 model [86]. This effect was reversed, and tumour growth impeded, by Robo1 blocking
191 antibodies or soluble Robo1 receptor. Slit/Robo signalling is implicated in multiple, often
192 contradictory, ways in several cancers relating to invasion, migration and apoptosis as well as
193 angiogenesis (Gara et al., 2015). In most cases the Slits and Robos are under expressed due
194 to promoter hypermethylation. Indeed there is evidence that androgen excess during pregnancy
195 can reduce Robo1 expression [84]. One consequence of this would be to impact angiogenesis.

196

197 Human trophoblast cells isolated at late stage pregnancy have been shown to express the
198 angiogenesis inhibitor, pigment epithelium-derived factor (PEDF), at higher levels than those

199 from early pregnancy [87]. Additionally, only late stage pregnancy derived cells were capable of
200 reducing angiogenesis of human placental endothelial cells. This anti-angiogenic effect could be
201 reduced with the addition of a PEDF blocking antibody. Recombinant PEDF was also shown to
202 induce an anti-angiogenic effect through inhibiting VEGF signalling. This suggests PDGF acts
203 in a paracrine manner to slow angiogenesis in the latter stages of pregnancy. Expression of
204 PEDF has also been shown to be reduced in PCa as compared to healthy control [88].
205 However, there is evidence that androgen can both activate [89] and reduce [88] PEDF
206 expression in testicular peritubular cells and PCa respectively. Whether androgens regulate
207 PEDF in the placenta remains unknown.

208
209 It is also worth noting that whilst the placenta is undergoing angiogenesis and remodelling, so is
210 the maternal endometrium. The imbalance of pro- and anti-angiogenic factors has also been
211 shown to play a major role in disorders such as preeclampsia, where vascular disruption is
212 evident in both the placenta and maternal endothelium during this essential vascular
213 remodelling period [90, 91]. A number of studies have indicated that a key component of
214 circulating angiogenesis inhibitors is whether or not the vascular endothelial cells are quiescent
215 or activated and therefore expressing Fas at higher levels [92].

216
217

218 **Conclusion**

219 In this review we have discussed the current understanding of androgen signalling and how this
220 relates to angiogenesis in placental and cancer contexts. Previous studies have reported
221 changes in androgen levels during pregnancy and in pathogenic processes including PCOS and
222 GDM which are associated with concomitant changes in placental angiogenesis. However,
223 further work is required to elucidate the complex role of androgens and their metabolites in

224 placental angiogenesis and development. The extensive repertoire of pharmacological inhibitors
225 of androgen signalling developed for PCa represent excellent tools to interrogate the androgen
226 signalling pathway in placental development. The availability of potent pharmacological agents
227 which can inhibit androgen synthesis (abiraterone) and conversion to estrogen (aromatase
228 inhibitors), coupled with AR-antagonists such as bicalutamide and enzalutamide (Figure 2),
229 afford the potential to further delineate the complex roles of androgens in placental
230 angiogenesis in animal models. Such approaches will also help advance understanding of the
231 life-long consequences of deregulated androgen signalling *in utero*.

232

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239

240 **Figure 1. (A)** Crystal structure (PDB: 2AO6) of the AR ligand binding domain in complex with
241 agonist R1881 and the LXXLL motif derived from SRC2/TIF2/NCOA2 [93]. The LBD is
242 represented in cartoon format (green) and shows the three layer antiparallel alpha-helical
243 sandwich conformation typical of NRs. The SRC2/TIF2/NCOA2 coactivator peptide is shown in
244 yellow and adopts an alpha helical conformation. Conserved leucine residues are shown in cyan
245 and contact the cofactor binding cleft on the LBD surface. The ligand R1881 is shown in red
246 with the ligand binding pocket. (B) Crystal structure (PDB: 1R4I) of the rat AR DNA binding
247 domain (DBD) bound to the direct repeat of the hexamer AGAACA as a direct repeat, separated
248 by three nucleotides (DR3). [94]. The double stranded DNA duplex is shown in wireframe. The
249 DBD dimer is represented in cartoon format (green) and zinc atoms are portrayed as grey
250 spheres. The DBD monomers adopt alpha-helical conformations of which one these, the DNA
251 recognition helix, contacts specific bases and sugar-phosphate backbone of the 'response
252 element'. Interactions between the DBD monomers stabilise the dimer.

253 **Figure 2.** Androgen deprivation therapies are important treatment approaches for advanced
254 prostate cancer. Abiraterone blocks adrenal and gonadal androgen biosynthesis by inhibiting
255 the Cyp17/17-a-hydroxylase/C17,20 lyase enzyme. Flutamide, bicalutamide and enzalutamide
256 block androgen signalling by acting as AR antagonists. ARN-509, also termed JNJ-56021927 is
257 in clinical phase III trials for advanced PCa (clinicaltrials.gov accessions: NCT02772588,
258 NCT02489318, NCT02123758, NCT02578797, NCT01946204, NCT01790126, NCT01792687,
259 NCT02106507, accessed November 10, 2016).

260 **Figure 3.** Evaluation of the expression of vascular endothelial growth factor (VEGF-A) in
261 prostate cancer specimens as previously reported (Wegiel et al., 2008). Representative staining
262 examples are provided for benign prostate hyperplasia (BPH), low and high grade malignant
263 prostate tissue. Reproduced with permission from Kashyap et al [54] in *Molecular Oncology*,
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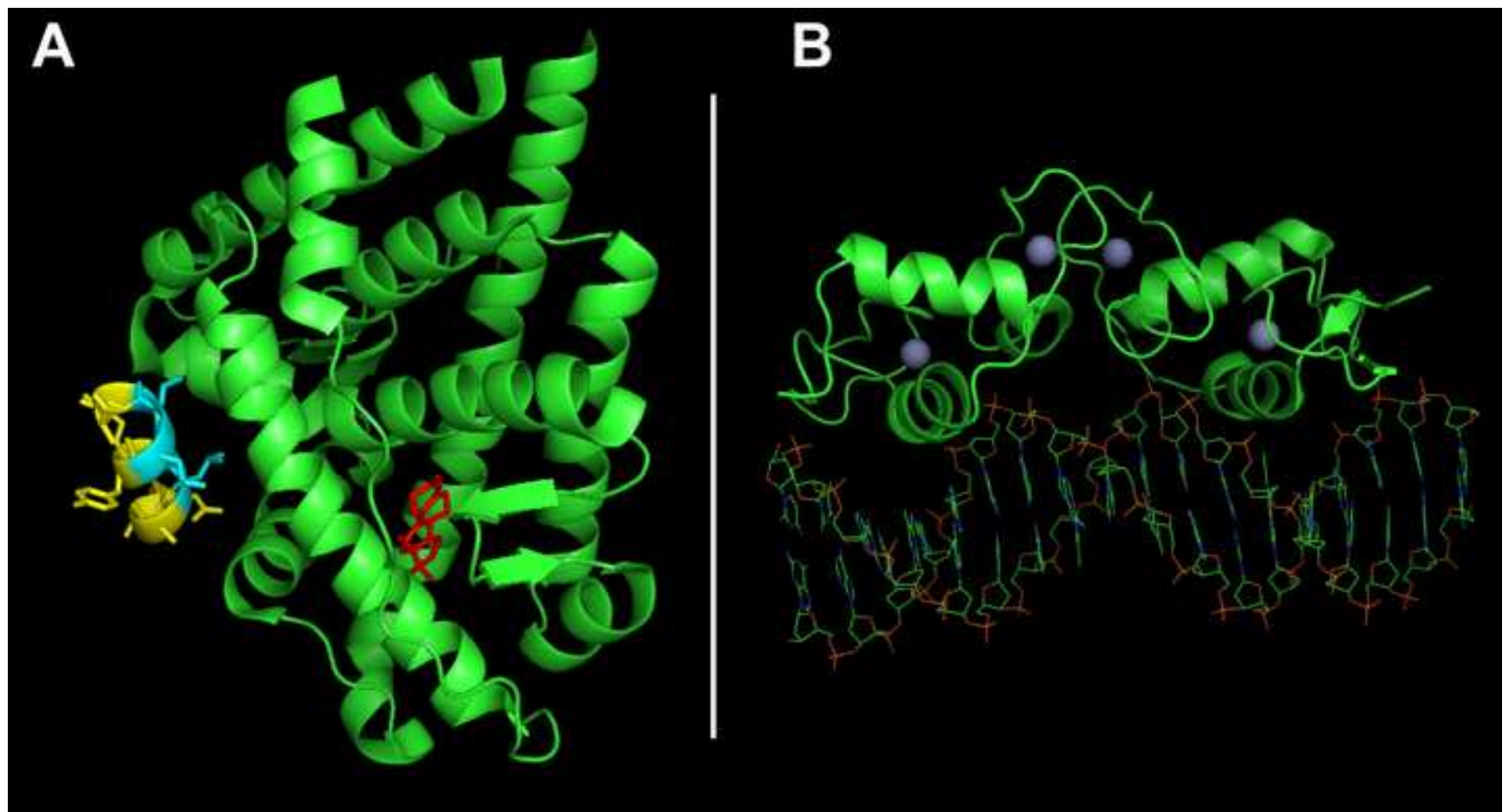
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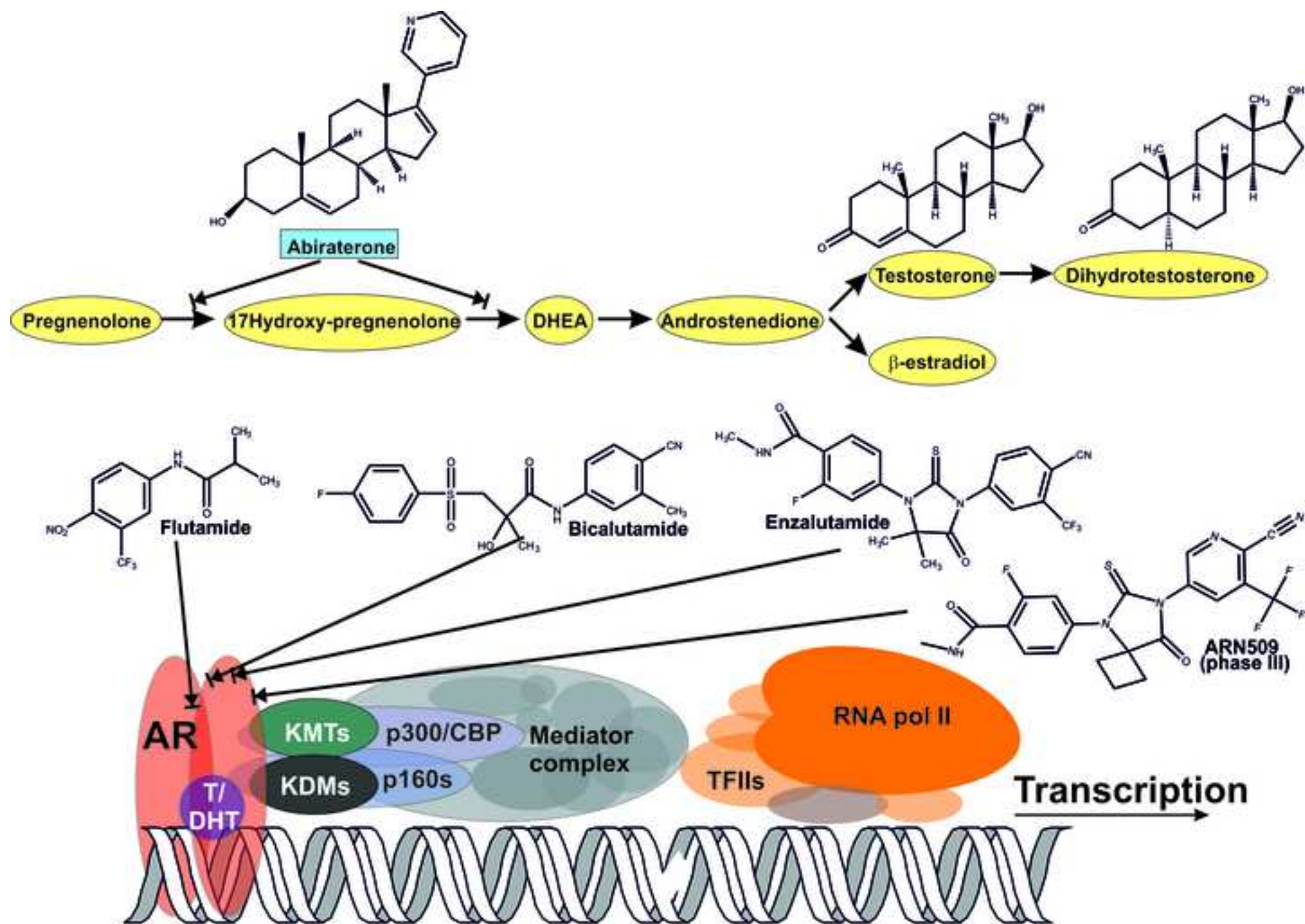
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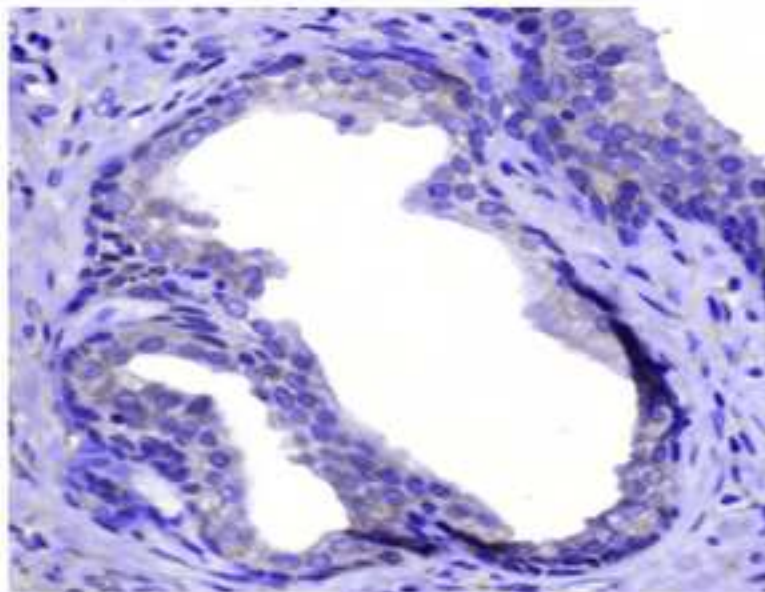
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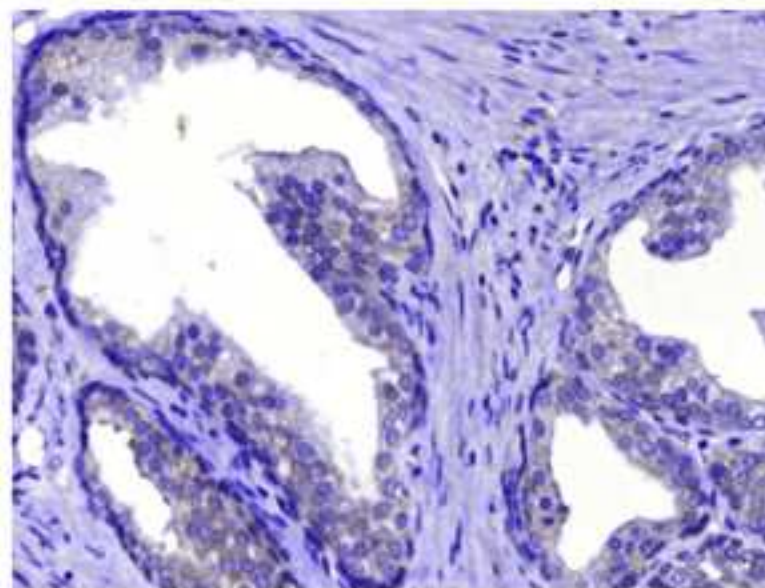
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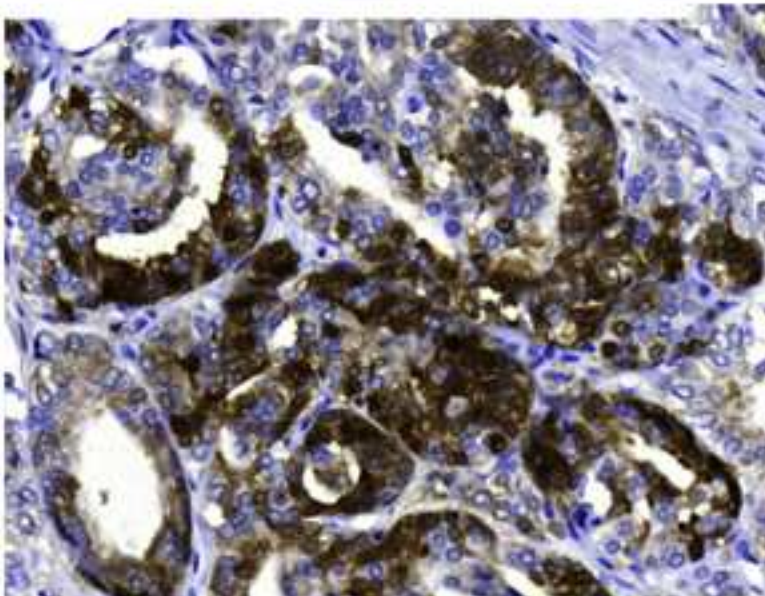
VEGF



BPH



Low



High