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Regulation of the prorenin - angiotensin system by oxygen and miRNAs; parallels between placentation and tumour development?

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ABSTRACT

Tissue renin-angiotensin systems (RASs) are involved in tissue growth and development as they are important regulators of angiogenesis, cell proliferation and migration. The placental RAS is most highly expressed in early gestation, at a time when the oxygen tension within the conceptus is reduced, and plays a key role in placental growth and development. Similar to the placenta, tumour development relies on proliferation, angiogenesis and invasion in order to grow and metastasize. The RAS is known to be upregulated in a variety of solid tumours, including ovarian, endometrial, cervical, breast and prostate. This review explores the roles of oxygen and microRNAs in regulating the normal expression of the placental RAS, providing insight into regulation of its development as well as the development of disease states in which the RAS is overexpressed. We propose that the placental RAS is downregulated by microRNAs that are suppressed during the physiologically normal 'hypoxic' phase of early placentation. Suppression of these miRNAs allows the placental RAS to stimulate placental growth and angiogenesis. We propose that similar mechanisms may be at play in solid tumours, which are characterised by hypoxia.

1. Introduction

The renin-angiotensin system (RAS) is a circulating endocrine system that controls blood pressure and salt and water homeostasis. However tissue renin-angiotensin systems also exist; many tissues express some or all components of the RAS and these systems can act independently of the circulating RAS. Tissue RASs play key roles in both physiological and pathological tissue growth, invasion and angiogenesis [1]. Exploration of the key factors regulating the normal and abnormal expression of these tissues RASs could provide novel insight into both the normal physiological development and regeneration of tissues such as the placenta, as well as the pathogenesis of disease states in which the RAS is over expressed, such as cancer.

The RAS plays a critical role in placental development. It is most highly expressed in early gestation placentae [2] and expression is altered in pregnancies compromised by placental insufficiency [3]. Inadequate placentation causes placental insufficiency, and contributes to pregnancy complications such as preeclampsia, intrauterine growth restriction (IUGR) and spontaneous abortion [4–6]; major causes of fetal and maternal morbidity and mortality.

Like the placenta, tumour growth depends on cell proliferation, angiogenesis and invasion in order to grow and metastasize. The RAS is upregulated in many cancers including ovarian, endometrial, cervical, breast and prostate and most of this research focuses only on Angiotensin II (Ang II)/Ang II type 1 receptor (AT_1R) signaling mechanisms [7–11]. The potential roles of tissue RAS pathways in tumour development has been reviewed by George et al. [12].

The shared attributes of tumour and placental development have been reviewed by Holtan et al. [13]. The highly proliferative, angiogenic and invasive capacity of tumour cells are the result of regulatory mechanisms that promote autocrine regulation of growth, evasion of apoptosis, sustained angiogenesis, vascular mimicry and tissue invasion which all occur in trophoblast cells [13]. Furthermore, mechanisms regulating immune evasion are shared between tumour and placental development, highlighting the potential similarities between cancer and placental biology.

This review examines the regulation of the RAS by oxygen and miRNAs in the placenta as well as in other tissues where the RAS is

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known to be important for growth and vascularisation. We also describe the potential roles for these pathways in regulating the RAS in tumours.

2. Tissue renin-angiotensin systems

In many tissues, prorenin, the inactive precursor to renin is produced; it can be activated by proteases [14] and by exposure to low pH or low temperature [15]. As well, non-proteolytic activation of prorenin occurs when prorenin binds to the (pro)renin receptor ((P)RR) also known as ATPase H (+)-transporting lysosomal accessory protein 2 (ATP6AP2)). This leads to a conformational change in prorenin so that it can now cleave angiotensin I (Ang I) from angiotensinogen (AGT). Ang I is cleaved by angiotensin converting enzyme (ACE) to Ang II, which exerts most of the known actions of the RAS by binding to one of two receptors, angiotensin II type 1 and type 2 receptor (AT_1R and AT_2R) (Fig. 1) [1]. In rodents, AT_1R exists in two forms (AT1a and AT1b [16]). In tissues, the Ang II/AT_1R interaction promotes proliferation, angiogenesis, migration, invasion and fibrosis [17–20]. In addition, Ang II/AT_1R can stimulate intracellular signaling pathways including mitogen activated protein kinase (MAPK)/extracellular signal-related kinase (ERK) and p85α-phosphoinositol 3-kinase (p85α-PI3K), which promote growth and vascularisation in tissues [18]. AT_1R is also pro-inflammatory and can increase the expression of pro-inflammatory mediators such as NF-κB, IL-6, IL-10 and TNF-α [21]. Ang II acting via the AT_2R mediates effects that are predominantly antagonistic to those of Ang II acting via the AT_1R; these include vasodilation and apoptosis (Fig. 1).

Additional RAS pathways exist. One pathway has actions that are opposite to the Ang II/AT_1R pathway. This pathway includes a homologue of ACE, ACE2, which cleaves a single amino acid from both Ang I and Ang II, forming Ang-(1–9) and Ang-(1–7), respectively [22]. Ang-(1–9) is subsequently cleaved by ACE to form Ang-(1–7). Ang-(1–7) acting on the Mas receptor has actions that antagonize the Ang II/AT_1R pathway, similar to Ang II/AT_2R. Another pathway involves the processing of Ang II by aminopeptidase A (APA) to produce either Ang III or Ang IV. Ang IV acting via the AT_4R, also known as insulin regulated amino peptidase (IRAP), induces vascularisation, inflammation, vasodilatation and hypertrophy (Fig. 1) [23].

The (P)RR contributes to proliferation, invasion, fibrosis and angiogenesis by stimulating intracellular signaling independent of Ang II production [24–28]. Additionally, (P)RR is the m8.9 segment of V-ATPase and is required for V-ATPase activity. The acidic extracellular environment created by H^+ secretion by this V-ATPase/(P)RR complex activates proteases (such as cathepsins) and matrix metalloproteases (MMPs), thus enhancing cellular invasion of adjacent tissues and stimulating angiogenesis [29]. The (P)RR/V-ATPase also activates the canonical Wnt/β-catenin signaling pathway which targets a multitude of genes also involved in proliferation, angiogenesis and invasion [30,31]. Thus, tissue RASs play a role in tissue growth and remodeling.

3. Placental RAS expression across gestation

Expression of the placental RAS changes throughout gestation (Table 1 [32–36]). The first trimester placenta has very high levels of expression of prorenin (*REN*), (P)RR (*ATP6AP2*), *AGT* and *AGTR1* compared with term placentae. Placental Ang II acting via the AT_1R has been shown to promote placental development. Ang II regulates cytotrophoblast differentiation *in vitro,* promotes cellular outgrowth (proliferation into cell columns) of human villous explant cultures [37], and promotes placental angiogenesis through vascular endothelial growth factor (VEGF) production [38].

Thus Ang II has been shown to have a number of actions that promote placental growth and development. There may also be a role for the (P)RR possibly activated by the extremely high levels of prorenin occurring early in gestation. The spatio-temporal pattern of the placental RAS, with high levels of prorenin and (P)RR co-localized to the villous cytotrophoblast and extravillous trophoblast in early gestation suggest paracrine/autocrine roles in placental growth (Table 1). The mechanisms responsible for the high levels of expression of the placental RAS in early gestation however, have not been fully elucidated.

4. Oxygen regulation of tissue RAS expression

4.1. Oxygen regulation of placental RAS

An important factor influencing placental growth and development is the oxygen tension within the conceptus. During the first

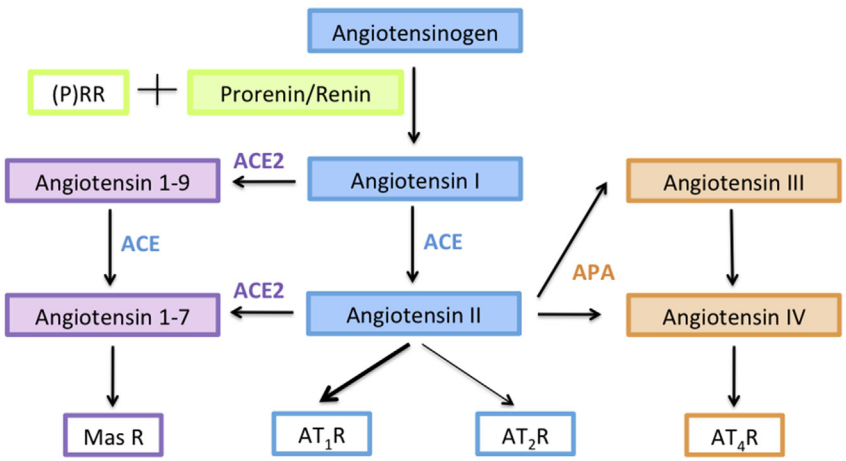

Fig. 1. The renin-angiotensin system cascade. Prorenin is activated by binding to the (pro)renin receptor ((P)RR) and possibly by proteolysis to cleave Angiotensin (Ang) I from Angiotensinogen (AGT). Angiotensin converting enzyme (ACE) then converts Ang I to the biologically active Ang II. Ang II can bind to angiotensin II type 1 receptor (AT_1R) to promote proliferation, angiogenesis, fibrosis, migration and invasion through stimulation of intracellular signaling pathways. Furthermore, Angiotensin (Ang) II binds to angiotensin I type 2 receptor (AT_2R) and antagonizes AT_1R activation. Aminopeptidase A (APA) allows conversion of Ang II to Ang III or Ang IV, which act on the AT_4R and can induce vascularisation, inflammation, vasodilation and hypertrophy. Ang I can also be further converted by angiotensin converting enzyme 2 (ACE2) to Ang-(1–7). Ang-(1–7) acts upon its receptor Mas. This results in antagonism of Ang II/AT_1R stimulation thus inhibiting proliferation, angiogenesis, fibrosis, migration and invasion.

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