Life Sciences 239 (2019) 117080

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Angiopoietin 2 signal complexity in cardiovascular disease and cancer

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ARTICLE INFO

Keywords:
Angiopoietin2
Adverse vascular remodeling
Low T3 state
Cardiovascular disease
Cancer

ABSTRACT

The angiopoietin signal transduction system is a complex of vascular-specific kinase pathways that plays a crucial role in angiogenesis and maintenance of vascular homeostasis. Angiopoietin1 (Ang1) and 2 (Ang2), the ligand proteins of the pathway, belong to a family of glycoproteins that signal primarily through the transmembrane Tyrosine-kinase-2 receptor. Despite a considerable sequence homology, Ang1 and Ang2 manifest antagonistic effects in pathophysiological conditions. While Ang1 promotes the activation of survival pathways and the stabilization of the normal mature vessels, Ang2 can either favor vessel destabilization and leakage or promote abnormal EC proliferation in a context-dependent manner.

Altered Ang1/Ang2 balance has been reported in various pathological conditions in association with inflammation and deregulated angiogenesis. In particular, increased Ang2 levels have been documented in human cancer and cardiovascular disease (CVD), including ischemic myocardial injury, heart failure and other cardiovascular complications secondary to diabetes, chronic renal damage and hypertension. Despite the obvious phenotypic differences, CVD and cancer share some common Ang2-dependent etiopathological mechanisms such as inflammation, epithelial (or endothelial) to mesenchymal transition, and adverse vascular network remodeling. Interestingly, both cancer and CVD are negatively affected by thyroid hormone dyshomeostasis.

This review provides an overview of the complex Ang2-dependent signaling involved in CVD and cancer, as well as a survey of the related clinical literature. Moreover, on the basis of recent molecular acquisitions in an experimental model of post ischemic cardiac disease, the putative novel role of the thyroid hormone in the regulation of Ang1/Ang2 balance is also briefly discussed.

1. Introduction

Angiogenesis, the formation of a vascular network from pre-existing vessels, is essential for wound healing in post-ischemic cardiovascular disease (CVD) and tumor growth. Activation of the angiopoietin/tyrosine kinase receptor (Ang/Tie) axis has been identified as the second most important switch signal for angiogenesis after the vascular endothelial growth factor (VEGF)/VEGF receptor pathway [1–4]. The angiopoietin family consists of four glycoproteins that are essential for blood vessel formation and maturation. Among them, the best characterized are Ang1 and Ang2 [4]. Ang1 is mainly expressed by mesenchymal cells and acts as a potent agonist of the Tyrosine kinase receptor 2 (Tie2) [5–6]. Under physiological condition, Ang1 enhances pro-survival pathways and the stabilization of normal mature vessels by inducing auto-phosphorylation of Tie2 [4–9]. Ang2 was initially identified by homology with Ang1 [10] and is expressed predominantly by endothelial cells, where it is stored in intracellular secretory granules called Weibel-Palade bodies (WPB) and promptly released after endothelium activation [11]. Like Ang1, Ang2 binds to Tie2 receptor, but with different pathophysiological effects. While Ang1 fosters endothelial stabilization, Ang2 can antagonize Ang1, blocking Tie2 activation and leading to vessel destabilization [4,10–12], which drives adverse remodeling of the vascular network including increased vascular permeability and vessel rarefaction. Whereas Ang1 is constitutively expressed, Ang2 expression is tightly regulated. In the presence of hypoxia and inflammatory stimuli, high amounts of Ang2 are produced leading to disruption of endothelial cell-cell junctions and cell-extracellular matrix (ECM) interactions with activation of adhesion molecules and leucocytes transmigration. Unlike Ang1, the expression of Ang2 is strongly up-regulated by Tumor necrosis factor alpha (TNFα) [13–14]. Thereafter, in a positive feedback loop, Ang2 promotes cell adhesion by sensitizing endothelial cells toward TNFα thus exacerbating the pro-inflammatory process [15]. In addition, Ang2 has been shown to enhance thrombin-induced monocyte adhesion and vascular leakage under pro-inflammatory conditions [16–17].

It is now clearly established that the role of Ang2 is context-

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https://doi.org/10.1016/j.lfs.2019.117080
Received 15 October 2019; Received in revised form 12 November 2019; Accepted 13 November 2019
Available online 19 November 2019

dependent: depending on the circumstances, it can favor abnormal endothelial cell (EC) sprouting and pathological angiogenesis by directly binding to integrin receptors and inducing phosphorylation of the integrin adaptor protein Focal adhesion kinase (FAK). A hyper-activation of this pathway is correlated with post cardiac ischemia, myocardial fibrosis and tumor progression [18–19].

Up-regulated Ang2 levels have been documented in a wide range of human disease such as cancer [4,20] and cardiovascular diseases (CVD), including myocardial ischemia (MI) and heart failure (HF) [21], or in cardiovascular complications secondary to chronic kidney injury, diabetes or hypertension [22]. Although exhibiting very different phenotypic outcomes, CVD and cancer share some common Ang2-dependent etiopathological mechanisms including inflammation, epithelial (or endothelial) to mesenchymal transition, vessel permeability and alteration of the vascular network.

In addition, both disease conditions are influenced by alteration of the thyroid hormone signaling. Of particular interest at this regard, is the non-thyroidal illness syndrome (NTIS), also known as low T3 state (LT3S). LT3S is a condition of reduced levels of the biologically active free T3 and increased levels of the metabolite reverse T3 (rT3) in otherwise euthyroid patients. Several reports have highlighted the association of NTIS with various cancer and CVD settings [23–33] and LT3S has been recognized as an independent risk factor for higher mortality in both conditions [24,29,34]. Interestingly, the association of LT3S with altered Ang1/Ang2 balance has been documented in a rat model of post ischemic myocardium in which T3 supplementation at the physiological level hindered such alteration in angiopoietins [35]. While the benefits of LT3S correction in CVD have been documented in a variety of clinical and experimental studies [31], the exploration of its role in cancer is still at its beginning [36]. Based on these premises, the aim of the present review is to highlight the complexity of the Ang2 signaling in the setting of CVD and cancer. To this purpose, the review includes an introductory section on the Ang2-dependent molecular pathways initiated at the cell membrane and a second part more specifically related to the clinical literature on cardiovascular complications and cancer. The connection between LT3S and Ang2 in post ischemic cardiac wound healing is also discussed.

2. Interaction of Ang2 with cell surface receptors

2.1. Tie2-receptor

Tie2 is the most important cell surface receptor for angiopoietins in both physiological and pathological conditions [1]. Although Ang2 mainly functions as a Tie2 antagonist [10,37–39], in particular conditions such as absence of Ang1, high Ang2 concentrations, and prolonged Ang2 exposure [40–43], it can act as a weak Tie2 agonist [44–45] (Fig. 1). Pioneering studies in cultured endothelial cells have shown that exogenous high concentrations of Ang2 promote phosphorylation of Tie2 [41–42], although with an effect not as potent as exogenous Ang1. In fact, Ang2 forms similar structural complexes with Tie2 as Ang1, but presents a lesser multimerised state that leads to a weaker intracellular response [46]. In cultured endothelial cells Ang2 is rapidly produced after inhibition of the Ang1/Tie2 signaling system. In this setting, Ang2 has been shown to activate Tie2 [40] and this activation is blocked using antibodies directed against Ang2, suggesting that Ang2 expression and secretion may be a compensatory response of EC when Ang1/Tie2 signaling is weak.

VEGF appears to be a key regulator of Ang2 mode of action. In the presence of VEGF, Ang2 induces migration, proliferation, and sprouting of new blood vessels. Conversely, in the absence of VEGF, Ang2 promotes endothelial cell death and vessel regression [47], thus suggesting that VEGF can convert the outcome of Ang2 stimulation from anti- to pro-angiogenic [47]. In quiescent vessels, in which only a limited amount of VEGF and Ang2 is available, Ang1 is released at high amount from pericytes and binds toTie2 receptors on EC inducing the phosphorylation dependent activation of downstream effectors including the Phosphatidylinositol 3-kinase/Protein kinase B (PI3-kinase/Akt), the extracellular signal-regulated kinase (ERK) pathway, and the endothelial nitric oxide synthase (eNOS) [2,9,48–49]. To promote cell quiescence, the activated Akt phosphorylates the transcription factor Forkhead box O1 (Foxo1), which results in Foxo1 nuclear exclusion and reduced expression of Foxo1 targets including Ang2 [50] and genes involved in the regulation of cell metabolism and growth [51]. Additionally, Ang1 induces trans association of Tie2 receptors at endothelial cell-cell contacts activating angiostatic mediators such as Delta-Like Ligand 4 (DLL4) and Notch which are fundamental to maintain cell-extracellular matrix interaction required for vascular quiescence. In this context, Ang2 activity is inhibited [52]. In presence of inflammatory stimuli, Ang2 is released in high quantities by ECs leading to an increase of nuclear Foxo1 localization, vascular leakage and the activation of adhesion molecules for leucocytes transmigration [52]. The underlying mechanism has recently been examined in detail by a gain- and loss-of-function approach in an experimental model undergoing normal or pro-inflammatory conditions [53]. Under physiological conditions, Ang2 acts as a Tie2 agonist: vessels show high phospho-Tie2 (p-Tie2), low nuclear Foxo1, and no leakage promoting vascular remodeling. In contrast, induction of Ang2 overexpression in presence of an infective pro-inflammatory treatment results in Tie2 antagonism with low p-Tie2, high nuclear Foxo1, promoting vascular remodeling and leakage. In this study, nuclear Foxo1 and cytoplasmic Ang2 result further increased by inhibiting the PI3K/Akt signaling during infection. Together, the results indicate that the opposite actions of Ang2 on Tie2 depend on the presence or absence of inflammation [53].

Multiple lines of evidence indicate that the agonistic versus antagonistic action of Ang2 on Tie2 signaling is further influenced by the presence of Tie1 [20], another tyrosine kinase receptor of the Tie family [54–55]. Despite the overall homology with Tie2, Tie1 remains an orphan receptor with no identified specific ligand [56]. At physiological conditions, Ang1 has been shown to bind to Tie1 and stimulate a low level of Tie1 phosphorylation at the cell-cell junctions in the vascular endothelium [55–57]. This action requires a direct molecular interaction of Tie1 and Tie2 proteins. Pro-inflammatory conditions block such a connection by promoting the release of the Tie1 extracellular domain while favoring the Ang2 dependent inhibition of Tie activity. As a consequence, a positive feedback loop through Foxo1-driven Ang2 up-regulation is established leading to vascular destabilization and leaking.

2.2. Integrin receptors

αvβ3, αvβ5, and α5β1 integrins have been identified as alternative angiopoietin receptors in EC subpopulations with low Tie2 expression (Tie2lowEC) such as the tip cells of vessel sprouts [58–59], or certain Tie2-negative non-endothelial cells [60–63] (Fig. 1). Direct binding of Ang2 to integrins induces phosphorylation of the integrin associated Focal adhesion kinase (FAK), a multifacet regulator of intracellular signaling involved in processes as cell motility, survival, proliferation and epithelial/endothelial to mesenchymal transition.

Through this signaling, Ang2 regulates cell–cell and cell–matrix interactions, both in ECs and non ECs. In Tie2lowEC and in tumor cells, the Ang2-integrin axis has been reported to stimulate FAK phosphorylation on tyr-397, promoting EC migration and aberrant sprouting angiogenesis [59]. Hakanappa and collaborators have demonstrated that Ang2, but not Ang1, directly activates β1-integrin in Tie2-silenced EC monolayer. In this study, autocrine Ang2 signaling promotes the formation of actin stress fibers, which changes the cytoskeleton architecture and cell junctions, thus favoring cell-matrix adhesion and leading to endothelial monolayer destabilization [64].

Evidence exists that the Ang2-integrin axis is also involved in macrophage polarization, a process of extensive phenotypical and functional alterations of macrophages observed in response to

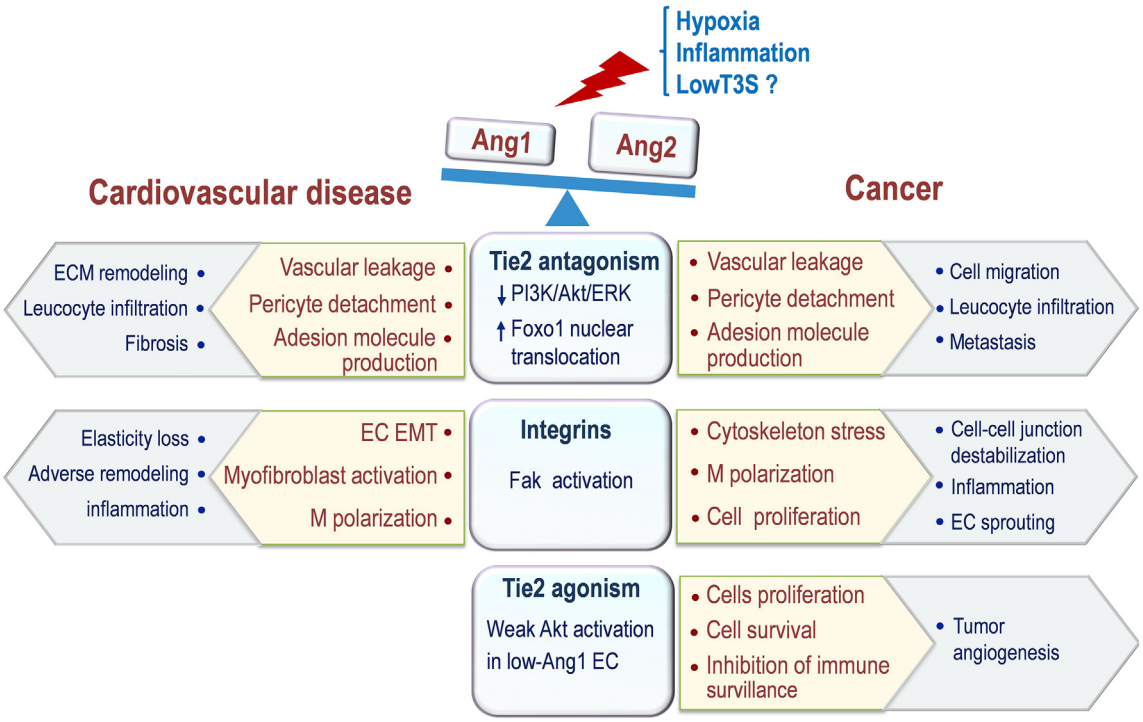

Fig. 1. Schematic overview of the noxious Ang2-dependent signaling pathways involved in the progression of cardiovascular disease and tumor. The putative role of low T3 state (LowT3S) is indicated. (Akt = Protein kinase B; Ang = angiopoietin; EC = endothelial cells; EMT = Endothelial to mesenchymal transition; Erk = Extracellular signal-regulated kinase; Fak = Focal adhesion kinase; Foxo1 = Forkhead box O1; M = macrophages; PI3K = Phosphatidylinositol 3-kinase; Tie2 = Thyrosine kinase 2).

inflammatory stimuli [65]. Several studies have highlighted the crucial role of the ERK pathway in determining the pro-inflammatory macrophage polarization [66–67]. Recently, Lee et al. have indicated that increased post ischemic Ang2 expression exacerbates macrophage polarization and inflammation in the border zone of myocardial infarction through its interaction with the integrin α5β1receptor and activation of the downstream p-ERK cascade. This pro-inflammatory effect of Ang2 is tightly controlled and depends on the presence of Tie2lowEC [68].

3. Role of Ang 2 in cardiovascular diseases

Angiogenesis is essential for the recovery of cardiac function after acute myocardial ischemia and in chronic heart diseases [69–71]. The formation of new functional collateral blood vessels into ischemic or hypoxic cardiac tissue requires a complex cross-talk between numerous cell types and growth factors [72]. Among the regulators of the vascular function, Ang2 has been suggested to provide a possible link between blood vessel formation and inflammation in a dose dependent manner [73]: while physiological Ang2 concentration or transient upregulation of Ang2 can stimulate revascularization, supraphysiological amounts or excessive duration of Ang2 exposure could exacerbate tissue inflammation and vessel disorganization, thus promoting vessel regression and vascular leakage [10,12,74]. High levels of Ang2 are observed in CVD, in which hypoxia and inflammation lead to endothelial activation, pathological angiogenesis and destabilization of the endothelial network [64]. Emerging reports show that Ang2 is associated with a greater risk of all-cause and cardiovascular mortality in the general population [75] and with higher mortality in MI and cardiogenic shock patients [76–77]. Importantly, Ang2 is considered a marker of endothelial activation not only in ischemic CVD but also in cardiovascular complications associated to chronic diseases such as kidney injury, diabetes or hypertension [12].

3.1. Ang2 in atherosclerosis, myocardial ischemic diseases and heart failure

Coronary heart disease is the main cause of death worldwide. Prompt reperfusion after an acute MI markedly reduces short term mortality; however, increased morbidity due to post ischemic HF development highlights the need for additional therapeutic strategies to blunt adverse cardiovascular remodeling.

The available evidence indicates that endothelial dysfunction and Ang2 up-regulation play a pivotal role in the pathophysiology of atherosclerosis and its cardiac manifestations such as acute MI and post ischemic heart disease evolution [21,68,76,78–81].

Ang2 is closely associated with the progression of atherosclerosis [79]. In human diseases, Ang2 has been found to be up-regulated within neovessels of advanced atherosclerotic lesions as compared to early lesions [78]. In a large population study, increased circulating Ang2 levels have been found to be associated with higher microvessel density, MMP2 activity and number of carotid plaques, which can lead to haemorrhage and plaque rupture and suggests that Ang2 may play a role in the development of unstable plaque [75,82–83]. In accordance, in vivo administration of antibodies against Ang2 in a mouse model of atherosclerosis, is able to reduce early atherosclerotic plaque development [84]. Recently, it has been also reported that high Ang2 levels in post-percutaneous coronary interventions can predict the occurrence of adverse cardiovascular events in the short to medium term [85].

In acute cardiac ischemic reperfusion (IR) high levels of Ang2 and reduced Ang1 production have been shown to cause endothelial dysfunction [86]. In this condition, Ang2 counteracts the anti-inflammatory and pro-survival action of Ang1 and promotes vascular permeability by inhibiting the Tie2 dependent signaling cascade [4,63]. On the contrary, infusion of Ang1 during IR injury promotes endothelial integrity and cardiomyocytes survival through EC-cardiomyocyte cross-talk mediated by the activation of VE-cadherin and integrin β1 pathways [4,63]. In accordance with these findings, inhibition of Ang2 production alleviates the post ischemic cell injuries in both in vivo and

in vitro models of IR [68,87].

The underlying mechanisms have been recently investigated in depth in a mouse model of IR [68]. In this study, Ang2 exacerbates post ischemic adverse cardiovascular remodeling by inducing pericyte detachment, expression of adhesion molecule, glycocalyx and ECM degradation, and pro-inflammatory processes. The up-regulation of Ang2 expression in EC of the border zone (BZ) of infarcted myocardium is directly regulated by Foxo1, which antagonizes Tie2 and activates p65, the pro-inflammatory component of Nuclear factor kappa- B (NF-κB) family. In turn, p65 enhances the endothelial expression of heparanase and adhesion molecules, further promoting ECM disorganization and inflammatory cell recruitment (Fig. 1). Furthermore, ECs of the disorganized BZ vessels show high level of Ang2-dependent FAK-phosphorylation (activation). Alike as in tumors, in this cardiac post IR setting Fak activation leads to endothelial to mesenchymal transition (EMT), thus suggesting that EMT serves as a putative mechanism for Ang2-induced abnormal vascular remodeling [19,68]. In macrophages, Ang2 causes the pro-inflammatory polarization by binding integrin α5β1 membrane receptor and activating the downstream effector p-ERK. To indicate the detrimental role of high Ang2 levels, antibody-mediated inhibition of Ang2 ameliorates cardiac hypoxia and inflammation after IR, strongly suggesting that it represents a potential promising therapeutic target in ischemic heart disease [68].

Altered Ang2/Ang1 balance has been observed in serum of patients with HF [21,77,81,88–89]. In acute HF, Ang2 and Ang2/Ang1 ratio are significantly increased and correlate negatively with left ventricular ejection fraction [88]. In addition, Ang2 and Ang2/Ang1 values are independent predictors of HF in acute MI patients during hospitalization [88]. In another study dealing with acute decompensated HF, Ang2 levels are higher in those patients with peripheral oedema and upper NYHA classes, thus acting as a predictor of poor prognosis [77]. A prognostic value of Ang2 has also been observed in chronic HF patients, in which Ang2 serum levels progressively increase with cardiac haemodynamic and functional decline [81,89].

3.2. Ang2 and cardiovascular alterations in type-2 diabetes mellitus, in chronic kidney failure and hypertension

An emerging body of evidence suggests that the imbalance between Ang1 and Ang2 in favor of Ang2 represents a culprit of the vascular alterations in patients with type-2 diabetes mellitus [90]. In the diabetic db/db mouse model, overexpression of Ang2 impairs myocardial angiogenesis and exacerbates cardiac fibrosis [91] by suppressing the Tie2 signaling, while increases the Intercellular adhesion molecule 1 (ICAM-1) and Vascular cell adhesion molecule 1 (VCAM-1) markers. Immunohistochemical analysis revealed a significant loss of capillary density. On the contrary, counterbalance of Ang2 by over-expression of Ang1 reverses the loss of capillary density and the formation of fibrous tissue in the db/db mouse hearts. These data suggest that pharmacological modulation of Ang1 or Ang2 actions may help to prevent or delay the onset of diabetic cardiovascular complications by restoring vessel architecture, favoring tissue repair and maintaining endothelial quiescence.

Ang2 is a prognostic biomarker of subclinical CVD or major adverse cardiovascular events in chronic kidney diseases. Altered Ang2/Ang1 balance has been identified as a link between kidney fibrosis and cardiovascular complications [92–94]. In the aorta of mice with chronic kidney diseases, Ang2 enhances the expression of the pro-fibrotic cytokine TGF-β1 and collagen in association with an increased EC-dependent expression of chemokines and attractants for monocyte. This action involves the recruitment of a specialized type of pro-inflammatory macrophages that express high level of the Ly6Clow antigen [95]. Conversely, Ang2 blockade attenuates the expression of monocyte chemokines and pro-fibrotic cytokines in the aorta artery, therefore targeting Ang2 to attenuate inflammation and collagen expression may provide a novel therapy for cardiovascular complications in chronic kidney diseases [96].

Altered Ang1/Ang2 balance has been documented in clinical and experimental settings of hypertension. Increased serum levels of Ang2 have been observed in hypertensive patients, especially in presence of atherosclerosis, probably due to the marked endothelial activation [97]. In line with this interpretation, Ang2 levels in hypertensive patients have been correlated with adhesion molecules and platelet levels and have been indicated as predictors of MI [97–99]. In experimental hypertension, high levels of Ang2 are produced by the EC WPB as a consequence of the increased wall stress [100]. Administration of exogenous Ang1 or reactive oxygen species scavengers inhibits the calcium-dependent release of Ang2 under stretch condition [98]. Loss of capillary density (microvascular rarefaction) in the interconnected cardiovascular, cerebrovascular and renal districts is another hallmark of the hypertensive disease. Accordingly, in spontaneous hypertensive rat model, a synthetic analogue of Ang1 was shown to enhance therapeutic angiogenesis via a massive activation of the Tie2 signaling [101]. Although highly plausible, given its destabilizing activity on EC, a direct involvement of increased Ang2 concentration in capillary rarefaction in hypertensive models has not been yet reported and this topics might deserve further investigations.

3.3. Ang2 and LowT3S in cardiovascular diseases

Proper TH levels are important in maintaining a healthy cardiovascular system. Several studies have demonstrated that TH or TH analogues have the capability to induce angiogenesis through genomic and non-genomic effects [102–105] that influence the expression of Ang1, Ang2 and Tie2 [4]. A non-genomic action of T3 and T4 initiates on plasma membrane integrin αvβ3 receptor [103,106], which elicits a rapid transduction of signals through the Mitogen-activated protein kinase (MAPK), the ERK 1/2 and Akt cytoplasmic kinases [102,107–108] and promotes new blood vessel formation [104,106,109]. In two different models of rat hypothyroidism, induced by thyroidectomy or propylthiouracil treatment, the expression of Ang1 in heart tissue correlates positively with TH function, while the expression of Ang2 is decreased by T3 treatment [110].

Angiogenesis is pivotal for the recovery of cardiac function after tissue damage in myocardial ischemia. In the last few years a LowT3S condition has been documented in several experimental and clinical settings of CVD, including IR and HF. Among other alterations, an imbalance of the circulating TH homeostasis favors impaired coronary blood flow and reduces density of small arterioles [30,31,111]. Regulation of the Ang1 and Ang2 system has recently been added to the list of T3-dependent effectors of vascular homeostasis [35]. In a rat model of cardiac IR, the persistence of a LowT3S at 3 days following IR is associated with Ang1 down-regulation and a reduction of the Ang1/Ang2 ratio in the peri-infarct area of the left ventricle. Early and short term T3 infusion at near-physiological dose (6 μg/kg die) restores both parameters and is associated with improved cardiac recovery, suggesting that normalization of Ang1 level and Ang1/Ang2 balance in the post IR heart could contribute to the cardioprotective effect of T3 [35]. The overall data suggest that euthyroidism reconstitution may affect the antithetical regulation of Ang1 and Ang2 isoforms observed in IR and may represent a potential promising therapy in ischemic heart disease. However, further studies are necessary to disclose the underlying mechanism.

4. Role of Ang2 in cancer

Ang2 expression is upregulated in a wide range of human cancer. Several in situ hybridization studies have revealed increased levels of Ang2 expression in cancers of different origin, including neuroendocrine tumors [112], hepatocellular cancer [113–114] and gastric cancer [115]. Acquired immune deficiency syndrome (AIDS)-associated Kaposi's sarcoma and cutaneous angiosarcoma, that are malignancies of

endothelial origin, show strong expression of Ang2, Tie1, and Tie2 in contrast to the low level expression in normal skin biopsies [116].

Increased levels of Ang2 are present in patients with worse outcome as observed in stage III and IV melanoma [117], and in colorectal cancer [118]. Furthermore, serum Ang2 concentrations and VEGF levels correlate with poor prognosis in small-cell lung cancer (SCLC), a poorly differentiated neuroendocrine malignancy, which presents a higher vascularization compared with non-small-cell lung cancer (NSCLC) [119]. At cellular level, some studies have reported increased expression of Ang2 in both EC and tumor cells [112,117], whereas other studies have shown Ang2 expression limited to the vasculature and not in tumor cells [115,118].

4.1. Ang2 and Tie2 activation in tumor

The generation of specific monoclonal antibodies, that bind Ang2 and prevent its interaction with Tie2, helped to establish the role for Ang2 in tumor growth. Although the action of Ang2 was initially believed to be antagonism of Tie2, several data support a model in which Ang2 promotes tumor growth via Tie2 activation. Since the majority of tumor EC is not exposed to significant levels of pericyte-derived Ang1, Ang2 functions to activate Tie2 signaling and its expression is induced to compensate for weak Ang1 signaling rather than to inhibit Ang1. Moreover, several studies demonstrated that the angiogenic tumor vasculature harbours EC subpopulation with low Tie2 receptor expression [59,120–121]. Accordingly, a recent work in primary cutaneous large B-cell lymphomas (PCBCL), has revealed a vasculature EC subpopulation with reduced expression of Tie2, both in aggressive and indolent PCBCL tumors; while the alternative Ang2 binding partners, the integrins, are strongly expressed only in the aggressive PCBCL, in association with potentiation of downstream Ang2-integrin signaling cascade such as phosphorylation of FAK at Tyr397 and sprouting angiogenesis [120].

An important contribution of the Ang2/Tie2 signaling in tumor progression may be to maintain the calibre of blood vessels and to promote the proliferation and survival of endothelial cells. In agreement with this hypothesis, animal models of teratomas exhibit high levels of phosphorylated Tie2 and larger blood vessels than wild-type healthy animals. Treatment with selective anti–Ang2 antibody, decreases Tie2 phosphorylation and vessel size, suggesting that Ang2 functions as a Tie2 activator in this model [122]. However, it has been hypothesized that different subsets of tumor vessels are exposed to different local concentrations of Ang2/Ang1 determining the net effect of the therapeutic Ang2 blockade on Tie2 phosphorylation; if most of the Tie2 agonist activity in sprouting vessels is mediated by Ang2, Ang2 blockade would decrease Tie2 activity [7]. In the presence of higher levels of Ang1, Ang2 inhibition would increase Tie2 phosphorylation by allowing greater access of Ang1 to Tie2.

Recently some authors have reported the presence of a specific subpopulation of monocytes expressing Tie2 receptor (TEMs) that significantly contributes to tumor angiogenesis in mice and humans [123–125]. These monocytes/macrophages are attracted into the tumors by EC-derived Ang2 interacting with its Tie2 receptor [126]. This subpopulation of macrophages is associated with vessels and is highly angiogenic, acting in a paracrine manner [125] (Fig. 1). It has been observed that the Ang2-stimulated TEMs induce the release of several pro-angiogenic factors causing the relapse of locally irradiated lung and breast carcinomas [127]. In addition, TEMs can reduce the therapeutic effect of vascular-disrupting agents, by promoting vascular repair, as observed in murine mammary tumors [128]. Therefore, targeting the Ang2-dependent TEM activation in the tumor microenvironment could represent a new strategies to suppresses tumor angiogenesis [123].

4.2. Ang2 and VEGF interaction in tumors

Several lines of evidence indicate that Ang2 and VEGF act in synergy to promote angiogenesis in solid tumors [129]. Using a human colon carcinoma in a mice model, Hashizume et al. have found that selective inhibition of Ang2 by the peptide-Fc fusion protein L1–7(N) reduces the number of vascular sprouts and tumor growth [130]. Strikingly, when the Ang2 inhibitor is combined with a function-blocking anti-VEGF antibody, the number of sprouts and tumor vascularity are more strongly reduced and tumor growth slows down compared with controls. The reduction in tumor growth is accompanied by decreased cell proliferation and increased apoptosis. In accordance, combined treatment with Ang2 and VEGF blockers provides better inhibition of tumor growth than the single agent in a number of tumor models [130]. As confirmed by successive studies, the inhibition of Ang2 could impose an additional stress on tumor endothelial cells beyond that provided by VEGF blockade alone [131–133].

Also, in contexts where Ang2 acts as a Tie2 agonist, it limits the therapeutic effects of VEGF inhibition and plays a protective role in tumor EC and vessel proliferation [20]. Indeed, besides having a protumoral activity, Ang2 can confer resistance to anti-VEGF therapy [12,134]. Moreover, Ang2 and VEGF act in synergy to suppress the ability of the immune system to recognize and eliminate the tumoral cells. This effect is attributed to the stimulation of key inhibitors of the immune surveillance such as the Cytotoxic T lymphocyte antigen 4 (CTLA-4), and the Programmed Death Ligand 1 (PD-L1) [135]. Accordingly, high serum Ang2 levels are associated with poor clinical response to the pharmacological targeting of the immune system inhibitors, known as immune check point therapy [136]. Anti-angiogenic agents against VEGF and Ang2 can normalize the immunosuppressive tumor microenvironment, and increase the infiltration of immune effector cells. Thus, combining anti-angiogenic therapies and immune check point therapy might better contrast tumor progression [136].

Another neoplastic process in which Ang2 and VEGF act in concert is vessel co-option [137]. This is an alternative mechanism of angiogenesis in well vascularized organs, such as the lung, where tumor cells grow and migrate along normal quiescent vessels (vessel co-option). During the initial phase of this process, extreme changes are imposed to the co-opted vessels that start to express Ang2 leading to vascular disruption and vessel regression. A hypoxic core is then formed in the tumor centre, with massive loss of tumor cells. This triggers the angiogenic switch, with the remaining tumor cells expressing high amounts of VEGF, inducing a robust pro-angiogenic response that ultimately rescues the tumor and allows its growth and progression. A therapeutic approach of dual inhibition of Ang2 and VEGF seems to be promising in unravelling the vessel co-option mechanisms involved for example in NSCLC [138].

Finally, in the clinical arena, a significant increase of VEGF and Ang2 plasma levels has been found after surgical tumor resection. Surgical resection is the main treatment for the vast majority of patients with locally confined solid tumors. However, the healing process necessitates extensive angiogenesis that supports a microenvironment favorable for tumor growth and metastasis and, at the same time, protects tumor cells from conventional chemotherapy. Therefore, inhibition of Ang2 and initiation of anti-angiogenesis therapies have been proposed for the early postoperative period, before the start of conventional chemotherapy [139].

Although all these notions are in favor of a double anti Ang2 and anti VEGF therapeutic strategy, the precise molecular events that ensue following Ang2 versus VEGF blockade remain to be further investigated.

4.3. Ang2 and epithelial to mesenchymal transition

Ang2 is a documented inducer of the epithelial to mesenchymal transition (EMT) [140]. In this process the well organized and tightly connected epithelial cells lose their characteristic phenotype and epithelial markers (i.e. cytokeratin or E-cadherin) and trans-differentiate into more disorganized and motile cells expressing mesenchymal

indicators or transcription factors (i.e. vimentine, N-cadherin,Twist, Snail) [141]. Accordingly, experimental inhibition of E-cadherin promotes invasiveness in a NSCLC model by up-regulation of N-cadherin expression [142]. In lung cancerous tissue from patients, Dong et al. have found that the abnormal Ang2 expression promotes EMT and tumor metastasis via inhibition of E-cadherin [140]. In this study, Ang2 is specifically over-expressed only in tissues of lung cancers but not in benign lung diseases. Moreover, in vitro silencing of Ang2 in human lung cancer cell lines by specific short RNA interference (siRNA) or anti-human Ang2 antibodies, can effectively inhibit the tumor growth or metastasis formation with reduced activation of the EMT process. In line with this findings, in patients with oral squamous cell carcinoma, Ang2 over-expression has been observed in association with reduced E-cadhering epithelial marker as well as pro-apoptotic mediators, to denote increased EMT [143].

Available data indicate that the tumor-associated macrophagies (TAMs) greatly contribute to EMT and Ang2 production [144]. TAMs are major players in the connection between inflammation and cancer. TAMs sense hypoxia in avascular areas of tumors and react by stimulating tumor angiogenesis, thus favoring proliferation, invasion and metastasis potential of the tumor cells. Besides, TAMs inhibit the anti-tumor immune response mediated by T cell. TAMs show elevated production of matrix metalloproteinase 9 (MMP9) that mediates ECM degradation and the release of proteins like Ang2, angiopoietin-like 4, placental growth factor, platelet-derived growth factor B, stem cell factor (kit ligand), stromal-derived factor 1, and VEGF [144]. All these factors directly mediate functional interaction between cancer cells and stromal cells, including blood vessel endothelial cells, lymphatic vessel endothelial cells, bone marrow-derived angiogenic cells and other bone marrow-derived cells that promote angiogenesis, lymphangiogenesis, and metastasis [145–146]. In particular, Ang2-dependent EMT has been documented in melanoma and Ang2 has been indicated as a marker for metastasis formation and an interesting therapeutic target in this setting [146].

4.4. Ang2 and low T3 state in cancer: can we hypothesize a connection?

A LowT3S has been observed in association to tumor progression in several cancer types [23–29]. The LowT3S is mainly the consequence of altered enzymatic processing of T4 in the peripheral tissues, which results in reduced T3 levels and increased content of rT3. Even though rT3 has been initially considered a biologically inactive metabolite of T4, evidence exists that increased rT3 levels may support tumor growth [147]. Consistently, restoration of T4 to T3 conversion in cancer cells leads to a robust down-regulation of oncoproteins and helps a shift of protein profile from proliferation to differentiation [148].

While there is general consensus on the pro-tumoral and pro-angiogenic effects of T4 via the non-genomic αvβ3 integrin receptor pathway, the role of T3 is less clear. On the one hand, T3 has a lower affinity for the αvβ3 integrin receptor, and pharmacological concentrations of the hormone are necessary to trigger αvβ3 integrin activation in vitro [147]. On the other hand, the classical genomic action of T3 seems to be required to contrast tumor invasiveness [149]. Therefore, it is expected that T4 reduction and maintenance of T3 physiological levels might provide protection in cancer patients. Accordingly, some authors have reported the loss of tumor mass in patients administered with T3 to maintain euthyroid state following T4 suppression [36]. Based on these premises, we speculate that a LowT3S in cancer may favor the Ang2-mediated tumor angiogenesis, and that euthyroidism reconstitution via T3 replacement may enhance the Ang1-dependent vessel stabilization and blunt tumor progression. Future work is needed to unravel these critical issues.

5. Conclusion

Ang2 upregulation has been observed in both CVD and cancer in association with worse prognosis. The available findings have clarified several Ang2-induced noxious pathways that are involved in adverse cardiac remodeling and tumor progression, and rank Ang2 as ideal biomarker and molecular therapeutic target. Acting in a context dependent manner, high Ang2 levels can either promote abnormal vascularization or favor endothelial instability leading to vascular leakage and cell infiltration (Fig. 1). While the first scenario is mainly responsible for tumor angiogenesis, the Ang2-dependent vessel destabilization has been reported as a common underlying mechanism in cancer and CVD progression. Disruption of the EC junctions in the tumor microvessel environment is a prerequisite for the migration of tumor cells in the blood flow and for formation of metastasis. In CVD, Ang2-mediated disruption of vessel integrity is responsible for vascular rarefaction and for enhancement of pro-inflammatory processes, which contribute to myocardial fibrosis, reduction of cardiac performance, and HF development (Fig. 1).

Besides hypoxia and inflammation, a LowT3S may represent a previously underestimated trigger of Ang2 up-regulation in pathological conditions, especially in the cardiovascular field. Here we have discussed the role of euthyroidism reconstitution in shifting the balance between Ang1 and Ang2 in favor of Ang1 in a model of cardiac IR. Such findings further confirm the detrimental effects of LowT3S in CVD and suggest T3 replacement as a potential promising therapy to blunt Ang2 up-regulation in CVD patients with LowT3S. Although the connection between LowT3S and altered Ang1/Ang2 balance in cancer has not yet been investigated, the available, indirect evidences encourage to explore this research field in depth.

Author contribution

Dr. Balzan S conceived and wrote the manuscript with input from all authors. All authors contributed analysis of the bibliographic material, critical discussion and substantial revision of the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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