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EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

Angiopoietin-1 and Angiopoietin-2 Inhibitors: Clinical Development

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Abstract

Purpose of Review The purpose of this review is to discuss the current understanding of the Tie2-angiopoietin system and its role in tumor growth and metastasis. This review also focuses on preclinical and clinical data published to date that have evaluated Tie2-angiopoietin inhibition.

Recent Findings Tie2 inhibition has shown significant promise in preclinical models, notable for decreased tumor burden and fewer sites of metastatic disease across various malignancies. However, data from human clinical trials have shown more mixed results. Trebananib, rebastanib, and MEDI3617 are the three Tie2-angiopoietin inhibitors that have been most widely evaluated in phase I and II trials. Further investigation into these therapies is ongoing.

Summary The Tie2-angiopoietin pathway continues to show promise in preclinical and some clinical trials, including studies on recurrent or metastatic breast and renal cell carcinomas. Further evaluation of these therapies, however, is warranted to better understand their optimal clinical utility.

Keywords Tie2 inhibition · Angiopoietin inhibition · Angiogenesis · Anti-angiogenic therapy

Introduction to Angiogenesis and the Angiopoietin-Tie2 Pathway

Angiogenesis is a complex process that is driven by interactions between extracellular matrix-derived angiogenic inhibitors and naturally occurring growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and angiopoietins [1]. It is a fundamental activity in many normal processes including wound healing; however, it also plays a key role in tumor growth and metastasis. The ability of growth factors such as VEGF and angiopoietin to promote endothelial cell growth appears to be primarily exhibited in hypoxic tissues, as is common in solid tumors [2]. VEGF, in particular, appears to dominate the angiogenesis pathway and has thus been a therapeutic target for aberrant vessel growth [3]. The angiopoietin-Tie2 pathway, however, also shows promise as a therapeutic target of angiogenesis in malignancy.

The Tie2 receptor is an endothelial cell-specific tyrosine kinase receptor whose ligands are of the angiopoietin family [4]. Angiopoietin-1 (ang1) and angiopoietin-2 (ang2) are the most well understood of the angiopoietins and traditionally function in an agonistic and antagonistic manner, respectively. Some data, however, demonstrate that ang2 may function as an agonist in variable settings [5]. Ang1, produced primarily by perivascular cells, binds the Tie2 receptor to promote vessel stability and quiescence. In contrast, ang2, which is released from endothelial cells, binds Tie2 and contributes to vessel permeability, instability, and vascular remodeling [4, 6, 7]. Together, these pathways function to maintain vessel homeostasis in the absence of disease (see Fig. 1 [9]).

Rationale for Angiopoietin-Tie-2 Inhibition

Data have demonstrated that in various malignancies, the ang1/ang2 and Tie2 pathways are significantly altered and promote aberrant angiogenesis. Ang2, but not ang1, levels have also been found to be significantly elevated in the plasma of patients with cancer as compared to healthy subjects [8]. Ang2 expression, in particular, has been shown to be significantly upregulated in tumor models, which leads to increased

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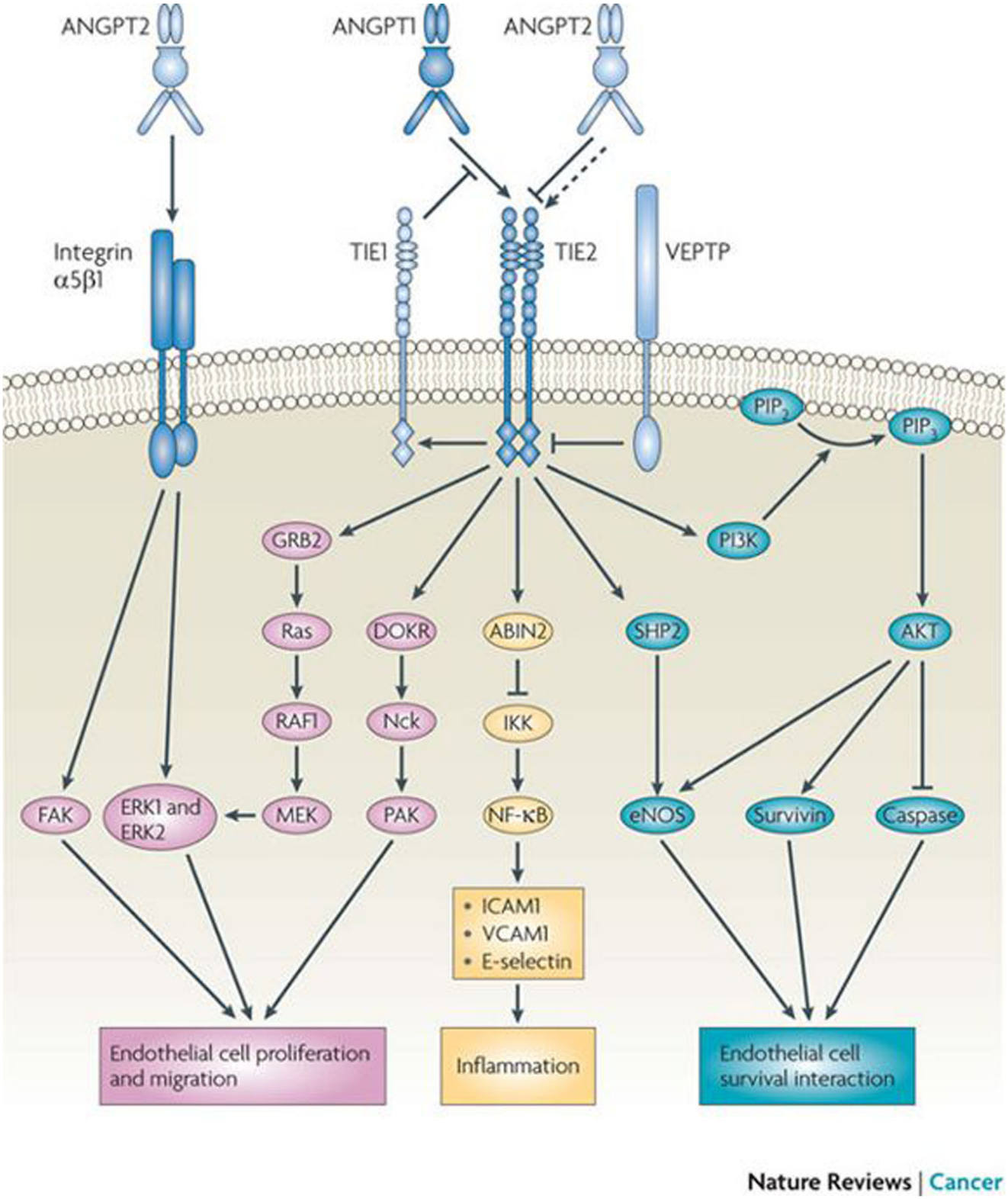

Fig. 1 Schema of the angiopoietin1/2 and Tie-2 pathway. From Huang, H. et al. [8], with permission from Springer Nature

Ang2-Tie2 binding and therefore vessel destabilization and eventual tissue hypoxia [4]. These steps are the first in what has been termed the "angiogenic switch." Tissue hypoxia in this setting in turn promotes VEGF expression. In concert, the VEGF and angiopoietin1/2-Tie2 cascades then promote tumor angiogenesis, typically at the tumor margin [7].

Tissue hypoxia also promotes recruitment of proangiogenic myeloid cells, in particular Tie2-expressing macrophages (TEMs) [10]. These macrophages, in the tumor microenvironment, have been shown to be immunosuppressive which may decrease tumor response to chemotherapy [11]. TEMs also promote activation of the ang2-Tie2 pathway, which is implicated as a key factor in development of metastatic disease. With increase in vessel permeability, tumor cells are allowed to intravasate into the vasculature and travel to distant sites [6, 12]. Given this current understanding of the ang2-Tie2 pathway, it stands to reason that this would be a potential therapeutic target.

Preclinical Indications for Angiopoietin-2 and Tie2 Inhibition

VEGF has been successfully targeted with medications such as bevacizumab, and both preclinical and clinical data demonstrate treatment with bevacizumab results in angiogenesis inhibition and decreased disease burden [13, 14]. Poor response and/or development of resistance to this therapy has been observed, however. This phenomenon has been attributed to both preexisting (tumor specific) and compensatory mechanisms such as TEM infiltration into hypoxic tissue and subsequent activation of the ang2-Tie2 cascade [15–17].

Ang2 inhibition with a humanized monoclonal antibody demonstrated tumor growth inhibition and regression of vasculature when evaluated in mouse mammary tumor models. Analysis of the lung tissue from these mice also demonstrated a lower incidence of pulmonary metastasis in the ang2 inhibitor-treated cohort [18]. Mouse models using late-stage pancreatic islet-cell tumors were also evaluated with ang2 blockade and demonstrated significant reduction in the mean tumor area and relative tumor vascular area [18]. Pancreatic neuroendocrine tumors (PNETs) have also been evaluated in mouse models using anti-angiogenic therapies including vascular endothelial growth factor receptor (VEGFR) and Ang2 antagonists. Data in this subset of malignancies demonstrated that, while neither VEGFR2 nor ang2 blockade alone affected total pancreatic tumor area (in VEGFR pretreated mice), the combination of the two therapies led to significantly smaller tumor areas compared to control mice or those treated with either monotherapy [16]. Additionally, in orthotopic glioma mouse models, tumor volume and microvessel density were significantly reduced with ang2 inhibition, with or without VEGF inhibition. An even greater reduction in tumor volume was noted with both ang2 inhibition and binding of the Tie2 receptor [19, 20].

Additionally, ovarian cancer models continue to demonstrate the therapeutic potential of the ang2-Tie2 pathway. Evaluation of ovarian cancer patients treated on ICON7 demonstrated that anti-angiogenic therapy with bevacizumab promoted Ang1-Tie2 binding and resulted in decreased circulating Tie2 levels. Tie2 also showed promise as a potential prognostic biomarker, as an increase of 50% in circulating levels was noted to be a predictor of disease recurrence. Additional analysis of this population revealed that high Ang1/low Tie2 values were associated with significantly improved PFS [21, 22]. In ovarian cancer xenograft models, mice treated with gene therapy to inhibit both VEGFR2 and Tie2 experienced significant reduction in tumor weights when comparted to mice treated with control vector and chemotherapy. This therapy proved beneficial in minimizing the development of ascites as well [23]. Together, these data provide significant preclinical evidence that inhibition of the ang2-Tie2 pathway may provide clinical benefit to patients with a variety of solid tumors.

Clinical Implementation of Angiopoietin2-Tie2 Inhibition: Trebananib

In light of the compelling preclinical data, several therapeutic agents have been developed to target the ang2-Tie2 pathway. Trebananib (AMG386), an ang1/2 neutralizing peptibody that inhibits the ligand's interaction with Tie2 receptors, has been evaluated in many early-phase trials and demonstrated safety and potential efficacy [24–27]. Karlan et al. examined women with recurrent epithelial ovarian cancer (EOC) treated with weekly paclitaxel and either 10 mg/kg, 3 mg/kg trebananib, or placebo. Median progression-free survival (PFS) was 7.2 months (95% CI, 5.3 to 8.1 months) in the 10 mg/kg trebananib arm, 5.7 months (95% CI, 4.6 to 8.0 months) in the 3 mg/kg trebananib arm, and 4.6 months (95% CI, 1.9 to 6.7 months) in the placebo arm. The hazard ratio for the trebananib arms combined versus the placebo arm was 0.76 (95% CI, 0.52 to 1.12; $p = 0.165$) [28]. In a phase III trial (TRINOVA-1), trebananib, in conjunction with paclitaxel, was used to treat women with recurrent, platinum-sensitive, or resistant ovarian cancer (progression-free interval (PFI) ≤ 12 months) who had received no more than 3 prior lines of therapy. Median overall survival (OS) was not significantly different in women who received trebananib plus paclitaxel versus those who received paclitaxel alone (19.3 versus 18.3 months; HR, 0.95; 95% CI, 0.81–1.11; $P = 0.52$). When evaluating patients with ascites at baseline, however, OS was significantly improved in those who received trebananib (14.5 versus 12.3 months; HR, 0.72; 95% CI, 0.55–0.93; $p = 0.011$). PFS was also significantly longer in the intent-to-treat cohort (12.5 versus 10.9 months; HR, 0.85; 95% CI, 0.74–0.98; $p = 0.024$) [29•, 30•]. The ENGOT-ov-6/TRINOVA-2 study was a phase III study, evaluating the efficacy of pegylated liposomal doxorubicin (PLD) with and without trebananib. This study included women who had received no more than 1 prior platinum-based

chemotherapy regimen (up to 3 total prior lines allowed) with PFI ≤ 12 months. Median PFS was similar between those who received trebananib and those who did not (7.6 versus 7.2 months). The objective response rate (ORR) of 46% versus 21% and duration of response (trebananib, 7.4 months [95% CI, 5.7–7.6]; placebo, 3.9 months [95% CI, 2.3–6.5]), however, were significantly improved in the trebananib arm compared to PLD alone [31]. TRINOVA-3, a phase III study evaluating trebananib in frontline therapy with carboplatin and paclitaxel, was suspended prior to completion of enrollment given the above findings [32]. Trebananib has also been evaluated in women with persistent and/or recurrent endometrial cancer. GOG229e evaluated women with disease refractory to curative or known effective therapy who had received no more than 2 prior chemotherapeutic regimens. Median PFS and OS were 1.97 (90% CI 1.77–2.1) and 6.6 months (90% CI 4.01–14.75), respectively. The overall conclusion was that trebananib had insufficient single-agent activity in this patient population to warrant further investigation [33•].

Trebananib has also been investigated in various gastrointestinal malignancies. In a phase II study evaluating frontline use, trebananib (at 10 mg/kg or 15 mg/kg) was combined with sorafenib in patients with advanced hepatocellular carcinoma. PFS at 4 months was 57% in the 10 mg/kg cohort and 54% in the 15 mg/kg cohort. Median OS was 17 and 11 months, respectively. These survival outcomes were shorter than historical controls (PFS at 4 months of 62%) who were treated with sorafenib alone [34]. Peeters et al. evaluated patients with metastatic colorectal cancer patients who had received only one prior fluoropyrimidine/oxaliplatin-based regimen. In this phase II study of trebananib with FOLFIRI, no improvement in PFS was demonstrated with the addition of trebananib versus placebo (3.5 vs 5.2 months, $p = 0.33$) [35]. A phase II evaluation of trebananib in combination with cisplatin and capecitabine in patients with metastatic gastroesophageal cancer also failed to demonstrate a survival advantage with trebananib. Median PFS in those receiving 10 mg/kg trebananib, 3 mg/kg trebananib, or placebo was 4.2, 4.9, and 5.2 months ($p = 0.92$) and ORR were 27%, 43%, and 35% respectively [36].

When studied in HER2-negative, locally recurrent, or metastatic breast cancer, the addition of trebananib to paclitaxel with or without bevacizumab did not improve PFS and the paclitaxel with trebananib only cohort demonstrated a longer median time of response and a shorter duration of response than other cohorts incorporating bevacizumab or excluding trebananib [37•]. A phase Ib study of trebananib with paclitaxel and trastuzumab in patients with HER2-positive locally recurrent or metastatic breast cancer, however, demonstrated promising results. Complete response was achieved in 18% of women receiving the 30 mg/kg dosage and 71% experienced partial response. Median duration of response in this cohort was 16.6 months, ranging from 8.2 to not estimable [38]. The I-SPY 2 TRIAL is currently open and evaluating trebananib in patients with invasive breast cancer who have not received prior cytotoxic therapy (NCT01042379).

In metastatic renal cell carcinoma, a phase I study of trebananib (at either 3 or 10 mg/kg) combined with sorafenib or sunitinib in patients with advanced renal cell carcinoma showed acceptable side effect profile of trebananib at both doses. The ORR was 53% in the trebananib plus sunitinib cohort. One of the 20 patients in the 10 mg/kg cohort experienced complete response and 47% of all patients treated with the combination of trebananib and sunitinib had a partial response. In the trebananib plus sorafenib cohorts, the ORR was 29% with no patients achieving a complete response and only 5 of the 17 obtaining partial response. The median time to progression (TTP) across the two trebananib plus sunitinib cohorts was 48.0 weeks. In the sorafenib and trebananib groups, the TTP was 40.3 weeks [39]. A phase II study of sunitinib with 10 mg/kg (cohort A) versus 15 mg/kg (cohort B) trebananib demonstrated an ORR of 58% and 63% respectively. PFS was 13.9 months in cohort A but not estimable in cohort B, suggesting a potential benefit for the addition of trebananib [40]. Currently, additional investigation using trebananib with or without bevacizumab, pazobanib, sorafenib, or sunitinib as well as in frontline therapy in patients with advanced renal cell carcinoma is underway (NCT01664182; NCT00853372).

Clinical Implementation of Angiopoietin2-Tie2 Inhibition: Rebastinib

Rebastinib (DCC-2036) is another novel agent aimed at the ang2-Tie2 pathway. It decreases Tie2-mediated capillary formation in endothelial cell lines and mitigated TEM-dependent tumor cell intravasation through endothelial cells. Breast cancer mouse models treated with rebastinib were noted to have a significant decrease in growth rate of the primary breast cancer as well as decreased development of lung metastases [5].

While there is a paucity of early- or late-phase trials of rebastinib, Cortes et al. have evaluated the use of this drug in patients with relapsed chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). This phase 1 study demonstrated an acceptable safety profile and 18/52 patients with CML demonstrated clinical response, including 4 with complete responses. None of the 5 patients with AML, however, demonstrated response to rebastinib [41]. A phase Ib study evaluating rebastinib with an antitubulin therapy plus paclitaxel or eribulin in women with metastatic breast cancer was recently presented at the 2018 American Association of Cancer Research Annual Meeting. Both arms incorporating rebastinib demonstrated antitumor activity. Two of 6 patients achieved partial response and 2 of 6 patients achieved stable disease when treated with paclitaxel plus rebastinib. One of 5

treated with eribulin plus rebastinib achieved partial response [42]. Additional studies are currently underway including a phase 1b/2 study that is currently accruing patients to evaluate rebastinib in combination with paclitaxel in advanced or metastatic solid tumors (NCT03601897). Another investigation into rebastinib in combination with carboplatin in patients with advanced or metastatic solid tumors is to begin recruitment this year (NCT03717415).

Clinical Implementation of Angiopoietin2-Tie2 Inhibition: MEDI3617

MEDI3617, a monoclonal antibody targeting ang2 and preventing its binding to the Tie2 receptor, is also under investigation. In mouse models, MEDI3617 inhibited tumor angiogenesis and growth [43]. Additional investigation of this agent demonstrated its ability to prevent destabilization of the endothelial/smooth muscle interaction [44]. In a phase I/Ib trial of patients with advanced solid tumors, MEDI3617 was administered as either a monotherapy, with bevacizumab or paclitaxel as doublet therapy, or with carboplatin and paclitaxel. Monotherapy proved to have an acceptable safety profile in all malignancies except for advanced ovarian cancer, where persistent, treatment-related edema was observed in 8 of the 15 enrolled patients. In all-comers who received MEDI3617 monotherapy ($n = 42$), the ORR was 2.4%. In the platinum-resistant ovarian cancer dose-expansion cohort treated with MEDI3617 monotherapy, an ORR of 6% was noted. ORRs of 7% and 15% were observed in the MEDI3617 with bevacizumab and MEDI3617 plus paclitaxel groups, respectively. On further evaluation, 1 ovarian cancer patient in the MEDI3617 and bevacizumab group experienced durable response longer than 68 weeks. Two patients in the MEDI3617 plus paclitaxel group had a similar response [45]. Currently underway is a study of MEDI3617 in patients with metastatic or unresectable melanoma (NCT02141542).

Conclusions

The ang2-Tie2 interaction is a key pathway in tumor angiogenesis and metastasis. As such, its inhibition is a logical target for therapeutic intervention. Preclinical data clearly demonstrate a reduction in tumor burden and angiogenesis and increased stability in vasculature. Phase 1 trials confirm the safety and tolerability of multiple agents targeting the ang2-Tie2 pathway including trebananib, rebastinib, and MEDI3617.

Further investigation of trebananib shows less promise as either a monotherapy or in combination with traditional cytotoxic chemotherapy when used in gastrointestinal or gynecologic malignancies. Completed and ongoing research in both breast and renal cell carcinoma, however, demonstrate potential therapeutic benefit. Studies of rebastinib and MEDI3617 have thus far established safety and tolerability of both agents; however, mixed results regarding ORRs warrant further investigation (NCT03601897, NCT02141542).

Compliance with Ethical Standards

Conflict of Interest Jessica Gillen declares that she has no conflict of interest.

Debra Richardson has received compensation from Genentech and Ipsen for participation on advisory boards, and has served on steering committees for and received travel grants from Tesaro and Karyopharm Therapeutics.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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