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The VEGF Pathway in Cancer and Disease: Responses, Resistance, and the Path Forward

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Antiangiogenesis was proposed as a novel target for the treatment of cancer 40 years ago. Since the original hypothesis put forward by Judah Folkman in 1971, factors that mediate angiogenesis, their cellular targets, many of the pathways they signal, and inhibitors of the cytokines and receptors have been identified. Vascular endothelial growth factor (VEGF) is the most prominent among the angiogenic cytokines and is believed to play a central role in the process of neovascularization, both in cancer as well as other inflammatory diseases. This article reviews the biology of VEGF and its receptors, the use of anti-VEGF approaches in clinical disease, the toxicity of these therapies, and the resistance mechanisms that have limited the activity of these agents when used as monotherapy.

Angiogenesis is a vital physiologic process needed for growth and development as well as wound healing and the menstrual cycle (Dvorak 2005; Bhadada et al. 2010). A major regulator of angiogenesis is vascular endothelial growth factor (VEGF) and its cognate receptor vascular endothelial growth factor receptor-2 (VEGFR2). Activation of the VEGF pathway has been identified in a large number of disease processes ranging from cancer to autoimmunity, retinopathy, and many more, which has led to the common perception that inhibition of the pathway would result in rapid and sustained clinical responses. As we have experienced in the past, optimism of our success was overstated while the underlying biologic mechanisms that diseases can use to adapt to inhibition of the VEGF pathway were underestimated. There are real but isolated examples of success with VEGF inhibitors but also a great deal of clinical disappointment. This article reviews some of our understanding of the VEGF pathway and the inhibitors developed to target it. We then review results from a series of preclinical and clinical trials examining the activity of both VEGF and VEGFR2 inhibitors, examining the potential reason for both areas of success and failure. Finally, we

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briefly discuss some of the future directions aimed to build on our successes while overcoming our failures.

ANGIOGENESIS

Our understanding of the biology that regulates angiogenesis has improved dramatically over the last 40 years. Initially thought to be the induction of a cytokine that induces endothelial cell proliferation and new blood vessel development, we now have a more detailed understanding of vasculogenesis (the formation of de novo endothelial cell precursors needed to initiate neovascularization) and angiogenesis (the stimulation of neovascularizaton from existing vessels) (Semenza 2007; Kassmeyer et al. 2009; Ribatti et al. 2009). Although this is not completely accurate, we will use "angiogenesis" and "antiangiogenesis" to refer to the process of neovascularization and its inhibition, even if the target is directed more toward vasculogenesis. Although lymphangiogenesis is another critical component of neovascularization and uses many of the same factors such as VEGF (which will also be targeted by VEGF inhibition), this process will be lumped into the general concept of "angiogenesis" (Lohela et al. 2009). The critical role of components other than endothelial cells, such as pericytes and matrix, have added another important layer onto our fundamental understanding of this process (Diaz-Flores et al. 2009). These provide us with opportunities to identify additional pathways to inhibit, but also provides tumors with additional potential escape mechanisms. The complexity of the neovascular process has become better delineated with the discovery of dozens of (rather than one) proangiogenic cytokines (e.g., basic fibroblast growth factor, PDGF, IL-8) and their cognate receptors (e.g., fibroblast growth factor receptor-1) that can stimulate angiogenesis (Murakami and Simons 2008; Cao 2009; De Val and Black 2009). Furthermore, multiple endogenous inhibitors of angiogenesis, such as endostatin, angiostatin, tumstatin, and thrombospondin have been identified that play an equally important role in regulating the angiogenic cascade (O'Reilly et al. 1994, 1997; Maeshima et al. 2000; Lawler and Detmar 2004; Maione et al. 2009; Ribatti 2009). Thus, angiogenesis is a complex interaction of many cell types, soluble stimulators, and inhibitors as well as the local matrix, inflammatory and immune cells, and bone marrow precursors, as well as the tumor, all acting in concert to determine the type, location, and abundance of the angiogenic response (Sozzani et al. 2007; Ahn and Brown 2009; Ramjaun and Hodivala-Dilke 2009). Because angiogenesis is an important adaptive response to the menstrual cycle, wound healing, cardiac ischemia, and many other physiologic processes, consideration of the consequences of inhibiting the VEGF pathway will need to be further studied (Yla-Herttuala et al. 2007).

THE VEGF PATHWAY

The concept that angiogenesis was an important and necessary aspect of disease and could therefore be used as a therapeutic strategy was first proposed by Judah Folkman in 1971 (Folkman 1971), 12 years before vascular permeability factor (VPF) was isolated (Senger et al. 1983) and 18 years before VEGF was sequenced (Ferrara and Henzel 1989). Interestingly, the sequence of VEGF was identical to that of vascular permeability factor or VPF, a finding that brought together important functions of this single molecule: endothelial proliferation and fluid leakage resulting in edema. Since its identification, other isoforms of VEGF and their receptors have been discovered (Roskoski 2008). Furthermore, alternative splice variants of VEGF have been identified including $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$, each with a different primary role (Ferrara et al. 2003). For example, $VEGF_{189}$ is the full-length protein, forms a homodimer, and with $VEGF_{206}$ has limited biologic activity because of their membrane localization as a result of heparin-binding sites, something that can be altered by proteolytic cleavage of a fragment of the protein. $VEGF_{165}$, a splice variant rather than a proteolytic product of the full-length clone, maintains some heparin-binding capacity but can also readily diffuse and likely

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accounts for the majority of the angiogenic stimulatory properties of VEGF, whereas $VEGF_{121}$ is an easily diffusible splice variant of VEGF that can no longer bind to the extracellular matrix. Three additional VEGF forms were identified based on their homology to VEGF-A and were named VEGF-B, VEGF-C, and VEGF-D. VEGF-C and VEGF-D appear most important in lymphangiogenesis and have binding affinity for VEGFR-3 (also called flt-4). VEGF-A and VEGF-B have increased binding affinity for VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1 or KDR). Although VEGF-A can bind both VEGFR-1 and VEGFR-2, most data suggest that binding of VEGF-A to VEGFR-2 accounts for the majority of the angiogenic stimulatory signal observed in vivo. VEGFR-1 may, in fact, be a decoy receptor with limited signaling capacity (Ho and Kuo 2007). Other receptors such as the neuropilins (NRP1 and NRP2) in the brain can compete with VEGF-A for the receptor (Miao et al. 1999; Klagsbrun et al. 2002). Because many preclinical and, especially, clinical studies of VEGF and VEGF inhibitors do not adequately address the varying roles of the cross talk between these different isoforms, splice variants, and receptors, negative outcomes of clinical trials may be the result of our poor understanding of these variables.

VEGF is produced by several cell types such as fibroblasts, inflammatory cells, and many tumor cells, often in response to increasing tumor hypoxia via the HIF-1a pathway. Although endothelial cells express high levels of VEGFR-2, its expression can be found on other cell types as well. The lower density of VEGFR-2 receptors on non-endothelial cells may explain the apparent specificity of VEGF as a vascular mitogen (Matsumoto and Claesson-Welsh 2001). The importance of VEGF signaling through the VEGFR in neovascularization has been shown in many model systems (Kuo et al. 2001; Ferrara et al. 2003) and is supported by the significantly elevated levels of VEGF mRNA in many tumor types (Berger et al. 1995). Other diseases associated with elevation in VEGF such as inflammatory conditions, hemangiomas, arthritis, and retinopathy suggest that non-malignant cell types can up-regulate VEGF and may also be appropriate targets of VEGF inhibition (Folkman 1995).

VEGF INHIBITORS IN CLINICAL TRIALS

The development of highly specific inhibitors of both the VEGF ligand (bevacizumab, VEGF-Trap, ranibizumab) as well as the VEGF receptor (cediranib, pazopanib, sorafenib, sunitinib, vandetanib, axitinib, telatinib, semaxanib, motesanib, vatalanib, Zactima) relates to the central role that this pathway plays in disease (see Table 1) (Ahmed et al. 2004; Baka et al. 2006; Jain et al. 2006; Faivre et al. 2007; Tabernero 2007; Choueiri 2008; Dadgostar and Waheed 2008; Sloan and Scheinfeld 2008; Lindsay et al. 2009; Porta et al. 2009). Preclinical data for the activity of these (and many other) VEGF pathway inhibitors are beyond the scope of this review (Timar and Dome 2008). Based on promising single agent or combination therapy, many inhibitors have entered human clinical trials for a wide range of diseases and have been thoroughly reviewed (see Table 2) (Kowanetz and Ferrara 2006; Ho and Kuo 2007; Kourlas and Abrams 2007; Los et al. 2007).

The particular focus of clinical trials will be those using formal prospective clinical trial structures where the activity of the arm containing a VEGF inhibitor (usually in combination with traditional chemotherapy and/or radiation therapy) can be compared with the standard therapy alone (Kessler et al. 2010). Most trials of single-agent VEGF inhibitors have not produced sufficient activity to warrant approval except in certain specific diseases such as renal cell carcinoma (RCC).

Perhaps the most studied of the anti-angiogenic agents, and the first to receive FDA approval in 2004, was bevacizumab (Avastin) (Grothey and Galanis 2009; Van Meter and Kim 2010). This recombinant humanized monoclonal antibody targets all of the isoforms of VEGF-A. When administered with irinotecan and bolus 5-FU/leucovorin (IFL) chemotherapy versus IFL alone as first-line therapy

Table 1. VEGF/VEGFR agents completing prospective clinical trials

Name	Synonyms	Target
AG013736	Axitinib	VEGFR1, 2, 3, PDGFR
AMG 706	Motesanib	VEGFR1, 2, 3, PDGFR, cKit
AZD2171	Cediranib	VEGFR1, 2, 3
BAY 43-9006, sorafenib	Nexavar	RAF, VEGFR2, 3, PDGFR, ckit
BAY 57-9352	Telatinib	VEGFR2, 3, PDGFR, c-kit
Bevacizumab	Avastin	VEGF
GW786034	Pazopanib	VEGFR, PDGFR, cKit
HuMV833		VEGF
JNJ-26483327		EGFR, VEGFR3
MLN518	Tandutinib	Type III RTK
Pegaptanib aptamer	Macugen	VEGF
PKC412	Midostaurin	Protein kinase C, VEGFR2
PTK 787/ZK 222584	Vatalanib	VEGFR1, 2, 3
Ranibizumab	Lucentis	VEGF
SU11248	Sunitinib	VEGFR, PDGFR, cKit
SU5416	Semaxanib	VEGFR1, 2
Sunitinib, SU11248	Sutent	VEGFR, PDGR
Trap-Eye		VEGF
VEGF Trap	Aflibercept	VEGF
ZD6474, Zactima	Vandetanib	VEGFR1, 2, 3, EGFR

for metastatic colorectal cancer, bevacizumab-IFL improved median survival from 15.6 to 20.3 ($p < 0.001$), progression-free survival (6.2 to 10.6 mo), and time to progression (6.7 to 8.8 mo) (Hurwitz et al. 2004). Improvements in overall survival (10.8 vs. 12.9 mo) and time to progression (4.6 vs. 7.2 mo) have been reported in another phase III trial of oxaliplatin, leucovorin, and 5-fluorouricil (FOLFOX 4) with and without bevacizumab as second-line therapy for previously treated advanced colorectal cancer. Single-agent bevacizumab failed to show significant activity (Ho and Kuo 2007). Improved survival in phase III studies of advanced non-small-cell lung cancer (NSCLC) (overall survival 10.3 vs. 12.3 mo, $p = 0.0075$) was also observed when bevacizumab was added to chemotherapy (Sandler et al. 2006). A phase III trial of bevacizumab and capecitabine compared with capecitabine alone improved the objective response rate (9.1% vs. 19.8%, $p = 0.001$) in previously treated metastatic breast cancer patients, although significant improvements were not observed for either progression-free survival or overall survival (Miller et al. 2005a). A separate phase III trial of bevacizumab in combination with paclitaxel in newly diagnosed metastatic breast cancer showed improved objective response rates and progression-free survival, although overall survival data are still pending (Ho and Kuo 2007). In December of 2010, the FDA removed approval for the use of bevacizumab for metastatic breast cancer based on follow-up studies that failed to show the activity identified in earlier studies. This decision is being appealed by the company. Bevacizumab and interferon have also been approved for advanced RCC (Rini et al. 2008; Summers et al. 2010). Bevacizumab has also recently been approved for recurrent GBM (Cohen et al. 2009b).

Phase III trials showing activity for small molecule inhibitors of the VEGFR-2 receptor include sorafenib (BAY 43-9006) and sunitinib malate (Sutent). These orally bioavailable agents show broad-spectrum activity against numerous kinases including VEGF receptors. Sorafenib received FDA approval for advanced/metastatic RCC based on phase III data showing

Table 2. Clinical trials of VEGF/VEGFR inhibitors

Name	Additional agents	Status	Disease	References
AG013736		II	RCC	Rini et al. 2009
AMG 706		II	Thyroid cancer	Sherman et al. 2008
AMG 706		I	Solid tumor	Rosen et al. 2007
AZD2171		II	GBM	Batchelor et al. 2010
AZD2171	Gefitinib	I	Solid tumors	van Cruijsen et al. 2010
AZD2171		I	AML	Fiedler et al. 2010
AZD2171		I	Solid tumors	Drevs et al. 2007
BAY 57-9352		I	Solid tumors	Eskens et al. 2009
Bevacizumab	Erlotinib	II	Biliary cancer	Lubner et al. 2010
Bevacizumab	Erlotinib	I/II	Squamous cell cancer	Cohen et al. 2009a
Bevacizumab	Erlotinib	II	Breast cancer	Dickler et al. 2008
Bevacizumab	Metronomic therapy	II	Breast cancer	Garcia-Saenz et al. 2008
Bevacizumab	± IFN-α 2b	II	Melanoma	Varker et al. 2007
Bevacizumab	Oxaliplatin and capecitabine + XRT	I	Rectal cancer	Czito et al. 2007
Bevacizumab	± Interferon-a	III	RCC	Rini et al. 2008
Bevacizumab		III	ADM	Patel et al. 2008
Bevacizumab		II	Ovarian	Burger et al. 2007
Bevacizumab		III	ADM	Scott et al. 2007
Bevacizumab	+ Gemcitabine	II	Pancreatic	Kindler et al. 2005
Bevacizumab		I-Peds	Solid tumor	Glade Bender et al. 2008
Bevacizumab	+ Irinotecan	II-Peds	HGG	Gururangan et al. 2010
GW786034		II	GBM	Iwamoto et al. 2010
GW786034		II	RCC	Hutson et al. 2010
HuMV833		I	Solid tumor	Jayson et al. 2005
JNJ-26483327		I	Solid tumors	Konings et al. 2010
MLN518		II	Renal cell	Shepard et al. 2010
Pegaptanib (aptamer)		II	ADM	Apte et al. 2007
PKC412		I	Advanced cancer	Fabbro et al. 2000
PTK 787/ZK 222584	Cetuximab	I	Solid tumors	Langenberg et al. 2010
PTK 787/ZK 222584	Tem + XRT	I/II	GBM	Brandes et al. 2010
PTK 787/ZK 222584	+ Pemetrexed + cisplatin	I	Solid tumor	Sharma et al. 2009
PTK 787/ZK 222584		I	Myelofibrosis with myeloid metaplasia	Giles et al. 2007
PTK 787/ZK 222584		I	AML	Roboz et al. 2006
PTK 787/ZK 222584		I	Liver metastases	Mross et al. 2005
PTK 787/ZK 222584		I	Advanced cancer	Thomas et al. 2005
Ranibizumab		III	ADM	Kaiser et al. 2007a,b; Boyer et al. 2009; Bressler et al. 2009; Brown et al. 2009; Lalwani et al. 2009; Campochiaro et al. 2010; Sadda et al. 2010
SU11248		II	NSCLC	Socinski et al. 2008; Ping et al. 2010
SU11248		II	Cervical carcinoma	Mackay et al. 2010

Continued

Table 2. *Continued*

Name	Additional agents	Status	Disease	References
SU11248		II	Head and neck	Fountzilas et al. 2010
SU11248		II	RCC	Motzer et al. 2006; Polyzos 2008; Kontovinis et al. 2009
SU11248		II	Neuroendocrine cancer	Kulke et al. 2008
SU11248		II	Breast cancer	Burstein et al. 2008
SU11248		II	Urothelial cancer	Bradley et al. 2007
SU11248		I	AML	Fiedler et al. 2005
SU5416		I-peds	Brain tumor	Kieran et al. 2009
SU5416	+ Irinotecan	I	Colorectal	Hoff et al. 2006
SU5416	+ Thalidomide	II	Melanoma	Mita et al. 2007
SU5416		II	Head and neck	Fury et al. 2007
SU5416		I	Solid tumor	O'Donnell et al. 2005
SU5416		I	Head and neck	Cooney et al. 2005
SU5416		I	Sarcoma	Heymach et al. 2004
SU5416		II	Melanoma	Peterson et al. 2004
SU5416		II	Prostate cancer	Stadler et al. 2004
SU5416		II	AML	O'Farrell et al. 2004
SU5416		II	Multiple myeloma	Zangari et al. 2004
SU5416	+ IFN	II	RCC	Lara et al. 2003
SU5416		II	AML	Fiedler et al. 2003
SU5416		II	RCC, sarcoma	Kuenen et al. 2003
SU5416		II	Myeloproliferative disease	Giles et al. 2003a
SU5416		II	AML	Giles et al. 2003b
Trap-Eye		I	ADM	Nguyen et al. 2009
VEGF Trap		I	Solid tumors	Lockhart et al. 2010
ZD6474, Zactima	± Paclitaxel + carboplatin	II	NSCLC	Heymach et al. 2008
ZD6474, Zactima		II	Multiple myeloma	Kovacs et al. 2006
ZD6474, Zactima		I	Solid tumors	Holden et al. 2005
ZD6474, Zactima		II	Breast cancer	Miller et al. 2005b
ZD6474, Zactima	+ XRT	II-Peds	HGG	Broniscer et al. 2010
ZD6474, Zactima	+ Vinorelbine/ cisplatin or gemcitibine/ cisplatin	I	NSCLC	Blackhall et al. 2010
ZD6474, Zactima	Docetaxel ±	III	NSCLC	Herbst et al. 2010
ZD6474, Zactima		II	Medullary thyroid cancer	Robinson et al. 2010a
ZD6474, Zactima	+ XRT + temozolomide	I	GBM	Drappatz et al. 2010
ZD6474, Zactima		II	Ovarian	Annunziata et al. 2010
ZD6474, Zactima		II	Medullary thyroid cancer	Wells et al. 2010
ZD6474, Zactima	+ Docetaxel/ prednisolone	II	Prostate	Horti et al. 2009
ZD6474, Zactima	Versus gefitinib	II	NSCLC	Natale et al. 2009

Continued

Table 2. *Continued*

Name	Additional agents	Status	Disease	References
ZD6474, Zactima	+ FOLFIRI	I	Colorectal	Saunders et al. 2009
ZD6474, Zactima	+ Pemetrexed	I	NSCLC	de Boer et al. 2009
ZD6474, Zactima	+ mFOLFOX6	I	Colorectal	Michael et al. 2009
ZD6474, Zactima		II	NSCLC	Arnold et al. 2007; Kiura et al. 2008
ZD6474, Zactima	± Docetaxel	II	NSCLC	Heymach et al. 2007
ZD6474, Zactima		I	Solid tumor	Tamura et al. 2006
ZD6474, Zactima		II	NSCLC	Lee 2005

improved progression-free survival (2.8 vs. 5.5 wk, $p < 0.001$) and overall survival (15.9 vs. 19.3 mo, $p = 0.02$) (Escudier et al. 2007). It has also received approval for hepatocellular carcinoma (Rossi et al. 2010). Similarly, sunitinib received FDA approval in early 2006 for imatinib-resistant gastrointestinal stromal tumors (GIST) and for metastatic renal cell carcinoma (RCC), showing improved progression-free survival for sunitinib versus IFN-α (11 vs. 5 mo), as well as objective response rate (31% vs. 6%) (Motzer et al. 2007). The broad spectrum of activity of these two inhibitors precludes clear attribution of their activity just to inhibition of the VEGF pathway.

VEGF inhibitors have also been successfully used for treatment of the wet form of age-related macular degeneration (AMD). A pegylated oligonucleotide aptamer selectively targeting VEGF165 called pegaptanib sodium (Macugen) and a recombinant, humanized anti-VEGF Fab fragment called ranibizumab (Lucentis) are both FDA approved for treatment of this disease (Gryziewicz 2005; Ciulla and Rosenfeld 2009). Not only have patients showed improvement in disease, but also many have shown significant improvement in vision, even when compared with other approaches such as photodynamic therapy (Rosenfeld et al. 2006).

Consideration of the unique environment for different tumors will likely affect the choice, activity, and toxicity of different antiangiogenic agents (Josson et al. 2010). Approaches for different diseases should consider these differences including breast (Chan 2009), brain (Miletic et al. 2009), renal cell (Bukowski 2009; Motzer and Molina 2009), NSCLC (Aita et al. 2008), and pancreas (Philip 2008), to name a few.

TOXICITIES OF VEGF PATHWAY INHIBITORS

In general, antiangiogenic agents have been well tolerated. Because many of the initial clinical trials of VEGF inhibitors, especially small molecule inhibitors, had several off-target effects, the actual toxicity profile of this class of agents has been difficult to assess. With more specific agents now in the clinic, a picture is emerging that suggests that, in general, VEGF pathway inhibitors are well tolerated, whether administered orally, intravenously, or intraocularly. Common toxicities thought to be related to on-target effects include fatigue, hypertension (Izzedine et al. 2007, 2009; Pande et al. 2007), proteinuria, delayed wound healing, and chemical hypothyroidism (often without clinical symptoms) (Veronese et al. 2006; Boehm et al. 2010; Geiger-Gritsch et al. 2010; Robinson et al. 2010b). Several rare side effects have also been reported in multiple trials and include bleeding and/or thrombosis (which can be severe or fatal), intestinal and nasal septal perforation (Hapani et al. 2009), effects on growth plates (Hall et al. 2006), and posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS) (Artunay et al. 2010). Initial concerns about frequent severe and fatal hemorrhages have not been observed clinically for most tumor types, although this potential side effect continues to be of concern, particularly in certain tumor subtypes (Hapani

et al. 2010). It is still not clear whether patients with severe side effects are poor or better responders to therapy.

ASSESSMENT OF THE ANGIOGENIC RESPONSE

Critical to the determination of activity of a clinical inhibitor, including those of the VEGF pathway, are methodologies that accurately detect the antitumor effect of the agents being tested. Overall survival and time to progression remain important determinants that can address the relative clinical importance of therapies and remain the gold standards. Treatments that cause significant tumor response followed by equally rapid tumor progression without any impact on time to progression or survival are less useful than those that may only stabilize the tumor but result in prolongation of survival. As discussed briefly above, VEGF was originally identified for its effect on permeability (VPF) (Senger et al. 1983), presumably the result of its stimulation of endothelial cell proliferation, which requires the cells to round up as they prepare for mitosis. Endothelial cells that break their junctions with neighboring endothelial cells will therefore allow some of the intravascular liquid to leak into the surrounding tissue. When the VEGF inhibitor bevacizumab was initially tested in patients with glioblastoma multiforme, a disease known to have significantly elevated VEGF levels and for which neovascularization is part of the diagnostic criteria of the disease, response rates by MRI of 60%–70% were reported (Vredenburgh et al. 2007). In hindsight, the "response" observed in these patients was likely related more to the decreasing permeability effect when VEGF is sequestered by bevacizumab than actual tumor "response" related to tumor cell kill (Verhoeff et al. 2009). Significant reduction in contrast enhancement (the response) can be observed within a day of treating patients with VEGF inhibitors (Batchelor et al. 2007) and can be lost (the resistance) when the inhibition is released. Proof that tumor escape has not actually occurred can be easily shown by restarting the inhibitor and getting the "response" back, something that has been observed during drug holidays for therapy-associated toxicities (Batchelor et al. 2007). This effect will be of critical importance as we continue to use radiologic tumor assessment to guide activity of this class of drugs and has led to the proposal in adults of new response assessment criteria that attempt to take some of this effect into account (Thompson et al. 2010; Wen et al. 2010).

RESISTANCE TO VEGF PATHWAY THERAPY

As correctly predicted in the original hypothesis of Dr. Folkman, ample preclinical data now support the critical importance of angiogenesis as a fundamental process of tumor progression. Because the neo-angiogenic stimulus is generated by the tumor through secretion of factors that can induce new vessel formation by acting on endothelial cells, it was predicted that resistance would not occur (Boehm et al. 1997). This was based on the assumption that endothelial cells responding to tumor secretion of cytokines are fundamentally normal cells, cannot mutate, and thus cannot evade therapeutic intervention. Unfortunately, clinical experience has not been as optimistic. Even in the clinical trials showing activity for inhibitors of the VEGF pathway based on response, time to progression, or overall survival, the vast majority of patients eventually succumb to their disease. Understanding these "resistance" mechanisms will therefore be critical for the long-term use of this class of inhibitors. Two major types of resistance—extrinsic and intrinsic—are presented below, although others may come to light as more attention is focused on this field. Others have defined resistance patterns in different ways that need to be discussed and evaluated (Ton and Jayson 2004; Bergers and Hanahan 2008; Azam et al. 2010).

Go-Around (Extrinsic) Resistance

1. The easiest resistance mechanisms to understand are those that do not reduce the activity of the inhibitor or alter the primary effect on the target, but rather provide a simple

redundant signal that makes the one being inhibited no longer essential. Thus, inhibition of the VEGF pathway can be easily overcome by up-regulation of other VEGF-independent pathways such as bFGF, IL-8, or any combination of the 40 or so angiogenic cytokines that have been discovered to date (Leek et al. 1994; Yan et al. 2006; Gerber et al. 2009; Voss et al. 2010). This type of resistance was to be expected. Redundancy in cellular signaling is observed in a large number of biological pathways and accounts for the resistance to many drugs including those for EGF, PDGF, and mTOR (Kornblau et al. 2006; Tabernero 2007). These alternative angiogenic pathways may also account for the very poor up-front response of certain tumor types to antiangiogenic therapy. Tumors that up-regulate multiple pathways early in their genesis would not be dependent on any single inhibitor and would thus fail to respond from the outset. The ability of tumors to express more than one angiogenic cytokine has been shown for many tumor types (Karcher et al. 2006; Samaras et al. 2009). Consistent with this idea has been the improved activity of combination approaches in preclinical models (Bozec et al. 2008). To be successful in the long term, a detailed understanding of all (or most) of the angiogenic cascades operating to maintain tumor growth will need to be identified and targeted simultaneously if this form of resistance is to be avoided (Wary 2004).

2. Another modality for getting around the blockage generated by VEGF pathway inhibition is to coopt existing blood vessels so that angiogenesis is no longer required. This is best visualized in the brain, where malignant gliomas can grow along existing blood vessels rather than as a discrete mass, a process called "gliomatosis cerebri." Mechanistically, this might be related to the tumor's response to hypoxia induced by anti-VEGF therapy in which promigratory and invasive phenotypes are favored to reach areas of improved oxygenation. Interestingly, there is some evidence to suggest that gliomatosis cerebri can occur with increased frequency in patients treated with VEGF inhibitors (Norden et al. 2008).
3. Tumors can up-regulate the metabolism of antiangiogenic agents through a variety of mechanisms, all of which would result in loss of response to therapy. Increased clearance of a drug, decreased penetration into the target cell (e.g., by change in local pH), or increased proteolytic degradation of protein inhibitors (thrombospondin, endostatin as examples) or antibodies (bevacizumab, VEGF-Trap as examples) are all possible mechanisms (Kitamura et al. 2008). Although patients are often referred to as having developed "resistance" when they initially respond to a drug but then lose the response, it is important to recognize that this effect is not actual endothelial or target resistance.
4. Finally, initial reports that tumor cells themselves could act as endothelial cells ensuring functional tube formation without a complete endothelial cell response is another potential method of getting around therapeutic antiangiogenic interventions (Hendrix et al. 2003; Barrett et al. 2005; Fujimoto et al. 2006). Follow-up studies have failed to show a strong or clinically significant role for this mechanism.

Classic Endothelial Cell (Intrinsic) Resistance

As initially predicted, the ability of normal endothelial cells, even those responding to tumor-induced angiogenic stimuli, appears limited. Tumor-associated endothelial cells have been reported to take up tumor DNA, which, in turn, could assist with development of true intrinsic resistance (Hida et al. 2004). Although this resistance mechanism must be considered as a possibility, it does not currently appear to be a major issue either in preclinical models or human response to antiangiogenic therapy.

SUMMARY

Antiangiogenic strategies for the control of tumor-mediated angiogenesis have progressed dramatically over the last 40 years. Multiple

inhibitors are in clinical trials, and several have been approved for use in the United States and Europe. Some of the initial excitement for this class of drugs has waned despite less than a decade of real experience. This has resulted from an underestimation of the complexity of neovascularization including the number of cell types and pathways involved, the adaptive response of established tumors once therapy is initiated, and the availability of a small set of inhibitors, many with limited activity, poor specificity, and great toxicity. In this regard, it is possible that antiangiogenic therapy may reveal its best efficacy when used on early tumors which have yet to convert or have just converted to angiogenic tumors. Such "proactive" trials are hard to conduct but, we hope, will be pursued. The field of oncology did not give up on radiation therapy or on chemotherapy within the first 10 years of their use, despite their limited impact on survival. Rather, as we began to understand the complexity of cancer, the opportunity for improved drug development and combinations including surgery, radiation, and chemotherapy have begun to result in cures. A similar maturation is needed in the field of anti-angiogenesis and has now begun. As combination approaches gain acceptance and are based on a more precise understanding of the subtle angiogenic profiles specific to any individual's tumor, our ability to select patients who are most likely to respond to VEGF targeting will occur. This will also allow therapy to take into account the escape mechanisms that the tumor might use with appropriate adaptation of the therapeutic plan.

Antiangiogenic therapy did not fail to meet our expectations—rather, our expectations were unrealistic. The original proposal by Dr. Folkman recognized the association of neovascularization and tumor growth, that endothelial cells are a unique "ecosystem" within the tumor, that tumor cells regulate endothelial cell proliferation, and that this, in turn, can affect the rate of tumor growth (Folkman 1971). All of this occurred before the discovery of either pro-angiogenic cytokines or inhibitors. Although Dr. Folkman was excited by the promise of VEGF-targeted therapy for cancer and other diseases, he also recognized the complexity of tumor-mediated angiogenesis. He therefore saw this approach as a success in laying the foundation for future research, understanding, and clinical intervention. So should we!

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