Pharmacology & Therapeutics 167 (2016) 1–12

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: M. Panagiotidis

Targeting the angio-proteostasis network: Combining the forces against cancer

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ARTICLE INFO

Available online 22 July 2016

Keywords:
Angiogenesis
Unfolded protein response
PlGF
VEGF
IRE1
Cancer

ABSTRACT

The VEGF family of pro-angiogenic factors has represented a pillar for targeted cancer therapy for more than a decade. In comparison, the field of protein homeostasis (proteostasis) focusing on the Unfolded Protein Response (UPR), an endoplasmic reticulum (ER) stress-induced signaling cascade, has just recently emerged as an attractive anti-cancer approach. Recent findings suggest that both signaling pathways are incontestably interrelated to ensure cell survival. Herein, we summarize recent findings that demonstrate how these two fundamental aspects of cancer cell survival intersect and provide genetic and pharmacological evidence of the interplay between angiogenic factors such as VEGF-A or PlGF and the individual members of the UPR such as IRE1, PERK and ATF6. We further describe how this interaction does not only affect the cancer cells, but also the surrounding microenvironmental niche that is also involved in tumor progression. Furthermore, by summarizing the recent therapeutic implications of both anti-angiogenic and proteostatic approaches, we emphasize how these novel findings could be used synergistically to improve cancer therapy.

1. Introduction

Since its discovery by J. Folkman more than 40 years ago, tumor angiogenesis has been recognized as a driver for cancer development, in part through the Vascular Endothelial Growth Factor (VEGF) signaling network (Moens et al., 2014). Indeed, the therapeutic importance of targeting VEGF signaling in both solid and hematological malignancies has been well documented in the past decade (Schmidt & Carmeliet, 2011). However, current anti-angiogenic therapies, that either target the ligand or its receptor, have been hampered by both tumor-acquired resistance and undesired side-effects, often resulting in insufficient outcome (Carmeliet & Jain, 2011a). Exploring interconnecting signaling pathways exerting a more subtle influence on the process of vascular bed expansion and therapy resistance could provide more therapeutic benefit. Such a potential pathway is the Unfolded Protein Response (UPR), a conserved stress response triggered within the Endoplasmic Reticulum (ER) (Stapor et al., 2014). The balance of protein demand and adequate synthesis is in part orchestrated in the ER, the site for biogenesis of secretory and transmembrane proteins (Diaz-Villanueva et al., 2015). Stresses typically associated with cancer, such as metabolic changes, nutrient deprivation, hypoglycemia and hypoxia, are known activators of both UPR and pro-angiogenic signaling. Not surprisingly, the UPR and angiogenesis are highly interconnected as these two processes restore nutrient and oxygen supply to attain cell survival (Binet & Sapieha, 2015). Herein, we summarize the current understanding of the

Abbreviations: ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; ATF6α, Activating transcription factor 6 alpha (also referred as ATF6); CHOP, C/EBP homologous protein; CLL, Chronic lymphoblastic leukemia; DCs, Dendritic cells; ER, Endoplasmic reticulum; ERAD, ER-associated protein degradation; ERO1α, ER oxidase 1α; HCC, Hepatocellular carcinoma; HIF1, Hypoxia-inducible factors 1; IRE1α, Inositol requiring enzyme 1 alpha (also referred as IRE1); kDA, Kilodalton; mRCC, Metastatic renal cell carcinoma; MM, Multiple myeloma; NSCLC, Non-squamous non-small cell lung cancer; OS, Overall survival; PERK, PKR-like ER kinase; PFS, Progression free survival; PLCγ, Phosphatidylinositol phospholipase C; PlGF, Placental growth factor; PNET, Pancreatic neuroendocrine tumor; RIDD, Regulated IRE-1α-dependent decay; ROS, Reactive oxygen species; TADCs, Tumor-associated dendritic cells; TAMs, Tumor-associated macrophages; TKIs, Tyrosine kinase inhibitors; UPR, Unfolded protein response; VEGF-A-D, Vascular endothelial growth factor A-D; VEGFR1–3, Vascular endothelial growth factor receptor 1–3; XBP1, X-box binding protein 1; XBP1s, X-box binding protein 1 spliced.

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http://dx.doi.org/10.1016/j.pharmthera.2016.07.007
0163-7258/

angiogenesis/UPR cross-talk and highlight how this interplay could be controlled for optimized cancer therapy.

2. The family of pro-angiogenic factors

Vascular development occurring during embryogenesis is defined as vasculogenesis, whereas novel vessel formation through sprouting or intussusception of existing blood vessels is termed angiogenesis, which has been extensively studied not only in the context of cancer, but also for instance inflammatory diseases (Carmeliet, 2003; Carmeliet & Jain, 2011a). It is mediated mainly by the VEGF family, a group of secreted dimeric glycoproteins with a molecular weight of ~40 kilodalton (kDa) (Olsson et al., 2006). In mammals, the VEGF family is comprised of five members, namely VEGF-A to D and placenta growth factor (PlGF) which bind to three VEGF receptors (VEGFR1 to 3; Fig. 1).

VEGFR1 signaling drives both hematopoiesis and the motion of hematopoietic cells, including endothelial cells, while VEGFR2 (or Flk-1) has been linked to vasculogenesis where it functions as the principal mediator of the mitogenic, angiogenic and permeability-enhancing effects of VEGF-A (Takahashi & Shibuya, 2005). Unlike VEGFR1 and 2, VEGFR3 is expressed on lymphatic endothelial cells and has been specifically linked to lymphangiogenesis.

VEGF-A can bind to both VEGFR-1 and VEGFR-2, however its biological effects are solely mediated through VEGFR2 while VEGFR1 acts as a decoy receptor. VEGF-A is the main angiogenic factor, whereas VEGF-C to -D, while displaying some angiogenic action through binding with VEGFR1 or 2, are predominantly pro-lymphangiogenic factors through binding to VEGFR3 (Takahashi & Shibuya, 2005; Secker & Harvey, 2015; Varricchi et al., 2015). PlGF selectively binds to VEGFR1 (also known as FLT1) and its soluble form (sFLT1) (De Falco, 2012), initiating an angiogenic response. Through binding with VEGFR1, PlGF competes with VEGF-A leading to an increase in soluble VEGF-A (Park et al., 1994).

While VEGF-A–D are essential for endothelial cell activation, proliferation and migration, PlGF signaling is specifically linked to pathological angiogenesis, an uncontrolled, persistent and unresolved formation of a – usually disorganized – vascular network (Chung & Ferrara, 2011). Tumor angiogenesis is typically characterized by a poorly formed vascular bed driven by overexpression of angiogenic factors and their receptors, to maintain tumor oxygen and nutrient supply, which are essential for tumor growth, metastasis and invasion. Consequently, targeting tumor angiogenesis has become one of the most appealing and applied strategies in anti-cancer therapy (Folkman, 2007; Schmidt & Carmeliet, 2011; Carmeliet & Jain, 2011a, 2011b; Moens et al., 2014). The differential role of VEGF family members and their receptors in malignancy, relates to the intrinsic characteristics of specific tumors. However generalized, VEGF and its receptors are induced and function as prognostic negative factors in a broad range of tumors (reviewed by (Costache et al., 2015).

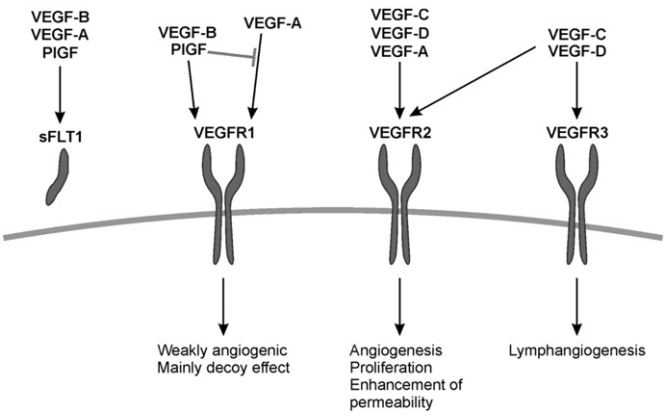

Fig. 1. Overview of the different VEGFs and their corresponding receptors. Schematic overview of VEGF family´ ligands and the signaling pathways they control through binding of specific receptors.

3. The Unfolded Protein Response

The endoplasmic reticulum (ER) orchestrates the production and controls the correct folding of secretory and transmembrane proteins and represents the key cellular organelle for maintaining proteostasis (Diaz-Villanueva et al., 2015). As such, the ER is highly dependent on adaptive systems, such as the UPR, to cope with cellular stresses. The UPR can respond to cellular stress either in an acute and reversible manner by lowering levels of unfolded proteins and restoring homeostasis or in the case of terminal and chronic stress by induction of pro-apoptotic signaling (Hiramatsu et al., 2015). Within the ER, three transmembrane sensors, namely Inositol Requiring Enzyme 1 alpha (IRE1α), PKR-like ER kinase (PERK) and Activating Transcription Factor 6 alpha (ATF6α), monitor the "health" of the ER (Bertolotti et al., 2000) (Fig. 2). Induction of ER stress initiates release of the ER chaperone 78 kDa glucose-regulated protein (GRP78) from each receptor which permits their activation (Bertolotti et al., 2000). Among the three signaling branches, IRE1 represents the most evolutionary conserved arm of the UPR and contains an endoribonuclease (RNase) and a serine/threonine kinase domain (Zhou et al., 2006). The RNase activity of IRE1 contributes to the splicing of the X-box binding protein 1 (XBP1) mRNA (Yoshida et al., 2001; Uemura et al., 2009) together with the tRNA ligase RTCB (Kosmaczewski et al., 2014; Lu et al., 2014). Through the removal of a 26-nucleotides intron and a change in the mRNA reading frame, a transcriptionally active protein (XBP1s) is translated and translocates to the nucleus to mostly enhance the transcription of genes involved in protein folding, secretion and ER-associated protein degradation (ERAD). Recent studies have also revealed a requirement for IRE1 RNase activity in RNA degradation through a mechanism known as Regulated IRE1-dependent decay (RIDD) (Maurel et al., 2014). The identification of RIDD indicates that other mRNA and miRNA aside from XBP1 are cleaved by IRE1, suggesting that an influence on cell signaling and cell behavior is more widespread than previously apparent. While initially, individual RIDD targets such as BLOC1S1 were dismissed as being dispensable, it is becoming more evident that RIDD is an intricate process acting in a cell type and sequence specific fashion, where distinct targets exert a more important influence on cell signaling than others, such as shown for PDAI6 or SUMO (Hollien et al., 2009; Moore et al., 2013; Tam et al., 2014; Moore & Hollien, 2015; Eletto et al., 2016).

Following dissociation from GRP78, PERK, a serine/threonine (eIF2αK3) kinase, phosphorylates Eukaryotic Translation Initiation Factor 2 Subunit Alpha (eIF2α) and attenuates CAP-dependent protein synthesis, consequently enabling translation of mRNA bearing either IRES sequences, or 5′ located μORFs such as Activating Transcription Factor 4 (ATF4), (Harding et al., 1999; Harding et al., 2000). This phosphorylation is also essential for starting the translation of ATF4 under hypoxic conditions (Rutkowski & Kaufman, 2003; Blais et al., 2004; Ameri & Harris, 2008). ATF4, in turn, induces the pro-apoptotic CCAAT-enhancer-binding protein homologous protein (CHOP) and Growth Arrest and DNA-Damage-Inducible 34 (GADD34). (Ma et al., 2002). In addition to phosphorylation of eIF2α, PERK also targets additional downstream molecules that function as cellular substrates, such as Nuclear factor (erythroid-derived 2)-like 2 (NRF2) that is an important player in angiogenesis (Cullinan & Diehl, 2004). Indeed, ER stress is associated with generation of reactive oxygen species (ROS) and UPR signaling enhances a mechanism able to alleviate ROS, specifically through PERK mediated NRF2 activation (Pytel et al., 2016).

The third arm of the UPR is composed of ATF6, a type II ER transmembrane protein which, unlike PERK and IRE1, is relocalized to the Golgi complex following export from the ER for its activation upon ER stress (Shen et al., 2002). Here, ATF6 is cleaved by site-1 (S1P) and site-2 proteases (S2P) through regulated intramembrane proteolysis (RIP) generating an active transcription fragment, named ATF6f (Ye