On the pro-metastatic stress response to cancer therapies: evidence for a positive co-operation between TIMP-1, HIF-1α, and miR-210

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INTRODUCTION

Late stage cancer with occurrence of metastasis is the greatest and most challenging problem for research aimed at the development of new therapeutic concepts and agents against malignant tumors. In fact, most cancer patients die of metastasis and not of the primary tumor (Sporn, 1996). Current therapies are genotoxic-based DNA-damaging agents and cell cycle inhibitors and show some efficacy in early stages of cancer only (Yamaguchi and Perkins, 2012). However, in the cell population of a progressing tumor, these therapies often select for clones which, due to their genetic and epigenetic instability, are predisposed to react to stress by adaptation and, if the stress persists, by escape and formation of metastasis. Recent recognition of the concepts of dynamic evolution as well as population and systems biology is extremely helpful to understand the disappointments of clinical trials with new drugs and may lead to paradigm-shifts in therapy strategies. This must be complemented by an increased understanding of molecular mechanism involved in stress response. Here, we review new roles of Hypoxia-inducible factor-1 (HIF-1), one transcription factor regulating stress response-related gene expression: HIF-1 is crucial for invasion and metastasis, independent from its pro-survival function. In addition, HIF-1 mediates pro-metastatic microenvironmental changes of the proteolytic balance as triggered by high systemic levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), typical for many aggressive cancers, and regulates the metabolic switch to glycolysis, notably via activation of the microRNA miR-210. There is preliminary evidence that TIMP-1 also induces miR-210. Such positive-regulatory co-operation of HIF-1α, miR-210, and TIMP-1, all described to correlate with bad prognosis of cancer patients, opens new perspectives of gaining insight into molecular mechanisms of metastasis-inducing evasion of tumor cells from stress.

Keywords: HIF-1α, microenvironment, microRNA, miR-210, MMP, pro-metastatic, TIMP-1, Met
VEGFR/PDGFR kinase inhibitors or VEGFR-specific antibodies increase multi-organ metastasis (Ebos et al., 2009) or metastasis to the liver and lymph nodes, respectively (Páez-Ribes et al., 2009).

The main explanation of these "surprises" relies on the too long ignored appreciation that tumors represent an eco-system of heterogeneous tumor and host cell populations, where mechanisms of evolutionary dynamics and population biology apply, leading to the conclusion that over-simplistic interference will yield unforeseen and even detrimental effects (Gatenby, 2009). In addition, it is necessary to more carefully analyze the complex interdependencies of targeted gene products including the activity and expression of connected proteins and its effect on signal transduction and cell behavior, in other words the systems biology of specific therapeutic interference (Krüger, 2009; Krüger et al., 2010; Sela-Passwell et al., 2011). With such mind-set it was possible to solve the paradox why elevated systemic levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), i.e., correlate with bad prognosis of many cancers (Zucker et al., 2000). There is data suggesting that broad-spectrum inhibition of MMPs by TIMP-1 interferes with the negative regulation of the MET tyrosine kinase by blocking the MET-shedding activity of ADAM-10 (Kopitz et al., 2007). MET activity is a key promoter of the invasive growth program in tumor cells (Boccaccio and Camoglio, 2006). In addition, broad-spectrum inhibition of MMPs leads to an evasive shift of proteolytic activity from the inhibited MMPs toward serine proteases such as the urokinase-type plasminogen activator (uPA) in the microenvironment, which was associated with a drastic promotion of tumor cells to metastasize (Kopitz et al., 2007). Such complexities and evolutionary adaptations of tumor cells or, as in the above case of the tumor microenvironment, are extremely relevant not only for therapeutic inhibition of MMPs but for all attempts to inhibit proteases as "obvious" tools for tumor cell invasion and metastasis (Krüger et al., 2010).

Such Darwinian selection of tumor cells with a more aggressive phenotype can also be the cause of problems with anti-angiogenic therapy (Gatenby and Gillies, 2004; Michieli, 2009). Inhibition of angiogenesis leads to hypoxia which was initially thought to lead to suffocation of tumor cells and subsequent total elimination of the tumor (Hanahan and Folkman, 1996; Dang and Semenza, 1999). However, malignant tumors meet the hypoxic challenge not only by induction of angiogenesis. Instead, in fast-growing neoplasias hypoxia selects for malignant tumor cells which are adapted to hypoxia by using a gene expression program allowing a metabolic switch from dependence on oxygen for energy generation to energy production under anaerobic conditions by glycolysis only (Gatenby and Gillies, 2004). In fact, malignant tumor cells are even able to leave the site if unfavorable conditions persist by initiating an invasive growth program (Penneccietti et al., 2003). This program is highly dependent on signaling of the MET tyrosine kinase receptor (Penneccietti et al., 2003) and ultimately leads to metastasis, the main cause of death for cancer patients.

The ability of tumor cells to respond to stress by inducing angiogenesis, performing glycolysis, and initiating the invasive growth program has to be maintained throughout the steps of the metastatic cascade (Gatenby and Gillies, 2004). Hypoxia-inducible factor-1 (HIF-1) is a transcription factor which seems to be crucial for all the above-mentioned stress responses of malignant tumor cells. In this review we propose a molecular mechanism from available data which explains how metastasis formation can be driven by an increase in stress on tumor cells by anti-angiogenic and anti-proteolytic agents. We summarize evidence for and propose a new context between one of the most central regulators of the proteolytic network, TIMP-1, the major regulator of tumor cell stress response, HIF-1, and its main downstream microRNA (miRNA) effector, miR-210.

**HIF-1α REGULATES RESPONSE OF TUMOR CELLS TO STRESS**

In addition to the surrounding tissue for nutrients, oxygen, and space disturbs the proteolytic balance and forces tumor cells to adapt, escape, or undergo apoptosis (Figure 1). Cell fate, i.e., whether a tumor cell succumbs to the stress by apoptosis (death), adapts by ensuring survival at the site (stay) or leaves in the search of better conditions (escape) is determined by HIF-1-dependent intracellular pathways (Figure 1). Under normoxic conditions HIF-1α, one of two subunits of HIF-1, is hydroxylated by iron- and oxygen-dependent prolyl-hydroxylases (Lando et al., 2002; Kaelin and Ratcliffe, 2008), modified by the E3 ubiquitin ligase von Hippel Lindau (Jaakkola et al., 2001), and subsequently degraded in the proteasome. A lack of oxygen renders the prolyl-hydroxylases inactive so that HIF-1α can associate with constitutively expressed HIF-1β and form the heterodimer HIF-1 (Majmundar et al., 2010). HIF-1 translocates to the nucleus, binds to hypoxia-response elements (HREs), and initiates transcription of target genes which allow adaptation to stress (Wenger et al., 2005).

HIF-1 can also be induced by hypoxia-independent factors (Wenger et al., 2005), such as inflammatory cytokines like IFN-γ and IL-4 (Majmundar et al., 2010) as well as NF-κB (Wilczynski et al., 2011). HIF-1α mRNA expression and protein stability are further upregulated by mTORC1 (Bernardi et al., 2006) and the PI3K pathway (Mottet et al., 2003), which can initiate a HIF-1-mediated response independent of hypoxic stress.

Recently, high level of metalloproteinase inhibitor TIMP-1 in the tumor microenvironment was discovered as a new inducer of HIF-1 in a liver metastasis model (Schelter et al., 2011b). Based on this observation, the induction of HIF-1α gene expression by TIMP-1 was further confirmed in vitro: Exposure of a lymphoma tumor cell line to recombinant TIMP-1 led to an increase in HIF-1α mRNA level, protein, and the HIF-1α downstream target CA-9 (Schelter et al., 2011b). This observation represents a new connection between the major regulator of stress response in tumor cells, HIF-1, and TIMP-1, a central player of the proteolytic network. TIMP-1 determines tissue homeostasis (Krüger et al., 2010) and can, if systemically elevated, promote metastasis (Kopitz et al., 2007). As metastasis accounts for 90% of solid tumor dependent deaths (Gupta and Massagué, 2006), the induction of the metastatic potential of tumor cells by TIMP-1 and HIF-1 must be considered crucial for successful treatment of malignant tumors.

**REGULATION OF TUMOR CELL INVASION BY HIF-1**

In addition to its critical role in tumor cell survival during hypoxic conditions in metastasis (Gatenby and Gillies, 2004), HIF-1 also directly promotes tumor cell malignancy by induction of an aggressive phenotype (Lu and Kang, 2010). HIF-1 leads to an upregulation of glycolysis while at the same time suppressing
FIGURE 1 | The proposed model of molecular mechanisms regulating the three choices of tumor cells under stress. Microenvironmental factors regulate the activity of HIF-1α. In addition to normoxia or hypoxia, changes of the proteolytic network can also determine the response of the tumor cell. While normoxia and proteolytic balance favor proliferation (right panel), which reflects the adaption of the tumor cell in situ, hypoxia or alterations in the proteolytic network promote the induction of pro-evasive mechanisms (left panel). Respiration is impaired upon HIF-1α stabilization not only by hypoxia but also in the case of proteolytic imbalance imposed by high TIMP-1 levels or similar environmental stress. It leads to upregulation of miR-210 which directly inhibits expression of the subunit D of the succinate dehydrogenase complex (SDHD) and simultaneously induces cell cycle arrest by inhibition of E2F3. Thus, the tumor cell switches to the evasive metastatic phenotype for which adaptation to hypoxia by their potential of executing anaerobic glycolysis is a prerequisite.

oxidative phosphorylation. Two consequences result from this metabolic adaptation: firstly, oxygen is no longer a limiting cofactor necessary for cellular energy supply. Secondly, lactate generated at the same time in large amounts can serve as a precursor for many metabolic intermediates needed for cell growth (Gatenby and Gillies, 2004). Secreted lactate can also be used by surrounding hypoxic tumor cells imported by the transporter MCT1, which in this context may be a possible therapeutic target (Sonveaux et al., 2008; Le Floch et al., 2011). Independence from oxygen and efficient lactate transport resourcefully exploit the available energy sources in the tumor (Sonveaux et al., 2008).

In order to balance the much less effective aerobic glycolysis, glucose uptake is increased by upregulation of glucose transporters like GLUT-1 by HIF-1 (Chen et al., 2001). In addition, a variety of pro-angiogenic factors including the VEGF (Forsythe et al., 1996) and PDGF (Bos et al., 2005) are upregulated by HIF-1 to ensure a sufficient supply of glucose and to escape the lack of oxygen resulting from the diffusion limit in solid fast-growing tumors.

Persistent lack of oxygen can ultimately lead to the selection of tumor cells which exhibit a more aggressive and invasive phenotype and allows escape from unfavorable conditions (Gatenby and Gillies, 2004). HIF-1 promotes metastasis by initiating epithelial-to-mesenchymal transition by the induction of the transcription factors Snail (Mak et al., 2010) and Twist (Yang et al., 2008), which in turn lead to a repression of E-Cadherin. Additionally, HIF-1 induces the expression of MET tyrosine kinase receptor (Pennacchietti et al., 2003) via HRE in the MET promoter region (Pennacchietti et al., 2003). MET-signaling in turn leads to an increase in cell motility and invasiveness which furnishes metastasis (Pennacchietti et al., 2003). Furthermore, HIF-1 promotes the expression of proteases enabling tumor cells to break through physical borders (Krishnamachary et al., 2003; Schelter et al., 2010).

The above-mentioned in vitro observations left it open, whether HIF-1α regulates tumor cell invasiveness directly in vivo and what molecular mechanisms determine direct pro-invasive functions of HIF-1 signaling (Bertout et al., 2008; Ruan et al., 2009). Until recently, it was hard to clarify this topic as the survival of tumor cells under microenvironmental stress usually depends on HIF-1 signaling (Semenza, 2003). Indeed, it could not be excluded that reduced metastasis upon HIF-1α depletion was simply a reflection of decreased survival (Schelter et al., 2010). Recently, this distinction was achieved using a hypoxia-tolerant tumor cell line, which does not rely on HIF-1 signaling for survival. It was shown that HIF-1 directly controls pro-invasive and pro-metastatic features of tumor cells independent of its promotion of cell viability (Schelter et al., 2010). Further, it was shown that HIF-1 plays a central role in the efficacy of metastasis formation and organ colonization by induction of MMP-9, one of the major gelatinases expressed by invasive tumor cells (Schelter et al., 2010). This separation of survival-dependent and independent HIF-1 effects allows differentiation between tumorigenic and metastasis-promoting effects of HIF-1, leading to a deeper insight into metastatic processes and stress response.

HIF-INDUCED miR-210 AND THE SWITCH TO ESCAPE MODE

Recently, an additional level of HIF-dependent transcriptional regulation was elucidated, which involved HIF-induced up-regulation of miRNA (Kulshreshtha et al., 2007). MiRNAs function as components of ribonucleoprotein complexes referred as miRNA-induced silencing complexes (miRISCs). They primarily regulate gene expression through inhibition of RNA translation by binding to
their target gene’s 3’ UTR. They also induce mRNA decay, resulting in the down-regulation of target mRNAs (Esquela-Kerscher and Slack, 2006; Ortholan et al., 2009; Fabian et al., 2010).

Upon hypoxia, microRNA miR-210 is induced by HIF-1 (Kulshreshtha et al., 2007). While a number of miRNAs are associated with stress response in tumor cells, miR-210 is the only “hypox-amir” which is most significantly upregulated in a number of cancers (Chan and Loscalzo, 2010). MiR-210 mediates a number of known HIF-1 downstream effects, most importantly the HIF-1 dependent suppression of oxidative phosphorylation (Chan et al., 2011).

Mechanistical insight into how HIF-1 inhibits mitochondrial respiration could be provided by studying the role of miR-210 in HIF-1 signal transduction: miR-210 regulates ISC1/2 expression, a protein associated with iron metabolism and leads to its repression upon stress (Chan et al., 2009). In addition, miR-210 was shown to target Succinate Dehydrogenase Subunit D (Puissegur et al., 2011), a component of the mitochondrial complex II. This provides evidence that miR-210 mediates the functional loss of the respiratory chain, the metabolic switch induced in tumor cells upon hypoxic stress (Gatenby and Gillies, 2004).

Moreover, miR-210 is also involved in cell cycle by regulation of the E2F3 transcription factor: miR-210 mediates the suppression of E2F3 protein expression and might attenuate cell proliferation (Giannakakis et al., 2008; Puissegur et al., 2011).

In addition, a recent study showed that not only HIF-1 induces miR-210 transcription but that vice versa miR-210 stabilizes HIF-1α (Puissegur et al., 2011). The inhibition of miR-210 shortens the HIF-1 activity which indicates a positive auto-regulatory loop based on the suppression of the afore-mentioned Succinate Dehydrogenase Subunit D (SDHD) by miR-210 (Puissegur et al., 2011). Low level of Succinate Dehydrogenase subsequently leads to an accumulation of succinate which in turn inhibits HIF-1α prolyl-hydroxylases (Selak et al., 2005). An inhibition of HIF-1α regulating enzymes delays the degradation of HIF-1α and stabilizes HIF-1 (Puissegur et al., 2011). Thus, HIF-1, miR-210, and SDHD are not only connected by linear transcriptional regulation but are indeed involved in an auto-regulatory loop on protein level which prolongs HIF-1 activity and signaling.

In conclusion, the effects of miR-210 on proliferation and metabolism together with the stabilization of HIF-1 lead to an accentuation of tumor cell stress response (Figure 1). Malignant cells are selected for their ability to evade stress present in their microenvironment. They are able to do so as they adopt a more aggressive phenotype and increase their metastatic potential as suggested by a very recent study (Ying et al., 2011).

In addition to the effect of stress-induced expression of miR-210 on tumor cells, one could speculate that miR-210 is involved in the manipulation of pre-malignant tissue and modulation of the microenvironment at metastatic sites. To successfully colonize potential target tissue, tumor cells depend upon stromal and vascular cells (Gupta and Massagué, 2006). Hypoxic regions within metastases and high acidity in the tumor cell microenvironment stimulate HIF-1 dependent stress response not only in tumor cells but also in their direct microenvironment (Dayan et al., 2008). Induction of HIF-1 signaling and the effects of miR-210 might therefore not only promote an aggressive phenotype in tumor cells but also indirectly support metastasis by modulation of neighboring cells. This speculation is supported by the observation that forced expression of miR-210 in endothelial cells stimulated the formation of capillary-like structures and VEGF response and thus might promote angiogenesis upon hypoxia (Fasanaro et al., 2008).

It is also possible that not only hypoxia but also hypoxia-independent induction of HIF-1, e.g., by TIMP-1 (Schelter et al., 2011b), could stimulate miR-210 transcription, as we have preliminary evidence that exogenous TIMP-1 can lead to miR-210 upregulation in mouse livers.

**TIMP-1, A POSSIBLE REGULATOR OF PRO-EVASIVE STRESS RESPONSE?**

TIMP-1 stands out as a soluble factor which does not only modulate the extracellular matrix by regulation of MMP-activity but as an inducer of HIF-1α, it also decides over cell fate by guiding tumor cells toward an invasive phenotype. The two mechanisms by which TIMP-1 interferes with the metastatic potential of a tumor cell can be demonstrated by the example of the HGF receptor MET. First, MET is stabilized on protein level by high TIMP-1 levels via the inhibitory effects of TIMP-1: as an inhibitor of ADAM-10, it prevents shedding of MET, leading to higher cell surface levels. This enables both the more effective signaling of HGF as well as HGF independent dimerization of MET which also results in increased signal transduction (Kopitz et al., 2007). Second, on a transcriptional level, TIMP-1 might activate HIF-1 which in turn upregulates the gene expression of MET by binding to the MET promoter (Pennacchietti et al., 2003).

A clue of the role of TIMP-1 in metastatic progression was recently shown utilizing a TIMP-1 knock down in tumor cells which significantly decreased tumor cell invasiveness and reduced the number of metastasis (Schelter et al., 2011a). Taken together with the newly discovered connection between TIMP-1 and HIF-1α expression, TIMP-1 evolves as an outstanding cutting point between stress response and the proteolytic network.

**CONCLUSION**

Until recently TIMP-1 and HIF-1α (and in consequence miR-210) were seemingly totally un-related factors whose elevation is associated with bad prognosis for cancer patients (Zucker et al., 2000; Chan and Loscalzo, 2010; Wilczynski et al., 2011). In this review, we propose a functional pro-metastatic co-operation of these factors that link microenvironmental conditions to stress response involving the emerging field of gene regulation by miRNAs. Recent attempts to understand the complexity of system-wide cell signaling networks led to a deeper understanding of how self-contained networks can engage in crosstalk and contribute to cancer progression. The link between the proteolytic network and stress-related signaling by the natural broad-spectrum inhibitor TIMP-1 is one example of how interference with one network impacts on cell fate-decisions mediated by another pathway.

There is now increasing evidence that current experimental therapy approaches to eradicate the primary tumor may indeed lead to increased tumor cell aggressiveness. This aggressiveness, in turn, seems to be a natural adaptation strategy to environmental pressure known from all aspects of evolutionary selection. Future therapeutic targets should consider the context of both the
flexibility and interplay of different balanced networks and the ability of tumor cells to adapt to environmental stress. Here, we evaluated recent evidence, of how changes in tissue homeostasis, e.g., by alteration in the proteolytic network can impact on metastasis by HIF-1 dependent increase in tumor cell invasiveness and aggressiveness. This link is provided by TIMP-1, which can elicit HIF-1 induced stress response (Schelter et al., 2010, 2011b) and lead to increased metastasis in addition to the pro-metastatic effects of TIMP-1 related to its inhibitory properties (Kopitz et al., 2007; Schelter et al., 2011a). Indeed, paradigm-shifts in the treatment of cancer (Gately, 2009), which include a more holistic focus of cancer (to Bernard Mari). We would like to thank Bastian Seubert and other members of our lab for helpful discussions. We apologize to our colleagues whose work could not be cited due to space limitations. Financial support came from European Union Research Framework Programme 7, project HEALTH-2007-201279/Microenvimet (to Bernard Mari and Achim Krüger) and Association pour la Recherche sur le Cancer (to Bernard Mari).

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REFERENCES

Bernardi, R., Guernah, I., Jin, D., Grinioudi, S., Alimonti, A., Teruya-Feldstein, J., Gorden-Cardo, C., Simon, M. C., Rafii, S., and Pandolfi, P. P. (2006). PML inhibits HIF-1 translation and neoangiogene-
sis through repression of mTOR. Nature 442, 779–785.

Bertrand, J. A., Patel, S. A., and Simon, M. C. (2008). The impact of O2 availability on human cancer. Nat. Rev. Cancer 8, 967–975.

Bocaccio, C., and Comoglio, P. M. (2006). Invasive growth: a MET-driven genetic programme for can-

REFERENCES

Bernardi, R., Guernah, I., Jin, D., Grinioudi, S., Alimonti, A., Teruya-Feldstein, J., Gorden-Cardo, C., Simon, M. C., Rafii, S., and Pandolfi, P. P. (2006). PML inhibits HIF-1 translation and neoangiogene-
sis through repression of mTOR. Nature 442, 779–785.

Bertrand, J. A., Patel, S. A., and Simon, M. C. (2008). The impact of O2 availability on human cancer. Nat. Rev. Cancer 8, 967–975.

Bocaccio, C., and Comoglio, P. M. (2006). Invasive growth: a MET-driven genetic programme for can-

didates in cancer research. Front. Bioi. 16, 803–814.

Casanovas, O., Hicklin, D. J., Berg-
ers, G., and Hanahan, D. (2005). Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreate-
atic islet tumors. Cancer Cell 8, 299–309.

Chan, S. Y., and Locascio, J. (2010). MicroRNA-210: a unique and pleiotropic hypoxia
dehydoxylase pathway. Mol. Cell 30, 4604–4613.

Gatenby, R. A. (2008). A change of strat-

egy in the war on cancer. Nature 459, 508–509.

Gatenby, R. A., and Gillies, R. J. (2004). Why do cancers have high aero-
obiliary glycolysis? Nat. Rev. Cancer 4, 891–899.

Giannakakis, A., Sandalatzopoulos, R., Greshock, J., Liang, S., Huang, J., Hasegawa, K., Li, C., O’Brien Jenkins, A., Katsaros, D., and Weber, R. L. (2008). miR-210 links hypoxia with cell cycle regulation and is deleted in human epiblastal ova-
tian cancer. Cancer Biol. Ther. 7, 255–264.

Gupta, G. P., and Massagué, J. (2006). Cancer metastasis: building a frame-
work. Cell 127, 679–689.

Hanahan, D., and Folkman, J. (1996). Patterns and emerging mechanisms of the angio
genic switch during tumorigenesis. Cell 86, 353–364.

Jaakkola, P., Mole, D. R., Tian, Y. M., Wilson, M. L., Gielbert, J., Gaskell, S. J., Kriegsheim, A., Hebestreit, H. F., Mukherji, M., and Schofield, C. J. (2001). Targeting of HIF-1 to the von Hippel-Lindau ubiquityla-
tion complex by O2-regulated prolyl hydroxylase. Science 292, 468–472.

Kaelin, W. G., Jr., and Ratchfile, P. J. (2008). Oxygen sensing by met-
azoans: the central role of the HIF hydroxylase pathway. Mol. Cell 30, 393–402.

Kopitz, C., Gerg, M., Bandappalli, O. R., Ister, D., Pennington, C. J., Hauer, S., Flechsig, C., Krell, H. W., Antolovic, D., Brew, K., Nagase, H., Stangl, M., von Weyhern, C. W., Brücher, B. L., Brand, K., Coussens, L. M., Edwards, D. R., and Krüger, A. (2007). Tissue inhibitor of metalloproteinases-1 promotes liver metastasis by induc-
tion of hepatocyte growth factor sig-
nal. Cancer Res. 67, 8515–8623.

Krishnamachary, B., Berg-Dixon, S., Kelly, B., Agani, F., Feldser, D., Fer-
reira, G., Iyer, N., LaBusch, J., Pak, R., and Taghavi, P. (2003). Regulation of colon carcinoma cell invasion by hypoxia-inducible factor 1. Cancer Res. 63, 1138–1143.

Krüger, A. (2009). Functional genetic mouse models: promising tools for investigation of the protolytic inter-
net. Biol. Chem. 390, 91–97.

Krüger, A., Kates, R. E., and Edwards, D. R. (2010). Avoiding spam in the protolytic inter-
net. Cardiovasc. Dis. 1803, 95–102.
Le Floch, R., Chiche, J., Marchiq, I., Medina, P. P., and Slack, F. J. Mak, P., Leav, I., Pursell, B., Bae, D., Frontiers in Pharmacology Krüger, A., Soeltl, R., Sopov, I., Kopitz, Cui et al. Pro-metastatic co-operation of TIMP-1, Hif-1α, and growth of glycolytic tumors. Cancer Res. 66, 1272–1275. Kuhlshreshtha, R., Ferracin, M., Wojcik, S. E., Garzon, R., Alder, H., Agosto-Perez, F. J., Davuluri, R., Liu, C. G., Croce, C. M., and Negrini, M. (2007). A microRNA signature of hypoxia. Mol. Cell. Biol. 27, 1859–1867. Lande, D., Pret, D. J., Whelan, D. A., Gorman, J. I., and Whitelaw, M. L. (2002). Asparagine hydroxylation of the HIF transactivation domain: a hypoxic switch. Science 295, 858–861. Le Floch, R., Chiche, J., Marchiq, I., Naitken, T., Ilk, K., Murray, C. M., Critchlow, S. E., Roux, D., Simon, M. P., and Pouységur, J. (2011). CD147 subunit of lactate/H+ symporters MCT1 and hypoxia-inducible MCT4 is critical for energetics and growth of glycolytic tumors. Proc. Natl. Acad. Sci. U.S.A. 108, 16663–16668. Lu, X., and Kang, Y. (2010). Hypoxia and hypoxia-inducible factors: master regulators of metastasis. Clin. Cancer Res. 16, 5928–5935. Majmundar, A. J., Wong, W. J., and Simon, M. C. (2010). Hypoxia-inducible factors and the response to hypoxia stress. Mol. Cell 40, 294–309. Mak, P., Leav, I., Pursell, B., Bae, D., Yang, X., Taglanti, C. A., Gouvin, L. M., Sharma, V. M., and Mercurio, A. M. (2010). ERβ impedes prostate cancer EMT by destabilizing HIF-1α and inhibiting VEGF-mediated snail nuclear localization: implications for Gleason grading. Cancer Cell 17, 319–332. Medina, P. P., and Slack, F. J. (2009). Inhibiting microRNA function in vivo. Nat. Methods 6, 37–38. Michiels, P. (2009). Hypoxia, angiogenesis and cancer therapy: to breathe or not to breathe? Cell Cycle 8, 3291–3296. Mottet, D., Dumont, V., Deccache, Y., Demazy, C., Ninane, N., Raes, M., and Michiels, C. (2003). Regulation of hypoxia-inducible factor-1α protein level during hypoxic conditions by the phosphatidylinositol 3-kinase/Akt/glycogen synthase kinase 3β pathway in HepG2 cells. J. Biol. Chem. 278, 31277–31285. Ortholan, C., Puiseugé, M. P., Ilie, M., Barby, P., Mari, B., and Hofman, P. (2009). MicroRNAs and lung cancer: new oncogenes and tumor suppressors, new prognostic factors and potential therapeutic targets. Curr. Med. Chem. 16, 1047–1061. Overall, C. M., and López-Otín, C. (2002). Strategies for MMP inhibition in cancer: innovations for the post-therapy era. Nat. Rev. Cancer 2, 657–672. Páez-Ribes, M., Allen, E., Hudock, J., Takeda, T., Okuyama, H., Viñals, F., Inoue, M., Bergers, G., Hanahan, D., and Canavosas, O. (2009). Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 15, 220–231. Pennacchietti, S., Michieli, P., Galvez, M., Mazzone, M., Giordano, S., and Comoglio, P. M. (2003). Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. Cancer Cell 3, 347–361. Puiseugé, M. P., Masure, N. M., Bertero, T., Pradelli, L., Grosso, S., Robbe-Sermesant, K., Maurin, T., Pradelli, L., Grosso, S., Robbe-Sermesant, K., Maurin, T., Lebriguet, C., Ninane, N., Raes, M., and Michiels, C. (2003). Regulation of hypoxia-inducible factor-1α protein level during hypoxic conditions by the phosphatidylinositol 3-kinase/Akt/glycogen synthase kinase 3β pathway in HepG2 cells. J. Biol. Chem. 278, 26182–26189. Schelker, F., Grandl, M., Seubert, B., Schaten, S., Hauser, S., Gerg, M., Boccaccio, C., Comoglio, P., and Krüger, A. (2011a). Tumor cell-derived Timp-1 is necessary for maintaining metastasis-promoting Met-signaling via inhibition of Adam-10. Clin. Exp. Metastasis 28, 793–802. Schelker, F., Halfweg, B., Baumler, P., Neu, C., Gorlach, A., Schrödlmair, F., and Krüger, A. (2011b). Tissue inhibitor of matrix metalloproteinases-1-induced scattered liver metastasis is mediated by hypoxia-inducible factor-1α. Clin. Exp. Metastasis 28, 91–99. Selak, M. A., Armour, S. M., Mackenzie, E. D., Boulahbel, H., Watson, D. G., Mansfield, K. D., Pan, Y., Simon, M. C., Thompson, C. B., and Gottlieb, E. (2005). Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α/β prolyl hydroxylase. Cancer Cell 7, 77–85. Sela-Passwell, N., Trahtenharts, A., Krueger, A., and Sagi, I. (2011). New opportunities in drug design of metalloproteinase inhibitors: combination between structure-function experimental approaches and systems biology. Expert Opin. Drug Discov. 6, 527–542. Semenza, G. L. (2001). Targeting HIF-1 for cancer therapy. Nat. Rev. Cancer 1, 721–732. Sonveaux, P., Végran, F., Schroeder, T., Wiertz, M. C., Verras, J., Rabiani, Z. N., De Saedeleer, C. J., Kennedy, K. M., Diepart, C., Jordan, B. F., Kelley, M. J., Gallez, B., Wahl, M. L., Feron, O., and Dewhirst, M. W. (2008). Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J. Clin. Invest. 118, 3930–3942. Sporn, M. B. (1996). The war on cancer. Lancet 347, 1377–1381. Wenger, R. H., Stiehl, D. P., and Camensch, G. (2003). Integration of oxygen signaling at the consensus HRE. Scien. STKE 2005, re12. Wilczynski, I., Duechler, M., and Czyz, M. (2011). Targeting NF-κB and HIF-1α pathways for the treatment of cancer: part II. Arch. Immunol. Ther. Exp. (Warsz.) 2011, 301–307. Yamaguchi, R., and Perkins, G. (2012). Finding a panacea among combination cancer therapies. Cancer Res. 72, 18–23. Yang, M. H., Wu, M. Z., Chiu, S. H., Chen, P. M., Chang, S. Y., Liu, C. I., Teng, S. C., and Wu, K. J. (2008). Direct regulation of TWIST by HIF-1α promotes metastasis. Nat. Cell Biol. 10, 295–305. Ying, Q., Liang, L., Guo, W., Zha, R., Tian, Q., Huang, S., Yao, J., Ding, J., Bao, M., and Ge, C. (2011). Hypoxia-inducible miR-210 augments the metastatic potential of tumor cells by targeting VMP1 in hepatocellular carcinoma. Hepatol. Res. 45, 2064–2075. Zuckler, S., Cao, J., and Chen, W. T. (2000). Critical appraisal of the use of matrix metalloproteinase inhibitors in cancer treatment. Oncogene 19, 6642–6650. Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Received: 24 April 2012; accepted: 24 June 2012; published online: 12 July 2012. Citation: Cui H, Grosso S, Schelker F, Mari B and Krüger A (2012) On the pro-metastatic stress response to cancer therapies: evidence for a positive cooperation between TIMP-1, HIF-1α, and miR-210. Front. Pharmacol. 3:134. doi: 10.3389/fphar.2012.00134 This article was submitted to Frontiers in Pharmacology of Anti-Cancer Drugs, a specialty of Frontiers in Pharmacology. 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