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Abstract

Redox reactions pervade all biology. The control of cellular redox state is essential for bioenergetics and for the proper functioning of many biological functions. This review traces a timeline of findings regarding the connections between redox and cancer. There is ample evidence of the involvement of cellular redox state on the different hallmarks of cancer. Evidence of the control of tumor angiogenesis and metastasis through modulation of cell redox state is reviewed and highlighted.

Keywords	Metastasis; redox metabolism; redox signaling; tumor angiogenesis
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Control of tumor angiogenesis and metastasis through modulation of cell redox state

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Abstract

Redox reactions pervade all biology. The control of cellular redox state is essential for bioenergetics and for the proper functioning of many biological functions. This review traces a timeline of findings regarding the connections between redox and cancer. There is ample evidence of the involvement of cellular redox state on the different hallmarks of cancer. Evidence of the control of tumor angiogenesis and metastasis through modulation of cell redox state is reviewed and highlighted.

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1. Redox and cancer: a historic background

Oxidoreduction reactions and processes pervade the biochemical foundations of biology at several levels: 1) There are many biochemical reactions catalyzed by oxidoreductases, the first group in the IUPAC Enzyme Classification. 2) Essential bioenergetics processes are based on electron transfer reactions, as illustrated by the chemiosmotic coupling of electron transport chain complexes and oxidative phosphorylation and photophosphorylation. 3) Cells use metabolic fuels to obtain the chemical energy required for maintaining them alive by oxidizing them under strict biological control. 4) Cells make use of $NAD(P)^+$/NAD(P)H ratios as sensors of their metabolic status and to switch on/off key enzyme activities leading to an integrated metabolic control. 5) Cells have developed a triple line of defense against oxidative stress with small antioxidant metabolites, antioxidant enzymes and damage repair enzymes. Taking all this into account, it is not surprising that there is a strict control of redox cellular status and cell redox imbalance is associated to many pathological conditions [1-5]. This is also the case of redox and cancer. From here on, in the present section we will summarize the timeline of discoveries concerning redox and cancer, thus providing a historic background for the topic before focusing our attention on what is currently known on the control of tumor angiogenesis and metastasis through modulation of cell redox balance (see also Figure 1).

In the middle of the last century it was proposed for the first time the possibility that the accumulation of free radicals, generated as a result of our oxidative metabolism, could be the main cause of the aging process, as well as the appearance of diseases such as cancer [6]. Initially, mitochondria were pointed out as the main source of free radical production and as a key factor in regulating the maximum life expectancy of organisms [7]. Soon, reference was made for the first time to the possibility of an evolutionary process taking place in the tumor mass, specific to each tumor, the consequences of which were processes of selection of the most aggressive clones, pointing to the need of specific therapies for each patient [8]. At the end of the seventies, the association between decreased superoxide dismutase (SOD) activity, increased levels of free radicals and the appearance of cancer was the first relationship between redox systems and tumor formation to be described [9]. This seminal observation produced an increase in the number of publications that related metabolic changes associated with redox processes to specific tumors, or that suggested the use of endogenous molecules with antioxidant capacity as possible anti-tumor therapies [10,11]. Some authors specifically

mentioned an "abnormal" oxidative metabolism in certain types of cancer [12]. The accumulation of evidence led to the proposal of the term "oxidative stress" and the opening of a new field of research [13,14]. A decade later, the number of publications specifically mentioning the redox state and its involvement with tumor processes had increased markedly (from 80 articles in 1984 to almost 300 in 1994, according to Pubmed database). In the nineties, the importance of redox factors in the response to hypoxia of tumor lines and the presence of alterations in the enzymatic activities of the redox system in some tumor types were observed [15,16]. Shortly after, the first publications appeared relating changes in gene expression with the homeostasis of the redox system, through the modulation of the activity of transcription factors by means of biochemical alterations of the redox balance [17,18], followed by investigations involving the production of ROS by mitochondria and the redox balance in tumor alteration [19], as well as publications on the role of the redox state in the control of cell proliferation [20], an altered trait in tumor cells [21]. By the end of the 20th century, several reviews were published on the importance of membrane redox systems in the tumor transformation process [22,23].

In the following decade, works were published that related changes in the redox state in tumor cells with the modification of the function and structure of proteins relevant to the carcinogenic process, either directly, as in the case of p53, or indirectly, with the alteration of the phosphorylation patterns of the Rb protein, essential in the transition from phase G1 to S in the cell cycle [24,25]. The accumulation of evidence linking an altered redox state with features such as the avoidance of apoptosis or the breakage of DNA chains, led researchers to think of the existence of a series of redox features, such as an intracellular pro-oxidant medium or relatively low levels of antioxidants in tumor cells, which could aid in the transformation and progression of cancer, as well as contribute to resistance against anti-cancer treatments [26]. Parallel advances in the understanding of the mechanisms of tumor progression made it possible to suggest new therapy strategies, combining, for example, the high density and irregular vascular permeability of tumors with the disruption of antioxidant defense in order to modify their oxidation state [27]. Some studies proposed redox enzymatic activities as possible therapeutic targets to stop tumor growth and metastasis [28]. It was shown that redox enzyme systems are not only regulated by master genes or tumor suppressors such as p53 or BRCA1 [29], but can also regulate the activity of those genes themselves, as has been observed in the case of PTEN and Grx5 [30].

The use of new technologies, such as ultrasequencing, proteomics, metabolomics and gene editing, is currently contributing to a better understanding of some of the mechanisms involved in the maintenance of the cell redox state and its relationship with cellular processes in transformed cells. These new data will be key in the future to raise new hypotheses of relationship between the importance of redox state and cancer.

2. All for one: redox state, the hallmark of hallmarks, and its role in cancer vascularization

The key role of the redox state in the regulation of most cell signaling pathways, through changes in the oxidation status of key cysteine residues [31], or through post-translational modifications such as glutathionylation [32], or nitrosylation [33], which in turn condition other subsequent post-translational modifications, offers a range of phenotypic possibilities for tumor cells that could allow the appearance of different cancer traits and their adaptation to variable conditions in the tumor ecosystem. This adaptability makes cancer a versatile and dynamically robust set of diseases in adaptive terms that co-evolve with their microenvironment [34,35]. Unfortunately, the role of the redox state in this complexity and in the appearance of the emerging properties of the tumor is still poorly understood. This is why it is convenient to contextualize the influence that the redox state and its components have on the variability of cancer traits. The biological redox state presents tissue and cellular specificity [36]. Some authors have proposed to use the determination of redox activity of tissues, and their specific alteration, as a marker of tumor progression status, highlighting the role of redox balance as a key feature of the carcinogenesis process, both at the beginning and at the end of the process [37]. Some studies suggest that a deregulation of redox homeostasis could be identified as a hallmark of tumor cells associated with progression and resistance to treatment [38], while in other cases it is not attributed as a trait per se, but as a factor underlying the alteration of the signaling networks of cancer hallmarks [39]. The excessive proliferation of the cells within the tumor causes them to end up exceeding the vascular limit that provides them with the oxygen and nutrients necessary to maintain this growth rate, so the strategy resulting from this stress situation is to promote the formation of new blood vessels from a pre-existing vascular bed, the process of angiogenesis, a target for therapy [40]. In fact, angiogenesis has been identified as one of the hallmarks of cancer [21,41]. It seems that cellular redox systems play an important role in the maintenance or modification of the cellular functions

associated with the endothelium [42], either by controlling the cellular destiny under physiological or pathological conditions of the cells that compose it or through signaling processes mediated by modifications of the cellular redox state [43-45]. However, it should be taken into account that it has recognized that tumor growth does not necessarily depends on to angiogenesis [46,47]. On the ground of the available data, it is likely that the metabolic status, and therefore the redox status of the cells, might have a role in determining whether the cell will behave in an angiogenic or non-angiogenic fashion.

3. Bioactive gases and the redox control of tumor angiogenesis

Some of the most important redox elements in these mechanisms are the endogenously produced bioactive gases NO, CO and H_2S. For a specific review on this topic, see [48].

3.1. Key roles of NO in the control of cancer progression and angiogenesis

The most studied of these three bioactive gases in relation to vascular function and the role in the angiogenic process is NO. In the context of tumor biology, NO exhibits a dual behavior, acting either as a protumor or an antitumor compound depending on its concentration (controlled by the expression and activity of NOS enzymes), the time frame in which it occurs and its interaction with other ROS produced in other cellular processes [49], affecting the phenotype of tumor cells. This becomes a serious problem when studying its importance as a possible therapeutic target [50]. NO is known for its direct relationship with diseases such as or its regulation of the cardiovascular system, acting mainly as a protective agent [51]. In contrast, the relationship of NO and its soluble receptor, guanylate cyclase (which generates the second messenger cGMP), with cellular processes such as differentiation and proliferation is still poorly understood, although it seems to be of great importance in carcinogenesis [52].

In melanoma cells, it has been observed that the post-translational modification by nitrosylation of the TSC2 component of the mTOR route activates proliferation [53]. This is important for the fate of endothelial cells during the angiogenic process, since it has been shown that the suppression of eNOS expression in these cells, through an intronic microRNA, inhibits their proliferation [54]. It has also been observed that vitamin D stimulates the production of NO, which, in turn, stimulates endothelial proliferation [55].

The relationship of nitric oxide with tumor progression and angiogenesis has long been known in different types of cancer, such as colorectal, gastric and prostate cancer, among others [56-58]. Within the tumor ecosystem, it is necessary that not only the tumor clones proliferate, but that the other cells that form it (such as endothelial cells) also do so in line with the rates of the transformed cells. To this end, a niche engineering strategy by tumor cells, modifying the phenotype of endothelial cells, is a good way to sustain the evolution of the tumor ecosystem. This appears to be a biunivocal relationship, with an increase in the expression of eNOS in tumor samples obtained in the context of stress situations in C57BL/6 mice inoculated with B16F10 melanoma cells [59]. Immune cells found in the tumor ecosystem may also contribute to the formation of new blood vessels under inflammatory conditions, mainly TAMs and a specific type of Tie-2 expressing monocytes (TEMs), through the release of pro-angiogenic factors [60].

NO regulates steps of the angiogenic process, such as the activation of matrix-9 metalloprotease (MMP-9) that can take place, either by attacking the Zn thiolate of the latent protein, or by preventing the binding to MMP-9 of its inhibitor, TIMP-1 [61]. However, its role in other aspects of angiogenesis is not so clear. In the process of tip cell sprouting, it has been discovered that signaling by NO derived from eNOS is key for cell migration [62]. It is known that NO is a mediator of permeability and vascular tone, as well as of blood flow in the vasculature associated with the tumor and that it regulates cell-cell interactions in the vasculature, as in the case of leukocytes, whose interaction with endothelial cells decreases when the concentration of NO increases, which could limit and reduce the effectiveness of immune therapy in tumors [63]. Very little is yet known about how the flows of this active redox element regulate the dynamics of the tumor ecosystem and its progression, but several studies indicate that NO-mediated signaling not only mediates the ability of leukocytes to interact with endothelial cells, but also participates in a reciprocal regulation between endothelial-tumor and perivascular cells (pericytes and vascular smooth muscle cells), affecting the dynamics of vascular smooth muscle cells, inhibiting their proliferative activity [64], or modulating its contractile apparatus, promoting the dephosphorylation of the light chain of myosin 2 (MLC2) and interrupting the actin-myosin cycle, which relaxes the vascular smooth muscle cells and allows the dilation of the vessels, increasing blood flow [65]. However, in the presence of thrombospondine-1 (TSP-1), an endogenously produced negative regulator of angiogenesis, NO-mediated relaxation is blocked [66]. TSP-1 is

elevated in the circulation of cancer patients, and its inhibitory action on NO could promote constriction of vascular beds external to the tumor and increase blood flow to the tumor, as opposed to the effect of NO, which acts by reducing blood flow to the tumor through vasodilation of peripheral tissues [65]. However, despite the latter, NOS expression in some tumor types is important, as there is correlation with the expression of genes important for tumor progression. In the case of breast cancer, it has been seen that a high expression of iNOS leads to an increase in the expression of the CD44 gene, which can form a complex with MMP-9 and increase the local concentration of this metalloprotease on the front of the tumor cell progression, as well as boosting the vascularization of the tumor [61].

One of the problems faced by anti-angiogenic therapies is the mimetic vasculogenesis process, whereby some of the cells that form part of the tumor ecosystem would have the capacity to acquire phenotypic characteristics of endothelial cells to end up forming structures similar to a vascular bed [67]. This type of mimicry has been observed in both tumor cells of different types of cancer that are capable of forming tube-like structures [68], or that have the potential to transdifferentiate into "pseudoendothelial" cells, as observed in glioblastoma tumor stem cells [69]. Tumor stromal cells, such as TAMs, can mimic vasculogenesis -also in glioblastoma- in those areas of the tumor where tumor cells present a high expression of cyclooxygenase-2 [70], and through the secretion of IL-6 [71]. It has been observed that CD44 and TSP-1 are overexpressed in tumors presenting mimetic vasculogenesis and bad prognosis [72]. This observation raises the possibility of a phenotypic transition mechanism orchestrated by NO produced through iNOS, overexpressed in the tumor, thus promoting an increase in the expression of mimetic vasculogenesis markers, such as CD44, which is fundamental for the formation of vascular structures, contributing to their permeability [73], and favoring the diversity of cell types that can contribute to the maturation of new structures [74]. In situations where NO production in the tumor is inhibited, perivascular NO gradients are established that normalize the tumor vasculature, allowing better oxygenation of the tumor, but also a possible way to improve the efficacy of treatments [75]. On the other hand, NO produced by endothelial cells can trigger changes in the polarization of TAMs between M1 and M2 phenotypes, also regulating the inflammatory process associated with the tumor [76]. More research is needed on how NO affects angiogenesis and mimetic vasculogenesis, also taking into

account the relationships that exist between the different cell types in the tumor microenvironment.

3.2. CO in the control of tumor angiogenesis

In addition to NO, CO produced in the HO-1 reaction also regulates the angiogenic process during tumor progression [48]. It appears that the activity of HO-1 has a dual effect (as with NO) on the tumor angiogenesis process, depending on the context or stage of disease [77]. TAMs, VSMCs, endothelial cells and tumor cells can generate CO, which contributes to increased VEGF concentration and stimulation of angiogenesis [65]. Part of this proangiogenic activity is mediated by the activation of the enzyme thymidine phosphorylase (TP), which in turn promotes the activity of cytokines IL-1ß, IL-6 and IL-8 [78]. However, CO derived from the action of HO-1 can also regulate the processing of pro and antiangiogenic miRNAs, with a fall in the activity of miRNAs that boost angiogenesis as opposed to those that have antiangiogenic activity, and a greater specific weight of this activity as opposed to that of PT [60]. Although the actual targets of CO are still not well known, CO is known to act as a regulator of NO signaling and a controller of H_2O_2 production by membrane NADPH oxidases [65].

3.3. H_2S and tumor angiogenesis

The last of the biogases with importance in the angiogenesis process is H_2S. Once again, it is a biogas with pro and antitumor characteristics, which promotes some hallmarks and limits others depending on their concentration [48,79]. Since H_2S potentiates angiogenesis in colon and ovarian cancer, cystathionine-beta-synthase (CBS, the main enzyme producing H_2S) could be a potential antiangiogenic target [80]. In colon cancer, the inhibition of H_2S production by CBS produce a decrease in the migratory capacity of endothelial cells in coculture and a lower formation of new vessels, as well as a lower blood flow within the tumor, in mouse xenografts [81]. Being the most recent addition to this triad of bioactive gases involved in the regulation of angiogenesis and tumor progression, little is known about the true function of H_2S, but its role in processes related to angiogenesis is already beginning to be uncovered. This is the case of a study on the effects of H_2S treatment after an episode of cerebral ischemia [82], and studies on the role of H_2S in relation to metabolic diseases that produce cardiovascular damage, such as hyperhomocysteinemia [65]. However, much

more experimental effort is required, not only to understand how H_2S regulates angiogenesis, but also to know how the signaling routes mediated by the three gases with biological activity are interrelated and regulated in a reciprocal way, trying to establish a possible signaling hierarchy. In this regard, there are some studies that already point to the importance of H_2S in the control of eNOS activity and in the production of NO [83]. It is also necessary to understand how the communication between these pathways is conditioned or not by the presence of certain cell types within a cell ecosystem, as it can happen in the case of a tumor. For instance, it has already been shown that H_2S can inhibit the proliferation of MSCVs and platelet aggregation within the angiogenic microenvironment [84], which could be of great importance for other hallmarks of cancer, such as metastasis. It would also be necessary to explore how the chemical derivatives of the interaction of these three bioactive gases affect angiogenesis, such as the HNO formed in the NOS reaction, which could have effects opposite to those of NO [85].

Figure 2 summarizes the mentioned connections of these three bioactive gases with angiogenesis and metastasis.

4. Other small molecules and enzymes playing a role in the redox control of tumor angiogenesis

4.1. Other small molecules

In addition to bioactive gases, other small molecules with redox activity are involved in the process of tumor angiogenesis. It has been previously observed how the balance of the nuclear NAD^+/NADH ratio in endothelial cells is correlated with the variation in GSH levels and the importance of pyridine nucleotides in the function of DNA repair enzymes [86]. Interestingly, not in the angiogenic process, but in the mimetic vasculogenesis process discussed above, it has been shown that nicotinamide, an essential component of NAD and NADP, inhibits the formation of these vascular-like structures in melanoma cells, which could be related to changes in gene expression motivated by the inhibition of enzymes such as histones deacetylases, or by failures in the function of enzymes that are key for damage repair [87].

Regarding GSH itself, it was shown that knocked out mice for intracellular adhesion molecule 1 (ICAM-1) have increased intracellular GSH levels in their aortic endothelial cells as compared to wild type mice and that this leads to VEGF-A-dependent

chemotaxis and NO production impairment, resulting in deficient angiogenic responses [88]. A more recent study with a ligustrazine-betulinic acid derivative of traditional Chinese medicine shows that the activation of GSH metabolism leads to angiogenesis inhibition [89]. Very recently, it has been shown that cysteine glutathionylation functions as a redox switch involved in the control of endothelial cell angiogenesis [90]. The central role of amino acids in the maintenance of cancer redox homeostasis has been recently reviewed, focusing on the contribution of amino acid skeletons to GSN and NAD(P) biosynthesis [91].

Melatonin is capable of restoring the redox balance through the regulation of the state of lipid peroxidation and the expression of the redox enzyme equipment, which decreases oxidative stress in different physiological and pathological contexts [92].

4.2. Superoxide dismutases, catalase and peroxidases

The roles of the different superoxide dismutases (SOD) in the regulation of VEGF production, in the response to antiangiogenic drugs or as mediators of the response to hypoxia have been previously studied [93-96]. In a blind in silico prediction program, our group identified SOD-3 as a target for antiangiogenic treatment and confirmed this prediction showing that an antibody blocking SOD-3 produced angiogenesis inhibition in vitro and in vivo [97].

Catalase overexpression reduces the angiogenic capacity and recruitment of new blood vessels to the tumor, by interfering with H_2O_2-mediated signaling [98], and promoting the emergence of a less aggressive and better-responsive phenotype to chemotherapeutics in the MCF-7 breast cancer cell line [99].

Glutathione peroxidases (Gpx) are important in different stages of carcinogenesis [100]. Gpx1 enzyme deficiency in mice promotes a decrease in the viability and number of endothelial cell progenitors, which also become more sensitive to oxidative stress, preventing angiogenesis in situations such as ischemia damage [101]. Gpx4 seems to play a key role through the regulation of the activity of some specific isoforms of lipooxygenases. The mutant heterozygous for Gpx4 has a vascular phenotype with higher density of microvessels and these are smaller in diameter as compared with wild type vessels. These effects can be reversed with inhibitors of 12/15-lipooxygenases [102].

4.3. The thioredoxin system

The importance of the thioredoxin (Trx) system as a possible tumor target has been underscored [103]. It also seems to be an important regulator of angiogenesis, through the control of endothelial cell functions by modulating the cell redox state [104]. Trx interaction protein (TXNIP), which inhibits Trx action, appears essential in the response of VEGFR2 to VEGF, as TXNIP regulates VEGFR2 phosphorylation by stimulating VEGF-promoted S-glutat.ionylation of key phosphatase in this process in endothelial cells, which also appears to be related to the regulation of endothelial cell migration [105,106]. Furthermore, TXNIP has recently been characterized as a tumor suppressor in the case of thyroid cancer [107].

The enzyme thioredoxin reductase (TrxR) also appears to be important in the angiogenesis process. It has been observed that selenium deficiency, important for the formation of selenoproteins such as TrxR, causes an inhibition in the TrxR activity of the endothelial cells in the tumor microenvironment, which correlates with a drop in VEGF levels [108]. In mouse lung cancer cells, KO in mitochondrial TrxR alters cell redox status, stabilizes prolyl hydroxylases, and inhibits HIF-1 cascade, suppressing tumor angiogenesis [109]. In the case of humans, in glioblastomas with intratumoral hemorrhage there is an increase in the expression of VEGF and TrxR1, which can be related to an increase in tumor angiogenesis [110].

Trx2 is a mitochondrial redox protein with a key role in promoting angiogenesis in cross-talk with NADPH oxidase (NOX) 4 [111].

Several compounds targeting the Trx system have been evaluated. Lamorustine, a member of the family of methyl isocyanates, interferes with tumor angiogenesis by targeting ASK-1, which forms a complex with reduced Trx in resting endothelial cells [112]. On the other hand, sulforaphane promotes an increased TrxR1 activity in endothelial cells and modifies communication with pericytes [113]. Our group has recently shown through a proteomics analysis that the treatment of endothelial cells with the anti-angiogenic compound (+)-aeroplysinin-1 affects the expression levels of redox proteins, including a marked reduction in the levels of the cytosolic TrxR1 [114].

4.4. Glutaredoxin and peroxyredoxin

It has been shown that the S-glutathionylation-dependent regulation of sirtuin 1 by glutaredoxin (Grx) is essential for the vascular development of zebrafish [115], although its role in tumor angiogenesis remains unknown.

Peroxyredoxin 2 (Prdx2) helps in the formation of vascular patterns in colon cancer cells HCT116 by vascular mimicry through the activation of VEGFR2, which is suppressed when siPrdx2 is used [116]. On the other hand, endothelial cells treated with the anti-angiogenic compound (+)-aeroplysinin-1 have increased protein levels of Prdx4 [114].

4.5. NAD(P)H oxidases

The important role of membrane NADPH oxidases (Nox) in the regulation of the angiogenesis process should be noted [117]. Being one of the main sources of ROS, and their location in plasma membranes, makes them suitable candidates for orchestrating signaling processes that modify the tumor ecosystem and condition the angiogenic microenvironment, favoring the interrelation between immune system cells, tumor cells and endothelial cells to trigger the whole process of tumor angiogenesis [118]. Interestingly, the phorbol ester-induced angiogenesis of endothelial progenitor cells seems to be controled by Nox-mediated gelatinase pathways [119].

Among the different types of NADPH oxidases, some seem to have a greater relevance for the angiogenic process. Mice deficient for Nox1, but not for Nox2 and Nox4, presented an inhibition of angiogenesis that was phenocopied using specific inhibitors of Nox1 and silencing the gene, through a mechanism that implied the inhibition of PPARα [120]. In CaCO-2 colon cancer cells, the phosphorylation of the transcription factor Sp1, which promotes its binding to the VEGF promoter and increases its production, requires the induction of the Ras signaling pathway by Nox1 [121]. In HT-29, another colon cancer line, the expression of key regulators of angiogenesis, such as VEGF or HIF-1α, as well as the density of blood vessels, were decreased when Nox1 was permanently silenced by shRNA [122]. The Nox1 subunit involved in regulating the angiogenesis process in prostate cancer appears to be p22(phox), whose knockdown decreases ROS production and inhibits tumor angiogenesis [123].

It has been shown that the proangiogenic factor deoxyribose-1-phosphate (dRP) acts intracellularly activating the Nox2 complex (but not Nox4) in endothelial cells, favoring the activation of NF-kB and increasing the expression of VEGFR2, which stimulates angiogenesis [124].

Much more information is available on the connections of Nox4 with angiogenesis. As mentioned above, the redox cross-talk of Nox4 and Trx2 in angiogenesis has been previously reviewed [111]. Nox4 isoform has been linked to the modulation of

proliferation, migration and adhesion in endothelial cells through the production of ROS and the promotion of VEGFR2 phosphorylation [125]. Studies in fibrosarcoma have shown that Nox4 KO produces a reduction in tumor vascularization, while the mutant KO for Nox1 produces the opposite effect and the mutant Nox2 has no effect on vascular density [126]. In renal carcinoma cells, Nox4 has been shown to promote angiogenesis through the accumulation of HIF-2α, so that silencing Nox4 blocks the accumulation of HIF-2α in the nucleus and, therefore, the angiogenic process [127]. As with other Nox variants, Nox4 also has p22(phox) as a regulatory element. However, it has been observed that, while the mutation of specific residues of p22(phox) inhibits the function of Nox1, Nox2 and Nox3, both the formation of the complex and the function of Nox4 remains intact when the mutated p22(phox) is expressed in lung cancer cells [128]. In glioblastoma cell lines, it has been observed that inhibition of Nox4 expression with a shRNA causes a decrease in the production of ROS and a decrease in the angiogenic capacity of tumor cells, as well as an increase in radiotherapy damage [129]. According to another recent study, Nox4 and Nox2 are essential to induce VEGFR2 phosphorylation in endothelial cells through increased production of ROS [130].
Nox are well characterized components of the not so well characterized plasma membrane electron transport system (PMETS). Our group has contributed to the study of the roles of PMETS in cancer, including tumor angiogenesis [22,131-134].

5. Nrf2 and NF-κB, two transcription factors with roles in the redox control of angiogenesis

The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of the expression of antioxidant proteins. Therefore, it should not be surprising that Nrf2 has been found to be involved in the redox control of angiogenesis. In general, Nrf2 acts as a double-edged sword in cancer [135], since its controlled, oscillating activation in normal cells via the canonical mechanism acts as a preventive action against cancer initiation, while its uncontrolled, constitutive activation participates in cancer promotion, progression and metastasis [136-138], as summarized in Figure 3. The term "Nrf2-addicted" has been coined to mention those cancer cells in which Nrf2 is aberrantly activated and for which Nrf2 inhibitors could be promising therapeutic agents [139-141].
Nrf2 seems to control different biological responses related to all the described hallmarks of cancer [137]. In particular, Nrf2 affects tumor metabolic reprograming

angiogenesis [137, 142]. It has been shown that Nrf2 knockdown reduces HIF-1a protein levels, thus decreasing the expression of VEGF, PDGR, angiopoietin and angiogenin and reducing blood vessel formation, most probably due to an indirect regulation of prolyl hydroxylase domain-containing proteins [143-145]. This agrees with the antitumor effects shown by different treatments inhibiting Nrf2 [146-148]. However, the double-sword behavior of Nrf2 should not be undervalued. In fact, Nrf2 inactivation has been shown to enhanced placental angiogenesis in a preeclampsia mouse model [149]. Furthermore, Nrf2 activation has been suggested as a therapeutic approach for angiogenesis-dependent diseases, including ocular, rheumatic and neurodegenerative diseases and cancer [136,150-154]. We showed that dimethyl fumarate, an activator of Nrf2, is a potent anti-angiogenic agent responsible for the described anti-psoriatic effect of the commercially available formulation Fumaderm [155].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is another transcription factor is another master regulator involved in the control of cellular responses to different damaging stresses, including oxidative stress. Therefore, it could be expected to be also involved in angiogenesis regulation. Surprisingly, there is still scarce information on this issue, which should be further investigated in the next future [156,157].

6. Metastasis: following the paved road of redox systems

The process of metastasis, the primary cause of cancer morbidity and mortality, is considered since a long time the last stage of the carcinogenic stage, as well as the most dangerous characteristic of any tumor cell and a fundamental factor in establishing the patient's prognosis [158]. The process of metastasis has long been thought to be the result of interactions between tumor cells and host cells [159], which are also part of the tumor ecosystem. Taken together, metastasis involves a series of phenotypic changes that begin in the primary tumor and continue along the path of the cells to the site of metastasis, as well as in the new niche, modifying the conditions of the niche, preparing it for the arrival of new metastatic cells from the primary tumor, in a kind of niche engineering, probably through collaboration between tumor clones [160-163].

The redox cell state also seems to have an important weight during metastasis, being those cell clones that present a greater increase in the levels of ROS those of greater metastatic potential [164]. Some authors propose that metastasis could be a tumor

strategy to avoid the excess oxidative damage that is generated in the primary tumor, with an important role for ROS in modifying the cytoskeleton that allows cells to acquire the invasive phenotype [165], helping in the acquisition of an "atavistic depressor" program that promotes unicellular survival [166]. The modulation of cell adhesion through the activation of cell surface integrins is another important step in the metastatic process that also appears to be regulated by redox elements. This integrin activation triggers a slight increase in oxidative stress with the consequent increase in ROS levels, and factors such as TGF-β, which reduces the expression and activity of Grx1 and favors EMT [167]. In MDA-MB231 cells it has been observed that the control of the cell redox state by the copper-dependent redox protein Memo promotes the migration and metastasis of these cells by increasing the levels of ROS in membrane protrusions and modifying the activity of key proteins in this process, such as Rac1 or RhoA [168]. In UM-UC-6 bladder cancer and HT-1080 fibrosarcoma cell lines, it has been shown that modulating the expression levels of SOD2 and catalase redox enzymes alters the levels of H_2O_2 in stationary state, modifying the phosphorylation patterns and the recruitment towards the membrane of p130cas, an essential protein for the reorganization of the cytoskeleton for the formation of focal adhesions during the migration process [169]. Recently it has been established that the AIF protein, involved in the regulation of cell survival or death, also possesses redox activity and influences the inactivation by oxidation of PTEN phosphatase, so that inhibition of the function of AIF prevents, in turn, is inhibition and activates the signaling by β-catenin, which promotes EMT and favors metastasis [170]. Interestingly, the oxidation of PTEN also conditions its cellular localization, in addition to its activity, dissociating it from the membrane [169].

The relationships between the cells that form the tumor, as mentioned above, also condition the process of metastasis, and the redox state that underlies these relationships seems to be of vital importance to condition the progress of migration and invasion associated with it. Recently it has been discovered that senescent fibroblasts secrete a Wnt antagonist, sFRP2, which influences the metastatic capacity of melanoma cells [171]. In this case the metastasis process (and also angiogenesis) is favored by a decrease in the expression of β-catenin which in turn decreases the expression of the MITF factor and APE1, which modulate a redox route involved in the detoxification of ROS. The state of oxidative stress that is generated promotes a phenotypic change that is associated with metastasis and resistance to chemotherapy, and that varies between

genetically identical clones depending on the age of the cells that accompany the tumor [171].

In addition, the metabolic changes noted above will also influence metastasis and, again, the maintenance of redox homeostasis linked to metabolism exerts a control over this process [172]. Specifically, the metabolic processes taking place in the mitochondria appear to be fundamental in the appearance of the metastatic phenotype. For instance, defects associated with complex I of the electron transport chain are correlated with an increase in metastasis, while a recovery of activity stops tumor growth and metastasis [173]. The generation of ROS appears to be attenuated as a consequence of the Warburg effect, thanks to a decrease in the flow of pyruvate to mitochondrial oxidative metabolism. This seems essential to increase resistance to death by anoikis, a cell death caused by the loss of anchors from the cell to the substrate, and which is a barrier against metastasis. In such a way, the Warburg effect would help enable the survival of metastatic cells during their "journey" to the site of metastasis [174]. It appears that when cells are detached from the matrix, a metabolic reprogramming process occurs that activates pyruvate dehydrogenase kinase 4 (PDK4), which in turn inhibits PDH and limits carbon flow in mitochondrial metabolism, so strategies that inhibit PDK4 may increase the susceptibility of metastatic cells to anoikis, thanks to increased oxidative stress [175]. However, in ovarian cancer cells with high invasive capacity it is observed an increase in pyruvate uptake and an increase in ATP generation with respect to less invasive cells, so that in this case a greater mitochondrial activity generates a greater metastatic capacity [176]. In another study, it has been observed that the levels of the enzyme phosphoglycerate dehydrogenase (PHGDH) are important for the establishment of metastasis in breast cancer cells, observing that tumors with inhibited PHGDH, whose levels of NADPH and GSH were ostensibly reduced, did not produce lung metastases and experienced an increase in the concentration of mitochondrial ROS [177].

Along with the avoidance of anoikis during metastasis, another important event for this process is the epithelium-mesenchymal transition (EMT). Little is known about the metabolic changes that take place during this complex cellular mechanism and, therefore, very little is known about how the redox state and its homeostasis may contribute to its occurrence. Some authors propose that during EMT there is a catabolic reprogramming that increases the activity of the electron transport chain and the generation of ATP, but that also increases the probability of generating ROS, something

that would be counteracted by an increase in the flow of the oxidative branch of the pentose phosphate pathway, increasing the levels of NADPH, and an increase in the catabolism of fatty acids to the detriment of their synthesis, the main consumer of NADPH during anabolism [178]. The EMT process seems to be associated with the appearance of a hypoxic environment in the tumor context. In several tumor lines, hypoxia triggers changes related to EMT 72 h after oxygen deprivation appears, being important at the beginning a transitory increase of ROS levels [179]. The control of this process is also determined by the tumor microenvironment and the cellular ecosystem that forms it. When the tumor microenvironment becomes very oxidative, there are associated changes in the tumor cells leading to a reorganization of the cytoskeleton, a decrease in E-cadherin that maintains intercellular junctions together with an increase in vimentin expression, and a facilitation of metabolic reprogramming, all of which favors EMT [180]. A recent study shows that in breast cancer cells MDA-MB-468 there is an increase in the expression of motility markers N-cadherin and SERPINE1 in response to an increase in ROS, and that this can be reverted by N-acetyl cysteine treatment [181]. On the other hand, the CAFs of the tumor ecosystem promote EMT through the secretion of metalloproteases that produce an increase in the concentration of ROS mediated by the COX-2 enzyme in tumor cells [182].

The antioxidant enzymes also contribute to regulate the process of metastasis. The activity of enzymes that metabolize glutathione varies between metastatic and non-metastatic melanoma cell lines, with the former being higher than the latter, which is also associated with a drop in the intracellular levels of GSH [183]. Gpx3 seems to have an important role in the regulation of the metastasis process in several types of cancer, so that the complete abolition of its activity, mainly through the methylation of the gene, promotes metastasis, while overexpression of the same reduces invasiveness in prostate cancer [184]. In gastric cancer, the hypermethylation of the Gpx3 promoter is associated with an increase in metastasis to the lymph nodes, and almost a third of the adjacent gastric tissue had the same hypermethylation [185]. This same type of metastasis, which shows tropism for lymph nodes, also occurs in cervical cancer in which Gpx3 is inhibited by hypermethylation of its promoter [186]. In both cases, the role of this redox enzyme as a potential tumor suppressor is pointed out. It seems that this phenomenon of hypermethylation not only takes place in the promoter of Gpx3, but that the isoform Gpx1, also in gastric cancer, presents the same profile and influences the metastatic capacity of the tumor [187]. It has also been shown that Grp3 can support

ovarian cancer progression and metastasis by effects on the extracellular redox microenvirnoment [188]. While Gpx3 and Gpx1 seem to be inhibited for the triggering of metastasis in some types of tumors, the isoenzyme Gpx2 is overexpressed in six hepatocarcinoma lines with different metastatic potential, so that inhibition by siRNAs decreases the migratory and invasive capacity of metastatic cells [189]. This dependence has also been observed in colon cancer cells, where Gpx2 activity is essential to neutralize H_2O_2 increases and favor metastasis [190]. However, it seems that in hepatocarcinoma also Gpx1 has a different role, with an increase in its activity enhancing invasion and metastasis when inhibiting the expression of SBP1 (selenium-binding protein 1), a negative regulator of Gpx1 that binds to it in conditions of oxidative stress, decreasing its activity and favoring the expression of HIF1-α [191]. It is necessary to establish the patterns of expression and activity of these enzymes in more types of cancer, and relate them to the fluxes of reducing and GSH equivalents that exist in tumor cells and in the other cells of the tumor ecosystem, as there could be a correlation between the loss or gain of activity of these enzymes and the levels of metabolites substrates for them in the tumor microenvironment.

In addition to Gpx, Trx are also involved in the metastatic process of some types of tumors. It has been shown that Trx1 promotes colorectal cancer invasion and metastasis and that this effect is mediated by crosstalk with S100P [192]. The inhibition of thioredoxin-like 2 in breast cancer cells produces an increase in ROS and prevents metastasis, so its expression is important in tumor progression [193], while different levels of thioredoxin reductase 1 seem to generate different metabolic profiles in different melanoma cell lines and contribute to the metastasis process, since its inhibition decreases the metastatic potential in vivo [194].

In gastric cancer, metastasis has been shown to be promoted by overexpression of nicotinamide nucleotide transhydrogenase [195]. Plasma membrane Nox activity control has also been related with metastasis [196,197]. A systemic redox imbalance, such as that caused by albumin oxidation in plasma, can also contribute to metastasis promotion [198].

The master regulator of antioxidant responses, Nrf2, has also been involved in metastasis control [137]. On the one hand, Nrf2 promotes EMT in cancer cell lines [199]. On the other hand, circulating metastatic cells overcome anoikis. This could be related to the capacity to grow in an anchorage-independent manner of cancer cells with constitutively high levels of Nrf2 [200]. However, here also the double behavior of Nrf2

emerges, since there are other studies showing that Nrf2 has anti-metastatic potential [201,202].

Regarding NF-κB transcription factor signaling, there are also some studies connecting it with control of metastasis [157,203-206].

7. Concluding remarks

An altered redox balance has been proposed, along with proteotoxic stress, as a new hallmark of cancer to be added to the ten so far described by Hanahan and Weinberg [21,137]. As shown along this review, this fact opens new options for the therapeutic treatment of cancer based on redox unbalance. Figure 4 summarizes the effector systems affected by cellular redox state giving outcomes involved in angiogenesis and metastasis.

Many questions regarding the role of redox control in cancer angiogenesis and metastasis remain to be elucidated. In particular, Nrf2 is involved in the regulation of both angiogenesis and metastasis but its double sword behavior remains to be fully understood [137]. The impact of redox balance in the tumor microenvironment should be also further studied and characterized, with special mention to the evolution of cancer within its complex ecosystem [207,208].

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Conflicts of Interest

No potential conflicts of interest were disclosed.

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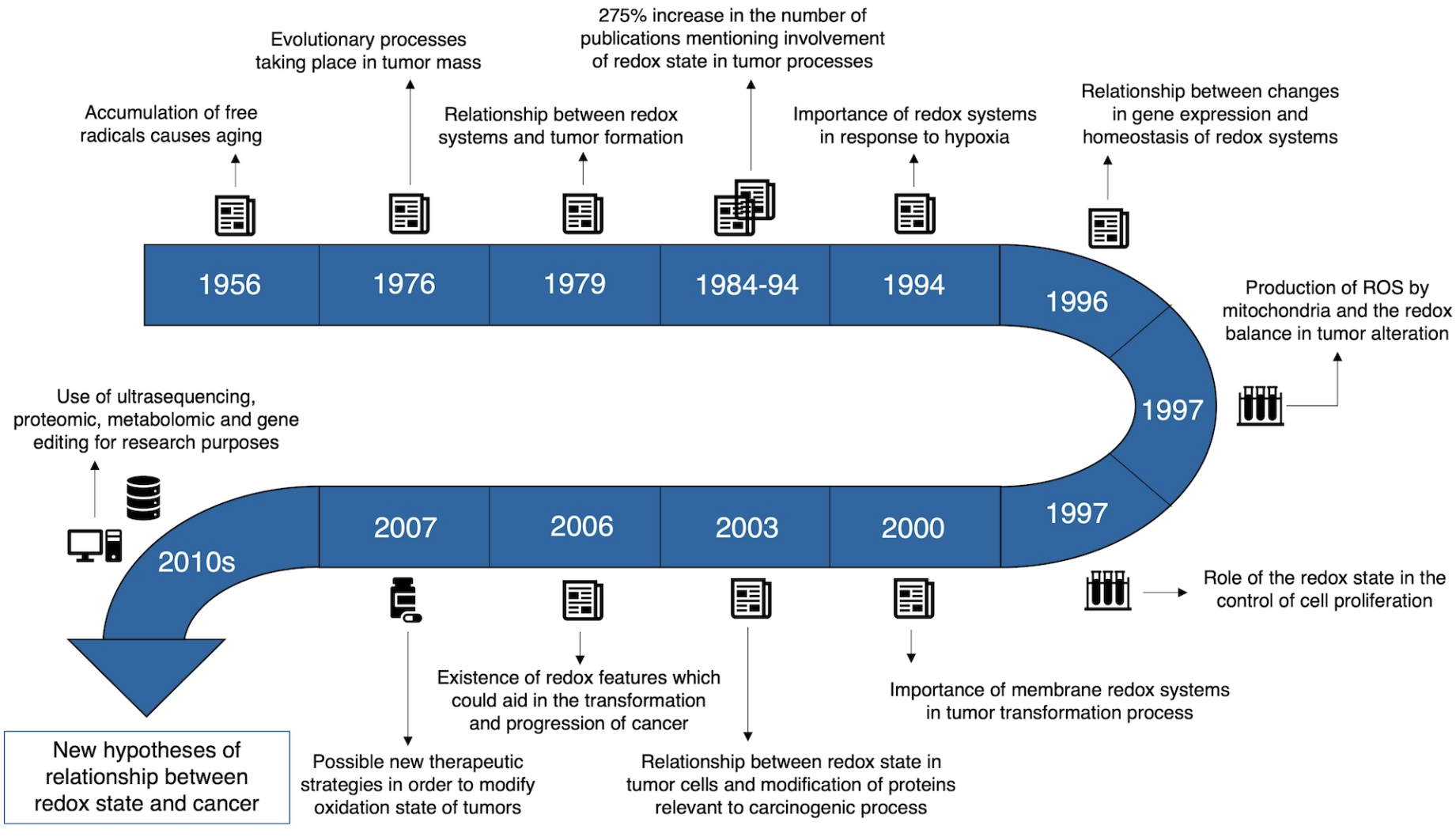
Figure legends

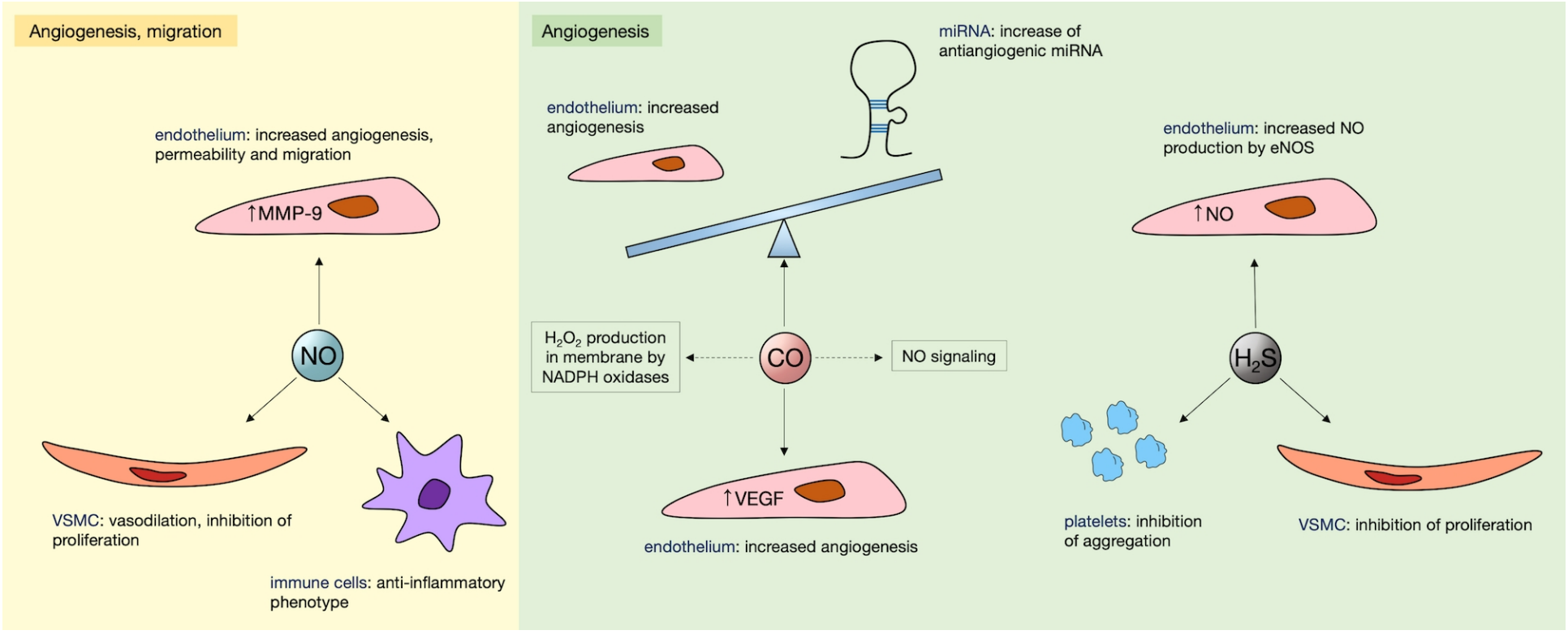
Figure 1. Timeline representing the most significant publications and research described in the historical background section of the present review in terms of redox systems and their relationship with tumorigenesis.

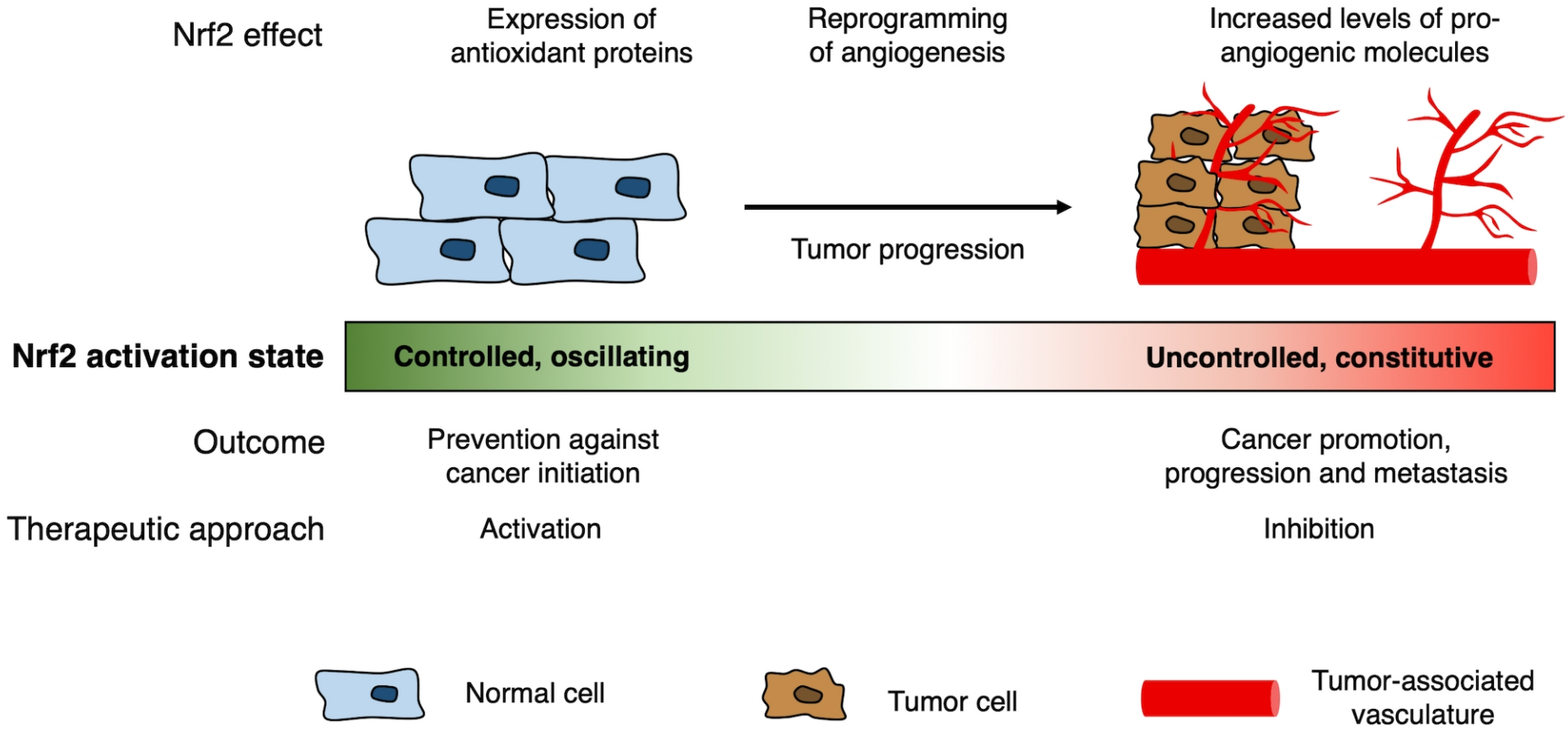
Figure 2. Effects of bioactive gases NO, CO and H_2S in the redox control of tumor angiogenesis and metastasis described in this work. Yellow represents control over angiogenesis and progression; green represents control over angiogenesis. MMP-9: matrix metalloproteinase 9; VEGF: vascular endothelial growth factor; VSMC: vascular smooth muscle cells.

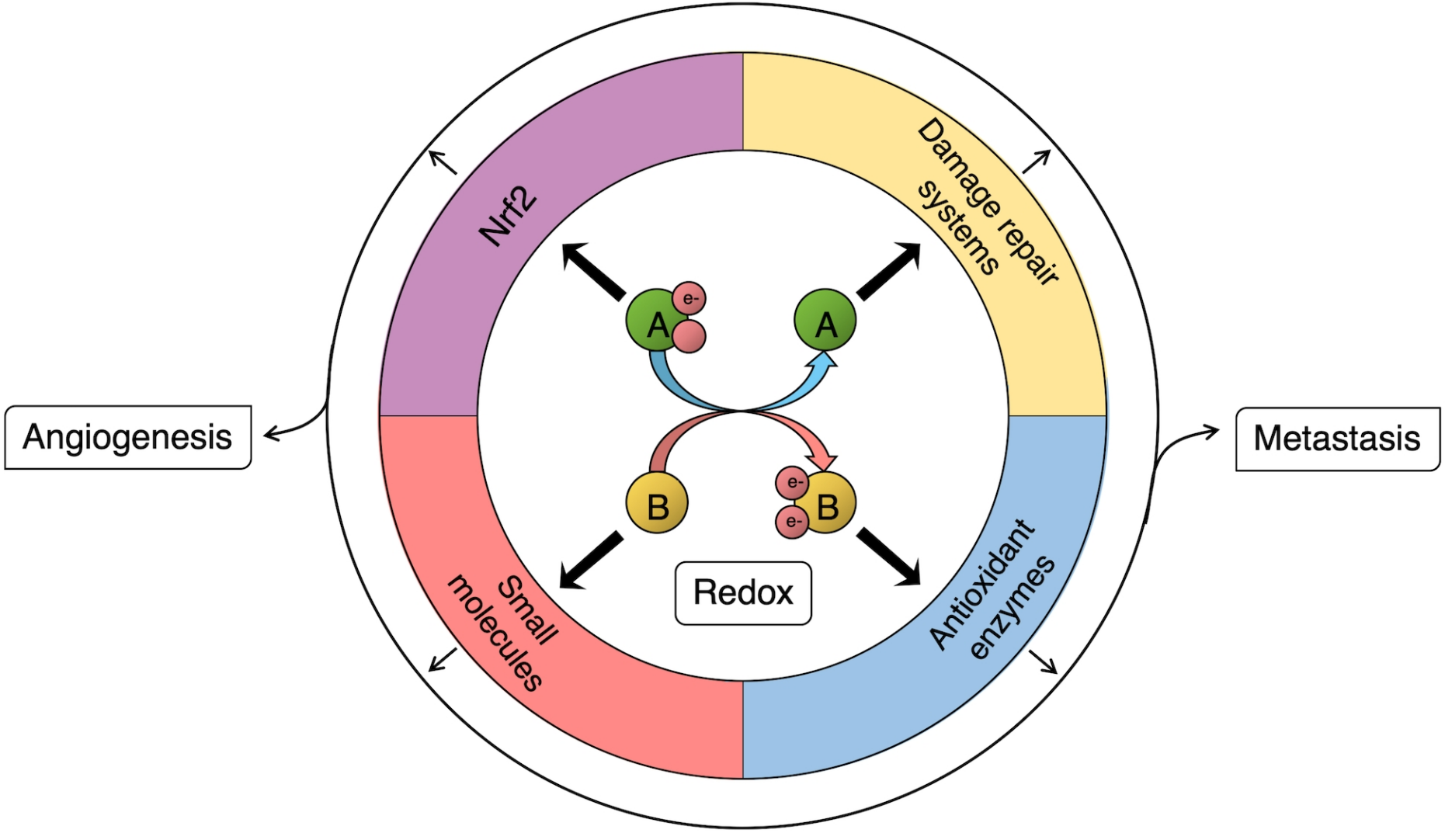
Figure 3. Double-edge sword behavior of Nrf2 in cancer. Controlled, oscillating activation results in preventive action against cancer initiation. At this stage, activating Nrf2 could serve as a preventive, therapeutic strategy. Uncontrolled, constitutive activation promotes cancer progression and metastasis. At this stage, inhibition of Nrf2 could be a suitable therapeutic strategy.

Figure 4. "Hallmarks of redox". Effector systems affected by redox state. Outcomes of the function of the four systems are reflected in tumor angiogenesis and metastasis.


Accumulation of free radicals causes aging
Evolutionary processes taking place in tumor mass
Relationship between redox systems and tumor formation
275% increase in the number of publications mentioning involvement of redox state in tumor processes
Importance of redox systems in response to hypoxia
Relationship between changes in gene expression and homeostasis of redox systems
1956
1976
1979
1984-94
1994
1996
1997
Production of ROS by mitochondria and the redox balance in tumor alteration
Use of ultrasequencing, proteomic, metabolomic and gene editing for research purposes
2010s
2007
2006
2003
2000
1997
Role of the redox state in the control of cell proliferation
Existence of redox features which could aid in the transformation and progression of cancer
Importance of membrane redox systems in tumor transformation process
New hypotheses of relationship between redox state and cancer
Possible new therapeutic strategies in order to modify oxidation state of tumors
Relationship between redox state in tumor cells and modification of proteins relevant to carcinogenic process


Angiogenesis, migration
endothelium: increased angiogenesis, permeability and migration
↑MMP-9
NO
VSMC: vasodilation, inhibition of proliferation
immune cells: anti-inflammatory phenotype
Angiogenesis
miRNA: increase of antiangiogenic miRNA
endothelium: increased angiogenesis
H_2O_2 production in membrane by NADPH oxidases
CO
NO signaling
↑VEGF
endothelium: increased angiogenesis
endothelium: increased NO production by eNOS
↑NO
H_2S
platelets: inhibition of aggregation
VSMC: inhibition of proliferation


Nrf2 effect
Expression of antioxidant proteins
Reprogramming of angiogenesis
Increased levels of pro-angiogenic molecules
Tumor progression
Nrf2 activation state
Controlled, oscillating
Uncontrolled, constitutive
Outcome
Prevention against cancer initiation
Cancer promotion, progression and metastasis
Therapeutic approach
Activation
Inhibition
Normal cell
Tumor cell
Tumor-associated vasculature


Nrf2
Damage repair systems
Small molecules
Antioxidant enzymes
Angiogenesis
Metastasis
Redox
A
e-
A
B
e-
e-
B

Conflicts of Interest

No potential conflicts of interest were disclosed.

CRediT author statement

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Miguel Ángel Medina: Conceptualization, Supervision, Investigation, Funding acquisition, Writing-Original Draft, Writing-Review & Editing.