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**Overview of angiogenesis and oxidative stress in cancer**

Andriolo LG *et al*. Angiogenesis, oxidative stress, and cancer

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**Abstract**

Neoplasms can be considered as a group of aberrant cells that need more vascular supply to fulfill all their functions. Therefore, they promote angiogenesis through the same neovascularization pathway used physiologically. Angiogenesis is a process characterized by a heterogeneous distribution of oxygen caused by the tumor and oxidative stress; the latter being one of the most powerful stimuli of angiogenesis. As a result of altered tumor metabolism due to hypoxia, acidosis occurs. The angiogenic process and oxidative stress can be detected by measuring serum and tissue biomarkers. The study of the mechanisms underlying angiogenesis and oxidative stress could lead to the identification of new biomarkers, ameliorating the selection of patients with neoplasms and the prediction of their response to possible anti-tumor therapies. In particular, in the treatment of patients with similar clinical tumor phenotypes but different prognoses, the new biomarkers could be useful. Moreover, they may lead to a better understanding of the mechanisms underlying drug resistance. Experimental studies show that blocking the vascular supply results in antiproliferative activity *in vivo* in neuroendocrine tumor cells, which require a high vascular supply.

**Key Words:** Neuroendocrine lung tumors; Angiogenesis; Oxidative stress; Neuroendocrine serum markers; Neuroendocrine tissue markers; Future therapy

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**Core Tip:** There are already several reviews in the literature that contribute to understanding angiogenesis and oxidative stress. However, this is the first review to report the latest cellular and molecular mechanisms of angiogenesis pathways while also discussing the genetics and biochemistry of oxidative stress in neoplasms. We also specifically discuss neuroendocrine lung tumors. These discoveries may be useful for new clinical and translational research studies.

**INTRODUCTION**

The angiogenesis process consists of the generation of new blood vessels. The migration and proliferation of endothelial cells from already existing vessels to new vessels are crucial in this process. During embryonic development, these cells are particularly active, whereas in the adult their turnover is slow and limited to certain physiological phenomena, such as ovulation, tissue repair, and scarring processes[1].

Angiogenesis is the result of a well-balanced process between proangiogenic and antiangiogenic factors. This balance can fail due to specific stimuli such as hypoxia, creating a pathological angiogenic process[2]. The prevalence of proangiogenic factors is associated with serious diseases, such as cancer, and with inflammatory and degenerative diseases, such as retinopathies, rheumatoid arthritis, and psoriasis. Insufficient angiogenesis is the basis of obliterating vascular diseases, such as obstructive coronary artery disease or peripheral obstructive arterial disease (Buerger’s disease), which are characterized by the downstream tissue ischemia of vascular occlusions[3].

Neoplasms can be considered complex biological structures constituted by aberrant cells and endowed with specific functions; there are mesenchymal-derived cells, inflammatory cells, and vascular cells communicating with one another[4]. To fulfill all their functions, including growth and metastasis, they can promote angiogenesis through the same neovascularization pathway used physiologically. Tumor progression occurs due to the proliferation of the tumor cells themselves and the interactions that the neoplasm sets up within the tumor microenvironment where distinct types of tumor cells secrete key cytokines[5] for tumor progression and metastasis[6].

Cancer cells in active and continuous replication need a constant supply of oxygen and nutrients. For this reason, the first mechanism that cancer cells use to ensure the survival and growth of its cells is angiogenesis. However, neoplastic angiogenesis is an aberrant process associated with the formation of tortuous vessels that are insufficient to fulfill cellular needs. Acidosis is the consequence of altered tumor metabolism in response to hypoxia and the heterogeneous distribution of oxygen between the core and periphery that tumor angiogenesis helps to create. In this way, the acidic environment selects a more aggressive neoplastic cell phenotype with a greater invasive and metastatic phenotype.

Metabolic, hypoxic, and oxidative stress is considered a distinctive marker of cancer[7]. To survive the metabolic stresses, cancer cells activate different types of mechanisms including evasion of apoptosis and immune surveillance, increasing the angiogenic activity to enhance the provision of oxygen and nutrients, activation of the epithelial-mesenchymal transition (EMT), and metastasis[7,8]. Positive feedback between angiogenesis and oxidative stress is evident when a cellular mechanism stands for both the stimulus and the result of this process (Figure 1).

Tumor-induced angiogenesis begins with the release and activation of many growth factors[9]. The most important of which is vascular endothelial growth factor (VEGF) with its receptors. The mechanism of angiogenesis is complex, and it passes through stages well defined by changes in the endothelium and the extracellular matrix[10]. It can be schematically described as follows. The first stage of angiogenesis is characterized by the “destabilization” of pre-existing vessels and the loss of connection between endothelial cells due to increased vascular permeability. The proliferation phase of the endothelial cells follows with the formation of new vessels. Various proteolytic enzymes are released during these phases and alter the density of the extracellular matrix to help the migratory activity of endothelial cells. The third stage of angiogenesis is characterized by the formation of primitive capillaries. Finally, the last stage involves the recruitment of supportive periendothelial cells, such as pericytes and muscle cells, as well as the reorganization of periendothelial cells[11].

The most powerful stimulus for angiogenesis is hypoxia. Hypoxia and angiogenic factors released by the tumor destabilize the pericytes and stimulate continuous angiogenesis[12]. Tumors maintain hypoxia primarily due to the heterogeneous distribution of oxygen between the core and the periphery that cancer cells generate[13]; this situation is also associated with acidosis. By maintaining a low pH, cancer cells can evade immune cells and be chemoresistant[14].

Reactive species, mainly represented by reactive oxygen species (ROS), are products generated by metabolic reactions that take place in the mitochondria of eukaryotic cells. If these reach a certain level they can be toxic to the cells. Physiological concentrations of reactive species can generally transduce signals before they are eliminated, whereas tumor cells need high concentrations of ROS to support their high proliferation rate due to their metabolism[15].

Among the several cellular strategies adopted by tumors to develop resistance to ROS are the so-called alternative metabolic pathways. These pathways prevent the accumulation of ROS without reducing the metabolic energy required by the tumor cells. The glycolysis with its parallel pathway and the pentose phosphate pathway, are examples of these pathways. The ROS levels are a sign of the damage that cells can withstand[16].

The therapeutic implications that follow are particularly important since the radiotherapy and chemotherapy currently available conduct their antitumor action precisely through the regulation of ROS levels. Therefore, the clinical response to pro-oxidant therapies has to be considered to enable truly personalized therapies. Consequently, the discovery of biomarkers capable of predicting this response is a challenge[17].

Somatostatin is a ubiquitous polypeptide produced by the delta cells of the digestive system and is present in the intramural plexuses of the intestine. Tumors originating from these cells produce and secrete somatostatin. Somatostatin exists in two biologically active forms, namely SS-14 and SS-28[18].

Several functions of somatostatin in the central nervous system are described. These include neuromodulatory, locomotor, and cognitive functions, inhibition of basal and stimulated secretion of distinct types of endocrine and exocrine cells, and regulation of cell proliferation and differentiation[19]. Specific membrane receptors are bound by somatostatin, of which there are five different subtypes called somatostatin receptors 1-5 (SSTR 1-5). These have maintained structural homology between distinct species (40%-60% of structural homologies) and mediate different biological actions by activating different intracellular signaling pathways[20,21].

Tumors that produce somatostatin have a typical histological architecture common to all neuroendocrine tumors (NETs) and a high somatostatin production. Somatostatin is a powerful inhibitor of neovascularization as many experimental data have shown. SSTR are expressed on endothelial cells, and the activation of quiescent endothelium is associated with an upregulation of SSTR2.

Somatostatin agonists inhibit VEGF, basic fibroblast growth factor, and growth hormone/insulin-like growth factor 1. Consequently, they can negatively regulate angiogenesis[22]. Furthermore, somatostatin can function as a powerful antitumor agent *in vivo* inhibiting both endothelial nitric oxide synthase and mitogen-activated protein kinases (MAPK) through SSTR3[23].

NETs represent a neoplasm that most benefit from metabolic radiotherapy and treatment with antiangiogenesis and pro-oxidant drugs. The presence of marked vascularization is a distinctive feature in most NETs, and this characteristic can be considered one of the diagnostic markers of neuroendocrine pathology[24]. Several studies have shown that microvascular density is 10 to 30 times greater in NETs than in other carcinomas[25].

**Tumor angiogenesis**

As previously mentioned, the most important tumor-induced angiogenesis mediator is VEGF and its receptors[9] (Table 1). Six subtypes of VEGF are recognized: VEGF-A; VEGF-B; VEGF-C; VEGF-D; VEGF-E; and placental growth factor[26]. VEGF-C and VEGF-D take part in lymphangiogenesis. VEGF-A plays a dominant role in the angiogenesis process and is simply referred to as VEGF[27].

*VEGF* gene transcription is regulated by hypoxia-inducible factor (HIF), which is a protein composed of a constant subunit (HIF-1β) and an oxygen-regulated subunit (HIF-1α or HIF-2α)[28]. In response to hypoxia, the level of VEGF increases significantly in the extracellular space. High concentrations of VEGF determine the degradation of the basement membrane and the destabilization of the pericytes, the growth of endothelial cells, and the formation of new vessels[29]. This process is highly involved in tumor progression and when small tumors receive their nourishment by passive diffusion[30]. Those over 2 mm2 undergo the formation of a hypoxic central core that stimulates the angiogenesis process[31]. This phase is called the “angiogenic switch” and is the release of many mediators of angiogenesis by the tumor cells in response to the reduced oxygen supply[32].

There are different mechanisms by which neoplasms stimulate angiogenesis[33]. The first and most important mechanism is germinal angiogenesis, which leads to the formation of new vessels from pre-existing capillaries and small venules. The endothelial cells undergo reactivation resulting in the formation of small shoots that grow and migrate into the adjacent connective tissue. Subsequently, an immature vessel is formed, stabilizing after the recruitment of pericytes and the reconstitution of the basement membrane. The new vessels are characterized by fenestrated endothelial cells, a discontinuous basement membrane, and rare pericytes. Consequently, the vascular network is permeable without efficient flow regulation and has an aberrant morphology with irregularly branched and tortuous vessels[34].

Another mechanism of tumor neovascularization is co-optation. In this case, the cancer cells grow along the normal vascular network. This mechanism is mainly observed in the brain, liver, and lung. It is particularly important in the early metastatic processes. Intussusception is the division of a pre-existing vessel into two new vessels and has been described in some aggressive tumors. Finally, in the vascular mimicry mechanism, a formation of vessels from the tumor cells themselves is observed. This process is seen in many aggressive tumors[35].

Pericytes are smooth muscle cells that stabilize the vessel walls and protect the normal vessels themselves from anticancer drugs, guaranteeing and promoting their target action. Hypoxia and angiogenic factors released by the tumor destabilize the pericytes and facilitate continued angiogenesis[8]. The reduction in their number leads to an increase in permeability and consequently the interstitial fluid pressure[36]. This leads to a further reduction in perfusion, the distribution of anticancer drugs, and acidosis[37]. Interstitial fluid pressure can be considered a marker of response to anticancer therapy[38].

Hypoxia can promote chemoresistance by increasing the ATP-binding cassette efflux pumps. Hypoxic cells are less proliferative than their normoxic counterpart and are therefore less subject to the chemotherapeutic cytotoxic effect[39]. Hypoxia also contributes to reducing the response to immunotherapy because it reduces immune activity[40].An increase in HIF1 levels prevents the activation of CD8+ T-helper lymphocytes, suppresses the cytotoxic effect of natural killer cells, and increases the expression of immunosuppressive mediators such as inducible nitric oxide synthase and interleukin (IL)-10 by dendritic cells.

Different therapeutic strategies have been developed in an attempt to make hypoxia an advantage. Drugs activated by an enzymatic reduction in a hypoxic environment with the production of cytotoxic compounds have been tested without a real confirmation in terms of clinical utility[41]. Similarly, attempts were made to increase the oxygen transport capacity of the plasma using hyperbaric therapy[42].

In 1993, Kim *et al*[43] treated a mouse model of rhabdomyosarcoma, glioblastoma, and leiomyosarcoma with anti-VEGF monoclonal antibodies, obtaining tumor growth arrest. Given the ineffectiveness of these antibodies *in vitro* this pioneering study showed how blocking the action of angiogenesis mediators had a direct effect on tumor growth. However, the effect of these drugs was not constant[44]. There are differences in antitumor responses based on dosage, duration of treatment, and tumor type.

Due to the tremendous vascularization that characterizes them, neuroendocrine lung tumors would most benefit from antiangiogenesis drugs. This observation refers to the architecture of normal endocrine glands that need a well-represented vascular network that allows continuous exchange between endocrine cells and the bloodstream including hormone secretion.

Another characteristic of NETs that would suggest an elective use of antiangiogenic therapy as the treatment of choice is their marked ability to synthesize and secrete elevated levels of VEGF-A[45]. In this aspect, they mimic the endocrine cells with the secretion of peptide hormones[46]. Pancreatic islet β cells show the secretion of elevated levels of VEGF-A, which appears to play a significant role in the development of the dense vascular network of normal endocrine tissues[47]. VEGF-induced angiogenesis is also important for tumorigenesis and tumor progression of NETs. The angiogenic phenotype is necessary for the transition from hyperplasia[48], and it can be blocked pharmacologically[49]. Even in this process, VEGF-A plays a decisive role[50].

The microvascular density of pancreatic NETs is higher in benign tumors than in malignant tumors and in this context is higher in low-grade than in high-grade malignant tumors. It is also characterized by a better prognosis. This observation is called the “neuroendocrine paradox.” To explain this phenomenon, it has been hypothesized that in pancreatic NETs the vascular density is a marker of differentiation rather than of aggressiveness[51]. Like their normal counterpart, well-differentiated neuroendocrine cells do keep the ability to promote the formation of a dense vascular network. Conversely, the tumor angiogenesis mechanism of poorly differentiated neoplasms is secondary to hypoxia and aberrant genetic alterations. This does not signify the absence of angiogenic activity in well-differentiated NETs but that it is low per unit of time considered.

Little is known of the process of angiogenesis in NETs originating from organs other than the pancreas, and any available data are scarce and contradictory[52]. As far as the lung is concerned, it appears to be similar to the pancreas, with the presence of high vascular density in well-differentiated NETs and low in high-grade NETs. However, all aspects are not yet completely clear, and further studies are needed, particularly in the area of high-grade and metastatic cancers where antiangiogenic therapies would find their main application.

Several antiangiogenic target drugs have been successfully assessed in metastatic NETs such as anti-VEGFA, anti-VEGFR, and tyrosine kinase inhibitors. However, other drugs already in use in the therapy of NETs have also shown an antiangiogenic action. Among these are the analogues of somatostatin and interferon alpha. Somatostatin analogues have shown antiangiogenic properties *in vitro* by inhibiting the proliferation of endothelial cells and the synthesis and secretion of VEGF. However, data on their use *in vivo* are controversial, probably due to their insufficient ability to compete with VEGF and other proangiogenic factors[53]. The data in favor of the use of interferon alpha for the treatment of carcinoids seems more convincing. There is a significant reduction in intratumor microvascular density, but it is not associated with a reduction in circulating VEGF levels.

The development of resistance to antiangiogenic drugs is one of the major problems linked to their use, which is similar to other targeted therapies. This effect would explain the lack of long-term response and the so-called “angiogenic explosion” after their suspension. When anticancer drugs with antiangiogenic action are used at high dosages, they only have an acute antitumor effect that is not reflected long term.

Acute hypoxia due to massive and non-selective vascular destruction selects and facilitates only the most aggressive cancer cells, preventing immune surveillance, favoring metastases, and promoting resistance to anticancer treatments. Their use at low dosages as an adjuvant in chemotherapy regimens has instead shown efficacy thanks to the establishment of the so-called “vascular normalization” phenomenon[54]. This consists of the selective destruction of only immature and aberrant vascularity while respecting the normal one. Vascular normalization also passes through the fortification of the vessel wall as a result of the recruitment of pericytes. Finally, antiangiogenic drugs also determine a tumor microenvironment[40] effect of normalization due to the reprogramming of many tumor processes that target blood vessels.

Several studies showed[55] that the biological basis of resistance is not found in the genetic mutations that occur in the target molecules but rather in the establishment of a secondary angiogenesis pathway. Malignant cells can simultaneously synthesize and secrete many proangiogenesis factors, among which angiopoietin-2 seems to be the one that plays the most important role. This alternative route was observed in the experimental models of NET[56] and could justify both the increase in serum levels of angiogenic cytokines during anti-VEGF/VEGFR therapy and the simultaneous and effective use of combined therapies that block multiple angiogenic routes.

The use of angiogenesis markers could be a promising way to monitor the efficacy of antiangiogenesis therapy, determine its optimal dosage, avoid related toxicity, and predict its response or resistance. Currently, microvascular density is the best-known tissue biomarker. However, many data from the literature[57] show that it is not predictive in response to antineoplastic therapy. Different approaches have yet to be explored using immunohistochemical, molecular, and serum methods.

**Oxidative stress**

Eukaryotic cells obtain the energy needed from aerobic respiration in the mitochondria. Due to this metabolic process, several reactive species are produced. They are required for signal transduction, enzymatic activity, gene expression, and protein folding in the endoplasmic reticulum and during apoptosis. Commonly, they are harmless. However, about 5% of reactive species can be toxic if they reach high concentrations.

***Biochemistry of oxidative stress***

The sources of oxidative stress can be both internal and external to the cell. Peroxisomes and P450 complex enzymes, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, and NADPH complexes are all internal sources of oxidative stress. Almost all enzymes act within the mitochondria. Ultraviolet rays, chemicals (*e.g.*, environmental pollutants, smoking, and alcohol), and exercise are, conversely, external sources of oxidative stress.

Based on the main atom involved we can divide the reactive species into four groups: ROS; reactive nitrogen species (RNS); reactive sulfur species; and reactive chloride species[58]. ROS and RNS are produced during the electron transport chain. ROS, which includes superoxide anion, hydrogen peroxide (H2O2), hydroxyl radical, singlet oxygen, and ozone, are the products of oxidative metabolism[59]. Some ROS, such as peroxynitrite anion and ONOO-, can react with nitric oxide. Subsequently, nitric oxide is converted to a hydroxyl radical and a nitrite anion.

The balance between ROS and endogenous antioxidants determines the damage that cells can suffer. After the alteration of this balance, oxidative stress is generated with subsequent damage to DNA, RNA, lipids, and proteins[60]. Reactive species cause DNA damage and malfunctions in the DNA repair mechanisms. The oxidation of DNA that takes place generates 8-hydroxy-2-deoxyguanosine, which is a product capable of causing mutations in DNA and increasing cellular aging and carcinogenesis[61].

Polyunsaturated lipids are abundant in the cell membrane and are also particularly susceptible to oxidation by reactive species. By peroxidation reactions, they release lipids and increase the permeability of the cell membrane, which can lead to cell death[62]. However, proteins are the main target of the reactive species. The carbonyl (aldehydes and ketones) and thiol groups (–SH) can be converted into reactive sulfur radicals[63]. Therefore, there is an alteration in the structure of the protein that leads to changes or loss of function.

The cell has three groups of defense mechanisms: endogenous antioxidants; natural antioxidants; and synthetic antioxidants[64]. The following are endogenous antioxidants: glutathione; alpha-lipoic acid; coenzyme Q; ferritin; uric acid; bilirubin; metallothionein; l-carnitine; melatonin; superoxide dismutase; catalase; glutathione peroxidase; thioredoxin; and peroxiredoxin (PRX). PRX is a group of ubiquitous antioxidant enzymes (PRX I-VI). They can modulate the H2O2 levels and transduce intracellular signaling. PRX III eliminates up to 90% of H2O2, and PRX V is even more effective against peroxynitrite.

The diet is a source of natural antioxidants such as ascorbic acid (vitamin C), tocopherol (vitamin E), carotene (vitamin A), lipoic acid, uric acid, glutathione, and polyphenolic metabolites. Finally, synthetic antioxidants include N-acetyl cysteine, thyroid hormones, pyruvate, selenium, butylated hydroxytoluene, butylated hydroxyanisole, and propyl gallate[65].

***Clinical importance of oxidative stress***

Several human diseases, such as neurodegenerative diseases (Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis), inflammatory diseases (arthritis), cardiovascular disease (atherosclerosis), allergies, immune system dysfunction, diabetes, aging, and cancer[66] are attributable to oxidative stress. During the acute inflammatory response, the chemical mediators released, such as ROS, also affect normal cells. In the case of a chronic inflammatory process, extremely high levels of ROS saturate the antioxidant mechanisms of the cell affecting the surrounding cells.

***Oxidative stress in neoplasms***

ROS are responsible for some cellular mechanisms implicated in tumor development and progression, including: (1) Cell proliferation (*e.g.,* activation of regulated extracellular kinase 1/2 and ligand-independent kinase receptor tyrosine kinase); (2) Apoptosis inhibition; (3) Tissue infiltration and metastasis (metalloproteinase secretion in the matrix extracellular, Met overexpression, and Rho-Rac interaction); and (4) Angiogenesis (release of VEGF and angiopoietin).

Several biochemical pathways are affected by oxidative stress (from epidermal growth factor receptor to mechanistic target of rapamycin) involving key signaling proteins, such as Nrf2, Keap1, Ras, Raf, MAPK, ERK1/2, MEK, p38, JNK, c-myc, p53, and PKC[67-69]. p38 acts as a key sensor of oxidative stress and is essential in the control of neoplastic development[70]. Unlike other MAPKs, p38 suppresses tumorigenesis by blocking proliferation and promoting apoptosis (Table 2).

***Genetics of oxidative stress in neoplasms***

A key role in the neoplastic transformation is played by genetic factors. A high level of ROS is associated with the increased metabolism observed in tumor cells; however, oxidative stress is less harmful to cancer cells than it is to normal cells. Cancer cells can adapt to the new conditions and proliferate, creating a new redox balance. This ability of cancer cells allows them to have a greater resistance to oxidation and oxidative stress than normal cells. It follows that the neoplastic cells can increase their metabolic rate and proliferation and avoid the damage caused by free radicals. However, this adaptive response alone cannot explain the high metabolic rate of tumors[71].

Genetic factors implicated in tumorigenesis may also directly or indirectly modulate ROS levels. The physiologic antioxidant activity is mainly regulated by the Nrf2 transcription factor in addition to specific antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, thioredoxin, and PRX. Nrf2 modulates the expression of many genes, including not only those that code for antioxidant enzymes but also genes that control immune and inflammatory responses, carcinogenesis, and metastasis[72]. ROS levels are controlled by Nrf2 and its repressor protein (Keap1). Furthermore, experimental data show that when treated with oxidation-inducing drugs Nrf2-free mice develop more severe intestinal inflammation than controls, suggesting a function for Nrf2 in preventing inflammation and carcinogenesis[73].

While Nrf2 was initially thought to be able to regulate oxidative stress by modulating the production of antioxidant enzyme antioxidant response element, subsequently kinase-dependent mechanisms have been described, such as MAPK, PI3K, and other alternative pathways for activation of Nrf2[74,75]. Somatic mutations that disrupt the Nrf2-Keap1 interaction have been identified in patients with non-small cell lung cancer[76] and esophageal cancer[77]. In breast cancer, the breast cancer tumor suppressor gene 1 (*BRCA1*) is mutated in 40%-50% of hereditary breast cancers, while it is absent or at a low level in 30%-40% of sporadic cases[78]. BRCA1 is responsible for DNA repair and can regulate Nrf2 and NFκB[79,80]. Nrf2 induces enzymes such as glutathione S-transferase, glutathione peroxidase, and oxidoreductase, which exert a protective action against ROS. In breast cancer cells the *BRCA1* gene reduces RNS damage to cells and helps them cope with oxidative stress. Redox factor 1/AP endonuclease 1 also participates in the reduction of ROS generation[81].

The Ras pathway (Ha-, N- and Ki-ras) is very important for regulating oxidative stress in cancer[82]. Ras activating point mutations are present in tumor cells (approximately 30% of tumors), resulting in a constitutively active protein. These mutations lead to an increase in ROS levels, which induces neoplastic transformation[83]. The *Ras* Val12 mutant activates the NOX4-p22phox NADPH oxidase system, which produces H2O2. Consequently, the response to *Ras* Val12-induced DNA damage is impaired by the inhibition of NADPH oxidase. NADPH oxidase, NOX4, can be considered a critical mediator of *Ras* Val12-induced oncogenic DNA damage[84].

If the *Ras* oncogene is overexpressed, cells show an increase in mitochondrial mass and an accumulation of ROS. Among these, the ROS generated by the respiratory chain in the mitochondria and the NOX enzymes in the cytoplasm are particularly important. NOX proteins are oncogenic proteins, and mitochondrial dysfunction is associated with tumorigenesis[85].

Mitochondrial dysfunction leads to DNA damage, decreased ATP levels, and activation of AMPK. The presence of the *K-ras* Val12 mutant in normal epithelial cells leads to increased peroxide levels and increased DNA damage. Peroxides can be generated by the COX-2 enzyme due to their correlation with K-ras[86]. Consequently, the COX-2 enzyme is also involved in many human cancers. Both peroxide production and DNA damage are reduced by pretreatment with the COX-2 antagonist SC58125. Therefore, several proteins including COX-2 and the transcription factor HIF-1α, which is activated in response to low oxygen concentrations, can influence the oncogenic activity of mutant K-rasVal12.

Overexpression of oncogenic proteins [Raf, reverse transcriptase of Mos, MEK, Myc, cyclin E and human telomerase reverse transcriptase (hTERT)] and inhibiting oncosuppressor genes (p53, p21CIP1, PTEN) can cause aging by increasing ROS levels. PTEN deficiency and Ras/MAPK activation could promote metastasis and EMT from prostate precursor cells[87]. Even in glioblastoma cells, PTEN deficiency, associated with high levels of Akt and ROS, leads to senescence. There is evidence that suggests the *hTERT* oncogene acts by modulating the redox system[88]. hTERT is localized in mitochondria, and its activity could influence the redox balance through the recruitment of the same mitochondria. Finally, hTERT inhibitors can induce mitochondrial-dependent apoptosis in target cells[89].

Many other genes are involved in regulating energy metabolism in cancer. *p53,* for instance, is one of the best-known tumor suppressors, and it is implicated in cellular energy balance in the mitochondria between glycolysis and the respiratory chain. Homologous cytochrome oxidase 2 is an important enzyme that mediates this effect, and its activity is very important for the regulation of the COX complex. Reduced homologous cytochrome oxidase 2 synthesis can cause low respiration and a high rate of glycolysis[90].

Sirtuins are a group of proteins involved in many cellular processes (aging, stress response, *etc*). Sirtuins are deacetylase enzymes regulated by NAD (positive activity) and NADH (negative activity). Sirt3 is the most studied of the three mitochondrial sirtuins and is known to act as a tumor suppressor. It is for this reason that it has been linked to longevity in humans. Kim *et* *al*[91] showed that in Sirt3 (-/-) murine embryonic fibroblasts, increased glycolysis, decreased oxidative phosphorylation, and increased ROS can be observed. Furthermore, the loss of Sirt3 increases cell tumorigenesis[92]. This process is accompanied by the activation of the HIF-1α target gene under hypoxic conditions.

**Neuroendocrine lung tumors**

Bronchopulmonary neuroendocrine neoplasms represent a group of rare neoplasms (accounting for almost 20% of all lung neoplasms)[93] arising from the proliferation of cells with both endocrine and nervous phenotypic characteristics that together form the diffuse neuroendocrine system[94].

Based on their morphological, structural, immunohistochemical, and ultrastructural characteristics, they can be divided into four groups according to the 5th edition of the World Health Organization classification on thoracic tumors[95]: typical carcinoid (TC); atypical carcinoid (AC); large cell neuroendocrine (LCNEC); and small cell carcinoma (SCLC). TC and AC are considered well-differentiated NETs, while LCNEC and SCLC are considered poorly differentiated tumors. TC and AC are low (corresponding to G1 NET) and intermediate (corresponding to G2 NET) grades, respectively, whereas LCNEC and SCLC are high grades (traditionally graded as G3 tumors). Although these four subgroups of neuroendocrine neoplasms may represent a continuum in the neuroendocrine differentiation spectrum, histological, immunohistochemical, and molecular studies have demonstrated that pulmonary carcinoids are different from poorly differentiated neuroendocrine carcinomas[96].

The first description of a bronchopulmonary carcinoid dates back to 1831 when Laennec[97], in his treatise on mediated auscultation of the lungs and heart, reported the case of a posthumous endobronchial mass. The clinical presentation can occur with cough, hemoptysis, and recurrent pneumonia (due to the functional exclusion of a bronchus by a growing mass) even if in most cases their clinical course is indolent[93].

The diagnosis is based on imaging methods, such as computed tomography and magnetic resonance imaging, bronchoscopy, bronchial biopsy or fine-needle aspiration biopsy, mediastinoscopy (in selected cases), scintigraphy with 111 In-pentetreotide (octreoscan), and functional studies such as the evaluation of the tumor secretion pattern. Although less than 5% of patients with bronchopulmonary carcinoids have symptoms such as carcinoid syndrome, Cushing’s disease, acromegaly, or syndrome of inappropriate antidiuretic hormone secretion, it is possible to detect secretion of amines, peptides, or hormones (endocrine, autocrine, or paracrine)[93].

However, the NETs most striking phenotypical characteristic is the massive vascularization[52] due to their marked ability to synthesize and secrete high levels of VEGF[45]. The experimental data available refer especially to the pancreatic NETs where the presence of high vascular density in NETs and low vascular density in neuroendocrine carcinoma is observed. The precise situation and the angiogenesis mechanism is not completely clear in neuroendocrine lung tumors. This review could provide a starting point for further future studies.

Experimental evidence has shown that the ROS released by the tumor due to metabolic stress are associated with different outcomes depending on their level[31]. Evidence shows that high levels of ROS directly lead cancer cells to cell death whereas low to medium ROS levels increase neoplastic progression, metabolism alteration, cell migration, EMT, and metastasis[98,99]. ROS also stimulate acute inflammation that becomes chronic when associated with prolonged ROS production[100]. NFκB and TGF-β are implicated in the relationships between chronic inflammation and carcinogenesis[101]. ROS are also responsible for p38 MAPK activation and TGF-β1-mediated EMT in many tumors[14]. Mitochondria are very important in determining neoplastic degeneration due to their production of endogenous ROS that subvert the metabolic process and oxidative phosphorylation[102].

Oxidative stress induces the production of ROS-dependent cytokines such as TGF-β, IL-6, IL-13, and VEGFA. A change to the mitochondrial redox and consequently the acid-base balance of the tumor microenvironment could represent a therapeutic strategy to improve the cellular function of T lymphocytes during immunotherapy treatment[103].

**CONCLUSION**

The use of angiogenesis and oxidative stress markers could be useful for evaluating the efficacy of antineoplastic drugs, establishing the optimal dosage, escaping from the related toxicity, and predicting its response or resistance.

**REFERENCES**

1 **Carmeliet P**. Angiogenesis in health and disease. *Nat Med* 2003; **9**: 653-660 [PMID: 12778163 DOI: 10.1038/nm0603-653]

2 **Hanahan D**, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996; **86**: 353-364 [PMID: 8756718 DOI: 10.1016/s0092-8674(00)80108-7]

3 **Carmeliet P**, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; **407**: 249-257 [PMID: 11001068 DOI: 10.1038/35025220]

4 **Bremnes RM**, Dønnem T, Al-Saad S, Al-Shibli K, Andersen S, Sirera R, Camps C, Marinez I, Busund LT. The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. *J Thorac Oncol* 2011; **6**: 209-217 [PMID: 21107292 DOI: 10.1097/JTO.0b013e3181f8a1bd]

5 **Jain RK**. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. *J Clin Oncol* 2013; **31**: 2205-2218 [PMID: 23669226 DOI: 10.1200/JCO.2012.46.3653]

6 **Yeh HW**, Hsu EC, Lee SS, Lang YD, Lin YC, Chang CY, Lee SY, Gu DL, Shih JH, Ho CM, Chen CF, Chen CT, Tu PH, Cheng CF, Chen RH, Yang RB, Jou YS. PSPC1 mediates TGF-β1 autocrine signalling and Smad2/3 target switching to promote EMT, stemness and metastasis. *Nat Cell Biol* 2018; **20**: 479-491 [PMID: 29593326 DOI: 10.1038/s41556-018-0062-y]

7 **Luo J**, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. *Cell* 2009; **136**: 823-837 [PMID: 19269363 DOI: 10.1016/j.cell.2009.02.024]

8 **Solimini NL**, Luo J, Elledge SJ. Non-oncogene addiction and the stress phenotype of cancer cells. *Cell* 2007; **130**: 986-988 [PMID: 17889643 DOI: 10.1016/j.cell.2007.09.007]

9 **Ferrara N**. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004; **25**: 581-611 [PMID: 15294883 DOI: 10.1210/er.2003-0027]

10 **Yancopoulos GD**, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature* 2000; **407**: 242-248 [PMID: 11001067 DOI: 10.1038/35025215]

11 **Bussolino F**, Mantovani A, Persico G. Molecular mechanisms of blood vessel formation. *Trends Biochem Sci* 1997; **22**: 251-256 [PMID: 9255066 DOI: 10.1016/s0968-0004(97)01074-8]

12 **Franco M**, Roswall P, Cortez E, Hanahan D, Pietras K. Pericytes promote endothelial cell survival through induction of autocrine VEGF-A signaling and Bcl-w expression. *Blood* 2011; **118**: 2906-2917 [PMID: 21778339 DOI: 10.1182/blood-2011-01-331694]

13 **Gatenby RA**, Gawlinski ET, Gmitro AF, Kaylor B, Gillies RJ. Acid-mediated tumor invasion: a multidisciplinary study. *Cancer Res* 2006; **66**: 5216-5223 [PMID: 16707446 DOI: 10.1158/0008-5472.CAN-05-4193]

14 **Riemann A**, Schneider B, Gündel D, Stock C, Thews O, Gekle M. Acidic priming enhances metastatic potential of cancer cells. *Pflugers Arch* 2014; **466**: 2127-2138 [PMID: 24531759 DOI: 10.1007/s00424-014-1458-6]

15 **Jelic MD**, Mandic AD, Maricic SM, Srdjenovic BU. Oxidative stress and its role in cancer. *J Cancer Res Ther* 2021; **17**: 22-28 [PMID: 33723127 DOI: 10.4103/jcrt.JCRT\_862\_16]

16 **Matés JM**, Campos-Sandoval JA, de Los Santos-Jiménez J, Márquez J. Glutaminases regulate glutathione and oxidative stress in cancer. *Arch Toxicol* 2020; **94**: 2603-2623 [PMID: 32681190 DOI: 10.1007/s00204-020-02838-8]

17 **Hanikoglu A**, Ozben H, Hanikoglu F, Ozben T. Hybrid Compounds & Oxidative Stress Induced Apoptosis in Cancer Therapy. *Curr Med Chem* 2020; **27**: 2118-2132 [PMID: 30027838 DOI: 10.2174/0929867325666180719145819]

18 **Hu Y**, Ye Z, Wang F, Qin Y, Xu X, Yu X, Ji S. Role of Somatostatin Receptor in Pancreatic Neuroendocrine Tumor Development, Diagnosis, and Therapy. *Front Endocrinol (Lausanne)* 2021; **12**: 679000 [PMID: 34093445 DOI: 10.3389/fendo.2021.679000]

19 **Lamberts SW**, Krenning EP, Reubi JC. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocr Rev* 1991; **12**: 450-482 [PMID: 1684746 DOI: 10.1210/edrv-12-4-450]

20 **Patel YC**, Greenwood MT, Panetta R, Demchyshyn L, Niznik H, Srikant CB. The somatostatin receptor family. *Life Sci* 1995; **57**: 1249-1265 [PMID: 7674817 DOI: 10.1016/0024-3205(95)02082-t]

21 **Reisine T**, Bell GI. Molecular biology of somatostatin receptors. *Endocr Rev* 1995; **16**: 427-442 [PMID: 8521788 DOI: 10.1210/edrv-16-4-427]

22 **Dasgupta P**. Somatostatin analogues: multiple roles in cellular proliferation, neoplasia, and angiogenesis. *Pharmacol Ther* 2004; **102**: 61-85 [PMID: 15056499 DOI: 10.1016/j.pharmthera.2004.02.002]

23 **Florio T**, Morini M, Villa V, Arena S, Corsaro A, Thellung S, Culler MD, Pfeffer U, Noonan DM, Schettini G, Albini A. Somatostatin inhibits tumor angiogenesis and growth via somatostatin receptor-3-mediated regulation of endothelial nitric oxide synthase and mitogen-activated protein kinase activities. *Endocrinology* 2003; **144**: 1574-1584 [PMID: 12639942 DOI: 10.1210/en.2002-220949]

24 **Takahashi Y**, Akishima-Fukasawa Y, Kobayashi N, Sano T, Kosuge T, Nimura Y, Kanai Y, Hiraoka N. Prognostic value of tumor architecture, tumor-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumors. *Clin Cancer Res* 2007; **13**: 187-196 [PMID: 17200354 DOI: 10.1158/1078-0432.CCR-06-1408]

25 **Marion-Audibert AM**, Barel C, Gouysse G, Dumortier J, Pilleul F, Pourreyron C, Hervieu V, Poncet G, Lombard-Bohas C, Chayvialle JA, Partensky C, Scoazec JY. Low microvessel density is an unfavorable histoprognostic factor in pancreatic endocrine tumors. *Gastroenterology* 2003; **125**: 1094-1104 [PMID: 14517793 DOI: 10.1016/s0016-5085(03)01198-3]

26 **Li X**, Eriksson U. Novel VEGF family members: VEGF-B, VEGF-C and VEGF-D. *Int J Biochem Cell Biol* 2001; **33**: 421-426 [PMID: 11312110 DOI: 10.1016/s1357-2725(01)00027-9]

27 **Claesson-Welsh L**, Welsh M. VEGFA and tumour angiogenesis. *J Intern Med* 2013; **273**: 114-127 [PMID: 23216836 DOI: 10.1111/joim.12019]

28 **Wilkins SE**, Abboud MI, Hancock RL, Schofield CJ. Targeting Protein-Protein Interactions in the HIF System. *ChemMedChem* 2016; **11**: 773-786 [PMID: 26997519 DOI: 10.1002/cmdc.201600012]

29 **Comerford KM**, Wallace TJ, Karhausen J, Louis NA, Montalto MC, Colgan SP. Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. *Cancer Res* 2002; **62**: 3387-3394 [PMID: 12067980]

30 **Folkman J**. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; **285**: 1182-1186 [PMID: 4938153 DOI: 10.1056/NEJM197111182852108]

31 **Hanahan D**, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70 [PMID: 10647931 DOI: 10.1016/s0092-8674(00)81683-9]

32 **Folkman J**, Hanahan D. Switch to the angiogenic phenotype during tumorigenesis. *Princess Takamatsu Symp* 1991; **22**: 339-347 [PMID: 1726933]

33 **Hillen F**, Griffioen AW. Tumour vascularization: sprouting angiogenesis and beyond. *Cancer Metastasis Rev* 2007; **26**: 489-502 [PMID: 17717633 DOI: 10.1007/s10555-007-9094-7]

34 **Cha S**, Kim HG, Jang H, Lee J, Chao T, Baek NI, Song IS, Lee YM. Steppogenin suppresses tumor growth and sprouting angiogenesis through inhibition of HIF-1α in tumors and DLL4 activity in the endothelium. *Phytomedicine* 2023; **108**: 154513 [PMID: 36332389 DOI: 10.1016/j.phymed.2022.154513]

35 **Sajib S**, Zahra FT, Lionakis MS, German NA, Mikelis CM. Mechanisms of angiogenesis in microbe-regulated inflammatory and neoplastic conditions. *Angiogenesis* 2018; **21**: 1-14 [PMID: 29110215 DOI: 10.1007/s10456-017-9583-4]

36 **Weis SM**, Cheresh DA. Pathophysiological consequences of VEGF-induced vascular permeability. *Nature* 2005; **437**: 497-504 [PMID: 16177780 DOI: 10.1038/nature03987]

37 **Helmlinger G**, Yuan F, Dellian M, Jain RK. Interstitial pH and pO2 gradients in solid tumors in vivo: high-resolution measurements reveal a lack of correlation. *Nat Med* 1997; **3**: 177-182 [PMID: 9018236 DOI: 10.1038/nm0297-177]

38 **Ferretti S**, Allegrini PR, Becquet MM, McSheehy PM. Tumor interstitial fluid pressure as an early-response marker for anticancer therapeutics. *Neoplasia* 2009; **11**: 874-881 [PMID: 19724681 DOI: 10.1593/neo.09554]

39 **Saggar JK**, Tannock IF. Chemotherapy Rescues Hypoxic Tumor Cells and Induces Their Reoxygenation and Repopulation-An Effect That Is Inhibited by the Hypoxia-Activated Prodrug TH-302. *Clin Cancer Res* 2015; **21**: 2107-2114 [PMID: 25677696 DOI: 10.1158/1078-0432.CCR-14-2298]

40 **Abou Khouzam R**, Brodaczewska K, Filipiak A, Zeinelabdin NA, Buart S, Szczylik C, Kieda C, Chouaib S. Tumor Hypoxia Regulates Immune Escape/Invasion: Influence on Angiogenesis and Potential Impact of Hypoxic Biomarkers on Cancer Therapies. *Front Immunol* 2020; **11**: 613114 [PMID: 33552076 DOI: 10.3389/fimmu.2020.613114]

41 **Yeh JJ**, Kim WY. Targeting tumor hypoxia with hypoxia-activated prodrugs. *J Clin Oncol* 2015; **33**: 1505-1508 [PMID: 25800764 DOI: 10.1200/JCO.2014.60.0759]

42 **Thews O**, Vaupel P. Spatial oxygenation profiles in tumors during normo- and hyperbaric hyperoxia. *Strahlenther Onkol* 2015; **191**: 875-882 [PMID: 26135917 DOI: 10.1007/s00066-015-0867-6]

43 **Kim KJ**, Li B, Winer J, Armanini M, Gillett N, Phillips HS, Ferrara N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993; **362**: 841-844 [PMID: 7683111 DOI: 10.1038/362841a0]

44 **van Beijnum JR**, Nowak-Sliwinska P, Huijbers EJ, Thijssen VL, Griffioen AW. The great escape; the hallmarks of resistance to antiangiogenic therapy. *Pharmacol Rev* 2015; **67**: 441-461 [PMID: 25769965 DOI: 10.1124/pr.114.010215]

45 **Terris B**, Scoazec JY, Rubbia L, Bregeaud L, Pepper MS, Ruszniewski P, Belghiti J, Fléjou J, Degott C. Expression of vascular endothelial growth factor in digestive neuroendocrine tumours. *Histopathology* 1998; **32**: 133-138 [PMID: 9543669 DOI: 10.1046/j.1365-2559.1998.00321.x]

46 **Christofori G**, Naik P, Hanahan D. Vascular endothelial growth factor and its receptors, flt-1 and flk-1, are expressed in normal pancreatic islets and throughout islet cell tumorigenesis. *Mol Endocrinol* 1995; **9**: 1760-1770 [PMID: 8614412 DOI: 10.1210/mend.9.12.8614412]

47 **Konstantinova I**, Lammert E. Microvascular development: learning from pancreatic islets. *Bioessays* 2004; **26**: 1069-1075 [PMID: 15382139 DOI: 10.1002/bies.20105]

48 **Hanahan D**, Christofori G, Naik P, Arbeit J. Transgenic mouse models of tumour angiogenesis: the angiogenic switch, its molecular controls, and prospects for preclinical therapeutic models. *Eur J Cancer* 1996; **32A**: 2386-2393 [PMID: 9059326 DOI: 10.1016/s0959-8049(96)00401-7]

49 **Bergers G**, Javaherian K, Lo KM, Folkman J, Hanahan D. Effects of angiogenesis inhibitors on multistage carcinogenesis in mice. *Science* 1999; **284**: 808-812 [PMID: 10221914 DOI: 10.1126/science.284.5415.808]

50 **Inoue M**, Hager JH, Ferrara N, Gerber HP, Hanahan D. VEGF-A has a critical, nonredundant role in angiogenic switching and pancreatic beta cell carcinogenesis. *Cancer Cell* 2002; **1**: 193-202 [PMID: 12086877 DOI: 10.1016/s1535-6108(02)00031-4]

51 **Couvelard A**, O'Toole D, Turley H, Leek R, Sauvanet A, Degott C, Ruszniewski P, Belghiti J, Harris AL, Gatter K, Pezzella F. Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. *Br J Cancer* 2005; **92**: 94-101 [PMID: 15558070 DOI: 10.1038/sj.bjc.6602245]

52 **Besig S**, Voland P, Baur DM, Perren A, Prinz C. Vascular endothelial growth factors, angiogenesis, and survival in human ileal enterochromaffin cell carcinoids. *Neuroendocrinology* 2009; **90**: 402-415 [PMID: 19816005 DOI: 10.1159/000245900]

53 **Walter T**, Hommell-Fontaine J, Gouysse G, Pourreyron C, Nejjari M, Villaume K, Causeret S, Hervieu V, Poncet G, Roche C, Scoazec JY. Effects of somatostatin and octreotide on the interactions between neoplastic gastroenteropancreatic endocrine cells and endothelial cells: a comparison between in vitro and in vivo properties. *Neuroendocrinology* 2011; **94**: 200-208 [PMID: 21677423 DOI: 10.1159/000328134]

54 **Jain RK**. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; **307**: 58-62 [PMID: 15637262 DOI: 10.1126/science.1104819]

55 **Crawford Y**, Ferrara N. Tumor and stromal pathways mediating refractoriness/resistance to anti-angiogenic therapies. *Trends Pharmacol Sci* 2009; **30**: 624-630 [PMID: 19836845 DOI: 10.1016/j.tips.2009.09.004]

56 **Casanovas O**, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005; **8**: 299-309 [PMID: 16226705 DOI: 10.1016/j.ccr.2005.09.005]

57 **Brown AP**, Citrin DE, Camphausen KA. Clinical biomarkers of angiogenesis inhibition. *Cancer Metastasis Rev* 2008; **27**: 415-434 [PMID: 18414993 DOI: 10.1007/s10555-008-9143-x]

58 **Sosa V**, Moliné T, Somoza R, Paciucci R, Kondoh H, LLeonart ME. Oxidative stress and cancer: an overview. *Ageing Res Rev* 2013; **12:** 376-390 [PMID: 23123177 DOI: 10.1016/j.arr.2012.10.004]

59 **Simic MG**, Bergtold DS, Karam LR. Generation of oxy radicals in biosystems. *Mutat Res* 1989; **214**: 3-12 [PMID: 2671698 DOI: 10.1016/0027-5107(89)90192-9]

60 **Veskoukis AS**, Tsatsakis AM, Kouretas D. Dietary oxidative stress and antioxidant defense with an emphasis on plant extract administration. *Cell Stress Chaperones* 2012; **17**: 11-21 [PMID: 21956695 DOI: 10.1007/s12192-011-0293-3]

61 **Matsui A**, Ikeda T, Enomoto K, Hosoda K, Nakashima H, Omae K, Watanabe M, Hibi T, Kitajima M. Increased formation of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, in human breast cancer tissue and its relationship to GSTP1 and COMT genotypes. *Cancer Lett* 2000; **151**: 87-95 [PMID: 10766427 DOI: 10.1016/s0304-3835(99)00424-3]

62 **Halliwell B**, Chirico S. Lipid peroxidation: its mechanism, measurement, and significance. *Am J Clin Nutr* 1993; **57**: 715S-724S; discussion 724S-725S [PMID: 8475889 DOI: 10.1093/ajcn/57.5.715S]

63 **Levine RL**. Carbonyl modified proteins in cellular regulation, aging, and disease. *Free Radic Biol Med* 2002; **32**: 790-796 [PMID: 11978480 DOI: 10.1016/s0891-5849(02)00765-7]

64 **Pisoschi AM**, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. *Eur J Med Chem* 2015; **97**: 55-74 [PMID: 25942353 DOI: 10.1016/j.ejmech.2015.04.040]

65 **Yoshida T**, Oka S, Masutani H, Nakamura H, Yodoi J. The role of thioredoxin in the aging process: involvement of oxidative stress. *Antioxid Redox Signal* 2003; **5**: 563-570 [PMID: 14580311 DOI: 10.1089/152308603770310211]

66 **Ebert T**, Tran N, Schurgers L, Stenvinkel P, Shiels PG. Ageing - Oxidative stress, PTMs and disease. *Mol Aspects Med* 2022; **86**: 101099 [PMID: 35689974 DOI: 10.1016/j.mam.2022.101099]

67 **Matsuzawa A**, Ichijo H. Redox control of cell fate by MAP kinase: physiological roles of ASK1-MAP kinase pathway in stress signaling. *Biochim Biophys Acta* 2008; **1780**: 1325-1336 [PMID: 18206122 DOI: 10.1016/j.bbagen.2007.12.011]

68 **Nguyen T**, Nioi P, Pickett CB. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. *J Biol Chem* 2009; **284**: 13291-13295 [PMID: 19182219 DOI: 10.1074/jbc.R900010200]

69 **Wiemer EA**. Stressed tumor cell, chemosensitized cancer. *Nat Med* 2011; **17**: 1552-1554 [PMID: 22146456 DOI: 10.1038/nm.2593]

70 **Luo Y**, Zou P, Zou J, Wang J, Zhou D, Liu L. Autophagy regulates ROS-induced cellular senescence via p21 in a p38 MAPKα dependent manner. *Exp Gerontol* 2011; **46**: 860-867 [PMID: 21816217 DOI: 10.1016/j.exger.2011.07.005]

71 **Wu Z**, Wang L, Wen Z, Yao J. Integrated analysis identifies oxidative stress genes associated with progression and prognosis in gastric cancer. *Sci Rep* 2021; **11**: 3292 [PMID: 33558567 DOI: 10.1038/s41598-021-82976-w]

72 **Hybertson BM**, Gao B, Bose SK, McCord JM. Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation. *Mol Aspects Med* 2011; **32**: 234-246 [PMID: 22020111 DOI: 10.1016/j.mam.2011.10.006]

73 **Khor TO**, Huang MT, Kwon KH, Chan JY, Reddy BS, Kong AN. Nrf2-deficient mice have an increased susceptibility to dextran sulfate sodium-induced colitis. *Cancer Res* 2006; **66**: 11580-11584 [PMID: 17178849 DOI: 10.1158/0008-5472.CAN-06-3562]

74 **Yu R**, Lei W, Mandlekar S, Weber MJ, Der CJ, Wu J, Kong AN. Role of a mitogen-activated protein kinase pathway in the induction of phase II detoxifying enzymes by chemicals. *J Biol Chem* 1999; **274**: 27545-27552 [PMID: 10488090 DOI: 10.1074/jbc.274.39.27545]

75 **Zhang Z**, Teruya K, Eto H, Shirahata S. Fucoidan extract induces apoptosis in MCF-7 cells via a mechanism involving the ROS-dependent JNK activation and mitochondria-mediated pathways. *PLoS One* 2011; **6**: e27441 [PMID: 22096572 DOI: 10.1371/journal.pone.0027441]

76 **Singh A**, Misra V, Thimmulappa RK, Lee H, Ames S, Hoque MO, Herman JG, Baylin SB, Sidransky D, Gabrielson E, Brock MV, Biswal S. Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. *PLoS Med* 2006; **3**: e420 [PMID: 17020408 DOI: 10.1371/journal.pmed.0030420]

77 **Kim YR**, Oh JE, Kim MS, Kang MR, Park SW, Han JY, Eom HS, Yoo NJ, Lee SH. Oncogenic NRF2 mutations in squamous cell carcinomas of oesophagus and skin. *J Pathol* 2010; **220**: 446-451 [PMID: 19967722 DOI: 10.1002/path.2653]

78 **Rosen EM**, Fan S, Pestell RG, Goldberg ID. BRCA1 gene in breast cancer. *J Cell Physiol* 2003; **196**: 19-41 [PMID: 12767038 DOI: 10.1002/jcp.10257]

79 **Bae I**, Fan S, Meng Q, Rih JK, Kim HJ, Kang HJ, Xu J, Goldberg ID, Jaiswal AK, Rosen EM. BRCA1 induces antioxidant gene expression and resistance to oxidative stress. *Cancer Res* 2004; **64**: 7893-7909 [PMID: 15520196 DOI: 10.1158/0008-5472.CAN-04-1119]

80 **Benezra M**, Chevallier N, Morrison DJ, MacLachlan TK, El-Deiry WS, Licht JD. BRCA1 augments transcription by the NF-kappaB transcription factor by binding to the Rel domain of the p65/RelA subunit. *J Biol Chem* 2003; **278**: 26333-26341 [PMID: 12700228 DOI: 10.1074/jbc.M303076200]

81 **Seo Y**, Kinsella TJ. Essential role of DNA base excision repair on survival in an acidic tumor microenvironment. *Cancer Res* 2009; **69**: 7285-7293 [PMID: 19723658 DOI: 10.1158/0008-5472.CAN-09-0624]

82 **Yagoda N**, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, Wolpaw AJ, Smukste I, Peltier JM, Boniface JJ, Smith R, Lessnick SL, Sahasrabudhe S, Stockwell BR. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. *Nature* 2007; **447**: 864-868 [PMID: 17568748 DOI: 10.1038/nature05859]

83 **Maciag A**, Sithanandam G, Anderson LM. Mutant K-rasV12 increases COX-2, peroxides and DNA damage in lung cells. *Carcinogenesis* 2004; **25**: 2231-2237 [PMID: 15284181 DOI: 10.1093/carcin/bgh245]

84 **Weyemi U**, Lagente-Chevallier O, Boufraqech M, Prenois F, Courtin F, Caillou B, Talbot M, Dardalhon M, Al Ghuzlan A, Bidart JM, Schlumberger M, Dupuy C. ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. *Oncogene* 2012; **31**: 1117-1129 [PMID: 21841825 DOI: 10.1038/onc.2011.327]

85 **Graham KA**, Kulawiec M, Owens KM, Li X, Desouki MM, Chandra D, Singh KK. NADPH oxidase 4 is an oncoprotein localized to mitochondria. *Cancer Biol Ther* 2010; **10**: 223-231 [PMID: 20523116 DOI: 10.4161/cbt.10.3.12207]

86 **Wang XQ**, Li H, Van Putten V, Winn RA, Heasley LE, Nemenoff RA. Oncogenic K-Ras regulates proliferation and cell junctions in lung epithelial cells through induction of cyclooxygenase-2 and activation of metalloproteinase-9. *Mol Biol Cell* 2009; **20**: 791-800 [PMID: 19037103 DOI: 10.1091/mbc.e08-07-0732]

87 **Mulholland DJ**, Kobayashi N, Ruscetti M, Zhi A, Tran LM, Huang J, Gleave M, Wu H. Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. *Cancer Res* 2012; **72**: 1878-1889 [PMID: 22350410 DOI: 10.1158/0008-5472.CAN-11-3132]

88 **Indran IR**, Hande MP, Pervaiz S. Tumor cell redox state and mitochondria at the center of the non-canonical activity of telomerase reverse transcriptase. *Mol Aspects Med* 2010; **31**: 21-28 [PMID: 19995569 DOI: 10.1016/j.mam.2009.12.001]

89 **Karnewar S**, Pulipaka S, Katta S, Panuganti D, Neeli PK, Thennati R, Jerald MK, Kotamraju S. Mitochondria-targeted esculetin mitigates atherosclerosis in the setting of aging via the modulation of SIRT1-mediated vascular cell senescence and mitochondrial function in Apoe(-/-) mice. *Atherosclerosis* 2022; **356**: 28-40 [PMID: 35961209 DOI: 10.1016/j.atherosclerosis.2022.07.012]

90 **Dickinson EK**, Adams DL, Schon EA, Glerum DM. A human SCO2 mutation helps define the role of Sco1p in the cytochrome oxidase assembly pathway. *J Biol Chem* 2000; **275**: 26780-26785 [PMID: 10854440 DOI: 10.1074/jbc.M004032200]

91 **Kim HS**, Patel K, Muldoon-Jacobs K, Bisht KS, Aykin-Burns N, Pennington JD, van der Meer R, Nguyen P, Savage J, Owens KM, Vassilopoulos A, Ozden O, Park SH, Singh KK, Abdulkadir SA, Spitz DR, Deng CX, Gius D. SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. *Cancer Cell* 2010; **17**: 41-52 [PMID: 20129246 DOI: 10.1016/j.ccr.2009.11.023]

92 **Bell EL**, Emerling BM, Ricoult SJ, Guarente L. SirT3 suppresses hypoxia inducible factor 1α and tumor growth by inhibiting mitochondrial ROS production. *Oncogene* 2011; **30**: 2986-2996 [PMID: 21358671 DOI: 10.1038/onc.2011.37]

93 **Gustafsson BI**, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. *Cancer* 2008; **113**: 5-21 [PMID: 18473355 DOI: 10.1002/cncr.23542]

94 **Klöppel G**. Tumour biology and histopathology of neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab* 2007; **21**: 15-31 [PMID: 17382263 DOI: 10.1016/j.beem.2007.01.004]

95 **WHO Classification of Tumours Editorial Board.** Thoracic Tumours. 5th ed. Lyon, France: International Agency for Research on Cancer; 2021. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Thoracic-Tumours-2021

96 **Brambilla E**, Lantuejoul S, Sturm N. Divergent differentiation in neuroendocrine lung tumors. *Semin Diagn Pathol* 2000; **17**: 138-148 [PMID: 10839614]

97 **Laennec R**. Traite de l’auscultation mediate et des maladies des poumons et du coeur. 1831, Paris: Mériadec Laënnec. Available from: https://gallica.bnf.fr/ark:/12148/bpt6k9738708j/f26.item.texteImage

98 **Hamanaka RB**, Chandel NS. Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. *Trends Biochem Sci* 2010; **35**: 505-513 [PMID: 20430626 DOI: 10.1016/j.tibs.2010.04.002]

99 **Sabharwal SS**, Schumacker PT. Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? *Nat Rev Cancer* 2014; **14**: 709-721 [PMID: 25342630 DOI: 10.1038/nrc3803]

100 **Mittal M**, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal* 2014; **20**: 1126-1167 [PMID: 23991888 DOI: 10.1089/ars.2012.5149]

101 **Karin M**. NF-kappaB as a critical link between inflammation and cancer. *Cold Spring Harb Perspect Biol* 2009; **1**: a000141 [PMID: 20066113 DOI: 10.1101/cshperspect.a000141]

102 **Lamouille S**, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2014; **15**: 178-196 [PMID: 24556840 DOI: 10.1038/nrm3758]

103 **Murphy MP**. How mitochondria produce reactive oxygen species. *Biochem J* 2009; **417**: 1-13 [PMID: 19061483 DOI: 10.1042/BJ20081386]

**Footnotes**

**Conflict-of-interest statement:** All the authors declare that they have no conflicts of interest.

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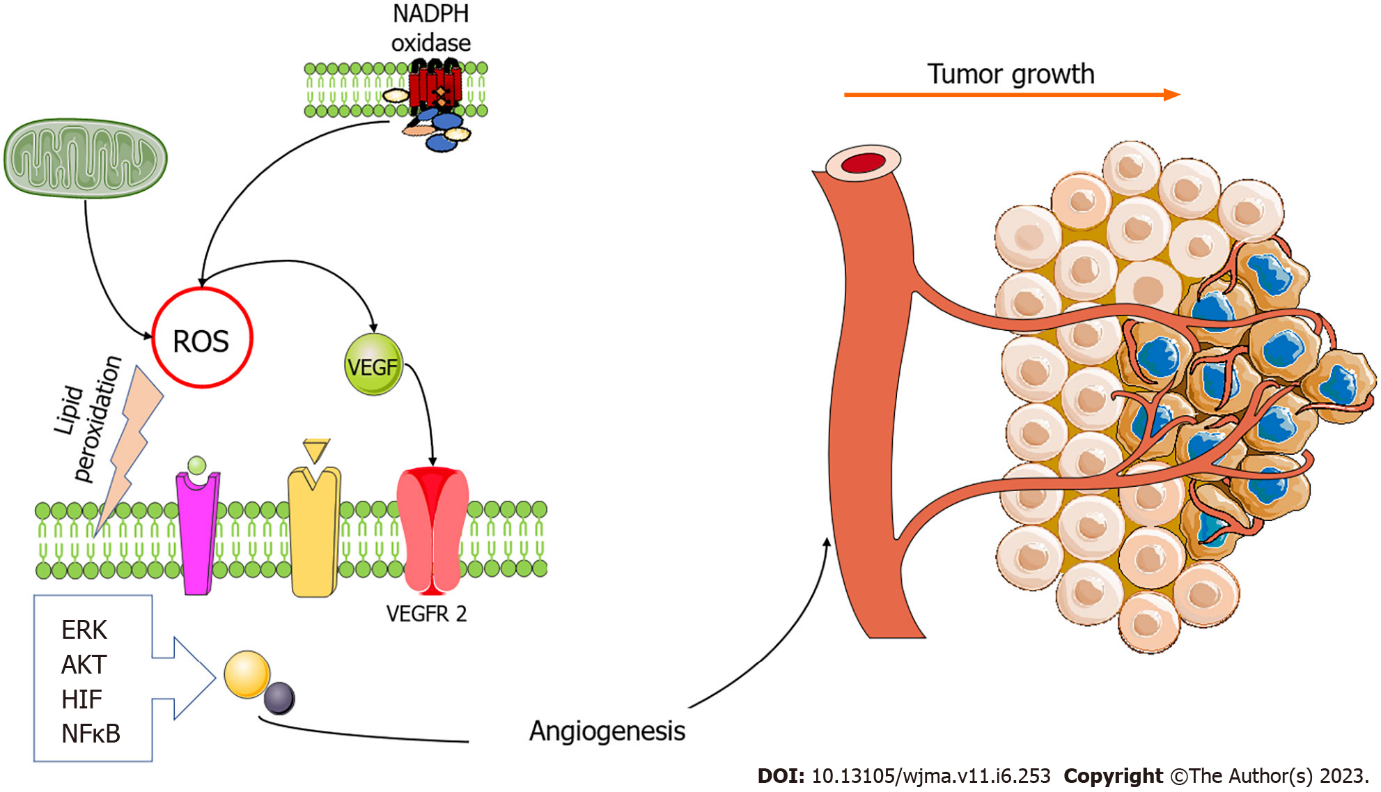
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**Figure Legends**



**Figure 1 The two main sources of oxidative stress, mitochondria, and nicotinamide adenine dinucleotide oxidases generate reactive oxygen species that trigger angiogenesis.** The vascular endothelial growth factor (VEGF) pathway is modulated by reactive oxygen species (ROS), and oxidative stress stimulates VEGF production in several cell types, including endothelial cells. ROS enhance angiogenesis by increasing hypoxia-inducible factor (HIF) 1 α, protein kinase B (AKT), and regulated extracellular kinase (ERK). However, oxidative stress also induces angiogenesis in a VEGF-independent manner by lipid peroxidation and generating metabolites that act either as ligands or by inducing post-translational modifications of proteins within angiogenic signaling pathways, such as nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) activation pathways. Figure was prepared using images from Servier Medical Art by Servier (https://smart.servier.com), which are licensed under a Creative Commons Attribution 3.0 Unsupported License. NADPH: Nicotinamide adenine dinucleotide; VEGFR2: Vascular endothelial growth factor receptor 2.

**Table 1** **Proliferation, migration, and differentiation by several factors/inductors implicated in angiogenesis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Inductors** | **Proliferation** | **Migration** | **Differentiation** |
| Heparin-binding peptide growth factors | | | |
| VEGF | Yes | Yes | Yes |
| PlGF | Weak | Yes | Unknown |
| FGF-1, FGF-2 | Yes | Yes | Yes |
| PTN | Yes | Unknown | Yes |
| HIV-tat protein | Weak | Weak | Yes |
| PDGF | Yes | Yes | Yes |
| HGF/SF | Yes | Yes | Yes |
| Peptide growth factors that do not bind heparin | | | |
| TGF- | Yes | Yes | Yes |
| TGF- | Inhibition | No | Yes |
| EGF | Yes | Yes | Yes |
| IGF-I | Yes | Yes | Yes |
| Inflammatory mediators | | | |
| TNF- | Inhibition | No | Yes |
| IL-8 | Yes | Yes | Unknown |
| IL-3 | Yes | Yes | Yes |
| Prostaglandins E1, E2 | No | No | Yes |
| Enzymes | | | |
| PD-ECGF/TP | No | Yes | Unknown |
| COX-2 | No | Yes | Yes |
| Angiogenin | No | Yes | Yes |
| Hormones | | | |
| Estrogen | Yes | Yes | Yes |
| Proliferin | Unknown | Yes | Unknown |
| Oligosaccharides | | | |
| Hyaluronan oligosaccharides | Yes | Yes | Yes |
| Gangliosides | Unknown | Unknown | Unknown |
| Hematopoietic factors | | | |
| Erythropoietin | Yes | Unknown | Yes |
| G-CSF | Yes | Yes | Unknown |
| GM-CSF | Yes | Yes | Unknown |
| Cell adhesion molecules | | | |
| VCAM-1 | No | Yes | Unknown |
| E-selectins | No | Yes | Yes |
| Integrins | No | Yes | Yes |
| Semaphorins (Sema3 e 4D) | No | Yes | Yes |
| Other | | | |
| Nitric oxide | Yes | Unknow | Unknow |
| Angiopoietin-1 | No | Yes | Yes |

COX-2: Cyclooxygenase 2; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; HGF/SF: Hepatocyte growth factor/scatter factor; IGF: Insulin-like growth factor; IL: Interleukin; PD-ECGF/TP: Platelet-derived endothelial cell growth factor/thymidine phosphorylase; PlGF: Placental growth factor; PDGF: Platelet-derived growth factor; PTN, Pleiotrophin; TGF: Transforming growth factor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; VCAM: Vascular cell adhesion molecule.

**Table 2 Molecular target of oxidative stress to promote tumor progression**

|  |  |  |  |
| --- | --- | --- | --- |
| **Molecular target of ROS** | **Protein or gene** | **Function and mechanism** | **Tumor type** |
| **ERK1/ERK2** | Protein | Promotion of cell proliferation and angiogenesis | Ovarian, colon, breast, and lung cancer |
| **Nrf2** | Protein | Regulation of oxidative stress by modulating the production of antioxidant enzymes | NSCLC and esophageal cancer |
| **Ref1 /APE1** | Protein | Reduction of ROS generation | Breast cancer |
| **PTEN** | Protein | Involvement in senescence; Association with high levels of Akt and ROS | Lung, liver, and breast cancer |
| **Ras** | Protein | Increases mitochondrial mass and ROS levels, causing DNA damage; Regulation of Nox4-p22phox system | 30% of human cancer |
| **mTOR** | Protein | Promotion of cell proliferation and metabolism that contributes to tumor initiation and progression; Regulation of autophagy and apoptosis | More than 70% of cancers (breast, lung, colorectal, prostate, head and neck, gynecologic, urinary bladder, renal cancer gastric carcinoma, glioblastoma, lymphoma, and medulloblastoma) |
| **P38** | Protein | Regulation of cell proliferation, cell differentiation, cell death, cell migration, and invasion. | Prostate, breast, bladder, live, and lung cancer, transformed follicular lymphoma and leukemia |
| ***BRCA*** | Gene | Regulation of antioxidant response; Controlling the Nrf2 and NFκB activity | 40%-50% of hereditary breast cancers |
| **hTERT** | Protein | Reduces oxidative stress intracellularly and extracellularly; Regulation of apoptosis | Gastric cancer, lung cancer, cervical and head cancer, glioblastoma, breast cancer, and ovarian cancer |
| **Angiopoietin** | Protein | Involvement in angiogenesis, lymphangiogenesis, and metastasis; Induction of hypoxia and cytokines | NSCLC |

Akt: Protein kinase B; *BRCA*: Breast cancer gene; ERK1/2:Extracellular kinase 1/2; hTERT: Human telomerase reverse transcriptase; NRF2: Nuclear factor erythroid 2-related factor 2; NSCLC: Non-small cell lung carcinoma; PTEN: Phosphatase and homolog of tensin; mTOR: Mammalian target of rapamycin; Ref/APE1: Redox factor/Apurinic/apyrimidinic endonuclease 1; ROS: Reactive oxygen species.



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