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REVIEW

ROS-mediated regulation of CXCR4 in cancer

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Abstract **Oxidative stress and the accumulation of reactive oxygen specie (ROS) play a role in cancer cells developing an advanced, phenotypic signature that associates with metastasis and progression. Increased ROS concentrations are involved in promoting cancer development and metastasis by inducing expression of oncogenes, suppressing activity of anti-survival molecules and by activating various cell survival and proliferation signaling pathways. Oxidative stress is higher in the epithelium of cancer patients than patients without the disease, and antioxidant trials are currently being explored as a therapeutic option. However, studies have shown that ROS increases expression of CXCR4 in cancer and immune cells. CXCR4 expression in tumors strongly correlates to metastasis and poor prognosis. Herein, we discuss an emerging relationship between ROS and CXCR4 in cancer cells.**

Keywords reactive oxygen species, CXCR4, HIF1α, metastasis, PI3K/AKT, ERK1/2

Introduction

The tumor microenvironment is a major player in cancer progression and metastasis. Some metastatic influences from the tumor microenvironment are due to various secreted molecules from immune cells, such as cytokines and chemokines, which results in decreased function of tumor suppressor genes, increased function of proto-oncogenes and cell survival signaling (Liu et al., 2011). The tumor microenvironment also secretes reactive oxygen species (ROS), which modulate anti-cancer and pro-cancer pathways to enhance tumorigenesis (Cook et al., 2004). ROS are a group of highly reactive oxygen containing molecules, where their accumulation typically functions as second messengers in intracellular signal transduction, and consequently, enhances cancer cell survival, proliferation and migration (Storz, 2005; Pan et al., 2009). Excessive accumulation of ROS, however, result in deleterious effects, such as genotoxicity and cell death (Simon et al., 2000).

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Reactive oxygen species

Reactive oxygen species are oxygen-derived free radicals, such as superoxide anion ($O_2^{\cdot -}$), hydroxyl radicals (OH^-), peroxyl ($RO_2^{\cdot}$), and oxygen-derived nonradical species like hydrogen peroxide (H_2O_2) (Turrens, 2003). The major cellular source of ROS is through the mitochondrial complexes I and III, where electrons from NADH or $FADH_2$ react with oxygen to produce superoxide anions (Turrens, 2003). ROS is also produced in the cytosol by intracellular enzymes such as oxidases, lipoxygenases and cyclooxygenases (Turrens, 2003). It is well established that ROS is implicated in oxidizing biomolecules such as DNA, lipids and protein, which over time can lead to cell death (Davies, 1993; Lindahl, 1993; Wagner et al., 1994). Under physiologic conditions, to prevent cellular damage, cells have developed several antioxidant systems to defend against the deleterious effects of ROS. Some of the main antioxidant systems used to maintain ROS homeostasis, are the glutathione, thioredoxin, superoxide dismutase (SOD) and catalase systems (Circu and Aw, 2010).

Interestingly, accumulating studies show that ROS play a critical role in regulating normal cellular function through gene transcription, cell signaling and post-translational modification (Pan et al., 2009; Chetram et al., 2011). It has recognized that loss of ROS homeostasis results in pathogenic effects and fatal diseases, such as diabetes, cardiovascular disease and cancer (Galaris et al., 2008; Hambali et al., 2011; Rains and Jain, 2011).

Reactive oxygen species in cancer

Tumorigenesis is characterized by a profound reprogramming of the genome, which ultimately activates oncogenes and inhibits tumor suppressor genes. Part of this reprogramming is due to elevated levels of ROS, which occurs as a result of the close proximity of DNA to hydroxyl radical generation, consequently modifying purine, pyrimidine and deoxyribose residues (Fraga et al., 1990). In cancer cells, increased ROS accumulation is generally due to loss of antioxidant or increased expression of pro-oxidants. For instance, Nelson et al. (2004) has observed somatic silencing of glutathione S-transferase (GSTP1), a member of cellular antioxidant systems, in almost all prostate cancer cases that were investigated. In addition to prostate cancer, GSTP1 was also silenced in various other malignancies, such as hepatocellular carcinoma and breast cancer (Tchou et al., 2000; Cho et al., 2012). Conversely, cancer cells also induce ROS generation through the expression of various pro-oxidants molecules, such as NOX and PUMA, and through changes in mitochondrial functions. Additionally, current evidence suggest that the tumor microenvironment consisting of immune cells, fibroblast cells and stromal cells work together to enhance the production of ROS, thereby promoting cancer progression (Cook et al., 2004). Together, the loss of antioxidants mechanisms and the gain of pro-oxidant mechanisms regulate ROS to facilitate tumor development and progression (Liou and Storz, 2010).

It is well established that ROS functions as a secondary-messenger that regulates cell survival pathways and ultimately promoting malignant transformation and progression (Storz, 2005). Emerging evidence indicates that ROS also promotes post-translation modification of kinases, phosphatases, tumor suppressors and oncogenic molecules, such as kinase p21ras, PTEN, p53 and HIF1α, respectively (Lee et al., 2002; Salmeen et al., 2003), and mediates cell survival and metastasis by regulating pathways such as PI3K/AKT and MAPK/ERK1/2 in the prostate, breast and leukemia (Kumar et al., 2008; Tomic et al., 2011). For instance, hydrogen peroxide activated the MAPK pathway to provide cellular protection and proliferation in response to oxidative stress, which correlated with sustained activation of protein kinase C (PKC) (Guyton et al., 1996; Wu et al., 2006). Ha and Yu (2010) described that ROS enhanced hepatocellular carcinogenesis via inhibition of PTEN in favor of AKT. Our laboratory, and others, also observed an inactivation of PTEN catalytic function by ROS, which correlated with increased expression of phosphorylated AKT (p-AKT) (Ha and Yu, 2010; Chetram et al., 2011). Moreover, ROS regulates transcription factors, directly or indirectly, resulting in cell cycle induction and apoptosis suppression (Gupta et al., 1999). Transcription factors such as Sp1, glucocorticoid receptor and Egr1 were described as redox-sensitive, and underwent modifications of their DNA binding domains or posttranslational modification sites to promote or inhibit gene expression (Ammendola et al., 1994; Esposito et al., 1995; Landriscina et al., 2009).

Chemokine (CXC) receptor 4 (CXCR4)

The secreted chemokine protein family mediates cellular functions, such as: (i) regulation of hematopoiesis; (ii) leukocyte maturation; (iii) angiogenesis; (iv) cellular trafficking; (v) homing of immune cells; and (vi) and development of lymphoid tissue (Hinton et al., 2010). Chemokine proteins were initially characterized by their ability to induce leukocyte migration recruitment (Loetscher et al., 2000). Since then, chemokines and their roles have been characterized in a variety of host tissues, and the roles that have been ascribed to chemokines make them favorable to cancer development, progression and metastasis: (i) immune cell induction and migration to a site of infection; and (ii) regulation of cell migration during normal tissue maintenance or development (Hinton et al., 2010).

Chemokine receptors are G protein-linked, transmembrane proteins found on the surfaces of endo- and epithelial cells of many tissues (Gupta et al., 1998). The family roster includes approximately 45 ligands and 19 receptors. As many as six receptors show affinity for one specific ligand. However, most ligands have an affinity for several receptors, and can bind to non-G protein coupled receptors (Lau et al., 2004). The subsequent activation of a chemokine receptor involves classical pathways of cell survival: phospholipase C (PLC-β), PI3K/AKT, and the MAPK cascade (Hinton et al., 2010). Stromal-cell derived factor 1α (SDF1α or CXCL12) is a conserved member of the α-chemokine subfamily and is considered the exclusive ligand for CXCR4 receptor (Balabanian et al., 2005). It has been suggested that SDF1α may also bind CXCR7; and ubiquitin was recently identified as an alternate ligand for CXCR4 (Cruz-Orengo et al., 2011; Saini et al., 2011).

Chemokine receptors are associated with a myriad of inflammatory illnesses (cardiovascular, allergic inflammatory, neuro-inflammatory and HIV-associated diseases) and cancer (Gerard and Rollins, 2001). The interaction between chemokines and their receptors have been shown to induce cell migration, cytoskeletal rearrangement, and adhesion of malignant cells onto endothelial cells for invasion, as activation of CXCR4-induced migration of immune cells, as well as embryonic development, growth regulation, angiogenesis, and hematopoiesis (Kucia et al., 2004; Wang et al., 2007). Studies have also implicated CXCR4 in malignant cancer development by its involvement in: (i) cell motility; (ii) adhesion; (iii) secretion of matrix metalloproteinases (MMPs); (iv) angiogenesis and (v) activation of metastatic-associated signaling pathways (G-proteins, PI3K/AKT, JAK/STAT, Src kinase and HER2) (Busillo and Benovic, 2007; Wang et al., 2007), which has been well demonstrated in several human malignancies.

Cancer mortality is often a result of primary tumor cell metastasis to distal organs, where the expression of CXCR4 tightly correlates with a metastatic cell phenotype. Müller et al. (2001) observed that CXCR4 was higher in malignant breast tumors compared to their normal, healthy counterparts, suggesting that CXCR4 expression correlated with increased metastasis- associated mortality. Tanabe et al. (1997) demonstrated that the expression of CXCR4 in surgically resected invasive ductal carcinomas significantly correlated with the degree of lymph node metastasis. Likewise, Taichman et al. (2002) observed that CXCR4 facilitated prostate cancer metastasis to the bone, the primary site of distal prostate cancer colonization.

ROS-mediated regulation of CXCR4

In cancer and other cell models, CXCR4 and SDF1α are upregulated in high ROS concentrations and/or hypoxic environments, where oxygen levels are reduced below normal conditions (Li et al., 2009). In these conditions, cells react by inducing expression of a hypoxia-inducible factor (HIF) transcription complex, which enhances the expression of targeted genes involved in adjusting to low oxygen concentrations (Fig. 1). A survey of malignant tissues demonstrated an increase in HIF1α expression in bladder, breast, colon and prostate tumors, which correlated with CXCR4 and SDF1α expression in breast tumors (Talks et al., 2000; Staller et al., 2003; Zhong et al., 2004). The heterodimeric HIF transcription complex consists of a regulatory HIF1α subunit and the constitutively expressed HIF1β subunit, both members of the basic helix-loop-helix (bHLH) and PER-ARNT-SIM (PAS) families of transcription factors (Wang et al., 1995). The HIF1α subunit acts as a transcription factor for CXCR4 by binding to the HIF1α response element (HRE) found in the promoter region of CXCR4 (Staller et al., 2003). Therefore, a tumor microenvironment that is rich in ROS may critically influence CXCR4-mediated expression and functions, ultimately encouraging cancer progression.

ROS-mediated regulation of CXCR4 expression and function is fairly new in cancer research. Wu et al. (2006) described that ROS sustained PKC and ERK1/2 activation, which led to epithelial-mesenchymal transition (EMT)-like scattering, migration and reduced growth of hepatoma cells. Models of ROS regulation of CXCR4 are scarcely described, but have been shown in immune cells. Lee et al. (2007) demonstrated that depletion of ROS by a ROS scavenger, N-acetylcysteine (NAC), promoted CXCR4-mediated activation of AKT in B cells. Lin et al. (2011) described that CXCR4 induced ROS production in hematopeoic stem cells. Finally, loss of ROS reduced secretion of SDF1α from human bone marrow osteoblasts and endothelial cells (Dar et al., 2011). We have shown in prostate cancer cells that ROS oxidized PTEN, rendering it inactive, which may have explained the concomitant increase in expression of p-AKT by ROS, and further suggest a regulatory role of ROS in cancer cells

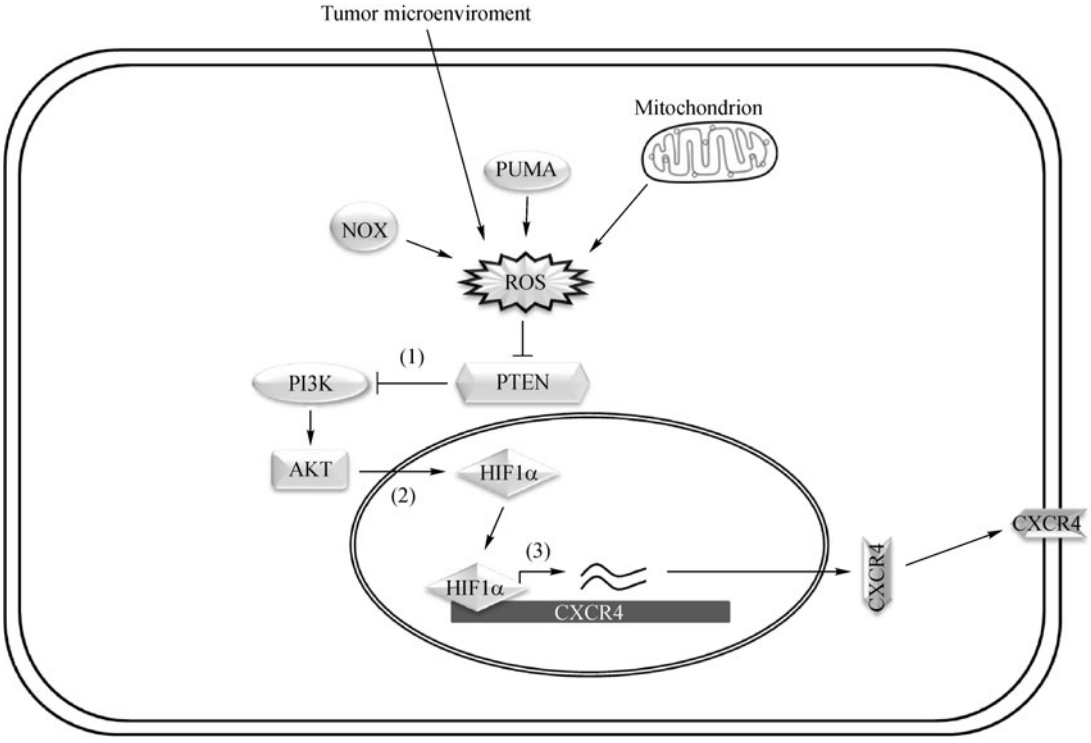

Figure 1 A schematic of ROS-mediated regulation of CXCR4 expression in cancer cells as described by (1) Chetram et al. (2011), (2) Lui et al. (2006) and (3) Staller et al. (2003).

(Chetram et al., 2011). Likewise, we observed an increase in CXCR4 expression upon ROS treatment, which also correlated with increased expression of p-AKT (Chetram et al., 2011). ROS enhanced prostate cancer cell migration and invasion in a CXCR4-dependent manner, which was abrogated my CXCR4 antagonist AMD3100 (Chetram et al., 2011).

ROS is used in current therapy to induce apoptosis in tumors (Ozben, 2007). Drugs, such as anthracyclines and epipodophyllotoxins, are used to induce ROS accumulation in cancer cells, hoping to create oxidative stress and induce cell death (Ozben, 2007). Conversely, the accumulation of ROS has been shown to activate survival pathways in cancer cells (Liu et al., 2006). Our findings in prostate cancer, along with immune studies, demonstrate that ROS may act as an inducing molecule, resulting in increased CXCR4 expression and subsequent cell survival mechanisms. Therefore, cells may increase ROS generation and expression of survival genes, like CXCR4, to escape oxidative stress and avoid death (Pani et al., 2010). We and others observed an increase in p-AKT expression, which activates HIF1α and may have led to the correlating increase in CXCR4 (Liu et al., 2006; Kumar et al., 2008; Chetram et al., 2011). We have also demonstrated that an absence of PTEN increased CXCR4 expression and function (Chetram et al., 2011). Interestingly, ROS inactivated PTEN through oxidation at cysteine residues, which further correlated with increased p-AKT expression and CXCR4 function, and elucidates a putative mechanism for cancer cell survival (Lee et al., 2002; Chetram et al., 2011). Moreover, p-AKT increased expression may be due to ROS-mediated inactivation of PTEN, and ultimately, CXCR4 expression. Therefore, it is possible that ROS may activate HIF1α and subsequently induce the expression of CXCR4 for cell survival (Li et al., 2009). To our knowledge, we are first in describing a link between ROS and CXCR4, which may suggest a potential mechanism of how cells may acquire increased CXCR4 and a metastatic phenotype, and a tendency to move to a distal organ. Concentrations of ROS have been generally considered apoptotic in cancer cells. We believe that ROS concentrations should be considered during therapeutic treatments, since survival mechanisms and metastasis can inadvertently be induced. Several key questions remain about ROS and CXCR4-mediated cancer progression, such as (i) whether survival mechanisms have already been activated in the primary tumor; or (ii) whether primary tumors induce survival mechanism after exposure to ROS, hypoxia and other deleterious microenvironments. ROS and oxidative stress have long been associated with tumor progression; however, the underlying mechanisms are well defined (Kumar et al., 2008). To improve the efficacy of oxidant cancer therapy, studies should consider neutralizing ROS molecules, instead of increasing concentrations, or take into account the stage and grade of tumors since oxidative stress can encourage a metastatic signature in cancer cells (Kumar et al., 2008).

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