ABSTRACT

The essay reviews the expression of NADPH oxidase (NOX4). It looks into how facilitates the generation of ROS and the physical and chemical properties of NOX4 relates with ROS. NOX4 plays a vital role in various types of cancers including lung cancer, colorectal cancer, breast cancer, hepatocellular cancer, and endometriosis ovarian cancer. Lastly, the essay discussed the expressions of NOX4 in many cancers and its significance.

KEYWORDS: NOX 4; NADPH; ROS; Tumorigenesis; Angiogenesis; Cancer.

1 NADPH oxidase-4 (NOX4) and reactive oxygen species (ROS)

NADPH oxidase 4 (NOX4) is a type of enzyme that the NOX4 gene encodes (Babior, 2004). It belongs to the family of NADPH oxidases. It plays a vital role in regulating some cellular functions that include cell growth, death, and cell expression. Vallet et al. (2005) research found that constitutive NADPH oxidase helps on the intracellular generation of superoxide when a complex is formed with CYBA, p22phox. NADPH also employs phosphatases inhibition in the regulation of signaling cascades (Anilkumar et al. 2008). It may work as an oxygen sensor that regulates the HIF activity and sets the KCNK3/TASK-1 (Han et al., 2016).

Regarding the essence of NOX4, its oxygen sensing ability supports hemostasis in aerobic organisms. Phagocyte-Type works as an oxygen sensor helping in the regulation of the synthesis of erythropoietin found in the renal cortex (Li et al., 2006). This occurs in the kidney. Martyn et al. (2006) noted that NOX4 safeguards the vasculature from the risk of inflammatory stress. In cases of high NOX4 expressing cancer cells, the modulation of NOX4-dependent reactive oxygen species by amino endoperoxides can induce apoptosis (Kleinschnitz et al.2010). NADP participates in the resorption of bones, lipopolysaccharide-mediated activation of NFkB, and apoptosis (Amatore et al. 2015). It also helps in the production of superoxide in the nucleus. It is also involved in the regulation of the gene expression when cell simulation occurs (Amara et al., 2010). It is essential to note that isoform 3 remains no functional. On the other hand, isoform 5 and isoform 6 exhibits low activity level. NADPH stimulates the production of superoxide which is one of the dominant reactive oxygen species in the arteries (Kawahara, Quinn & Lambeth, 2007). However, there is the likelihood that ROS generation can make the vascular tone to increase by inactivating the endothelium-derived nitric oxide (NO). It can also cause the artery tone to decrease under psychological conditions.

Gill et al. (2018) argued that in most cases, the expression of NOX4 is high in the distal renal tubule. Here, it generates intracellular superoxide. Schürmann et al. (2015) acknowledged that oxygen sensing implicates NOX4 for the regulation of erythropoietin which is a HIF-dependent gene. NOX4 in the renal cells serves as a big source of intracellular reactive oxygen species (ROS) (Vallet et al., 2005).

2 Physical and chemical nature of NOX4 related with ROS

NOX4 can be defined as a foible membrane found in the NOX-family of NADPH oxidases that has constitutive activeness (Montezano et al. 2018). Among the enzymes in the NOX family, NOX4 require either activator subunits or calcium that serve as upstream activators. NOX4 releases hydrogen peroxide. NOX4 ROS functions as an oxygen sensor since P02 regulates its activity (Boltana, Doñate, Goetz, MacKenzie & Balasch, 2009). Constitutive NADPH oxidase helps on the intracellular generation of superoxide when a complex is formed with CYBA, p22phox. NADPH also employs phosphatases inhibition in the regulation of signaling cascades. It may work as an oxygen sensor that regulates the HIF activity and sets the KCNK3/TASK-1 (Vallet et al., 2005). Regarding the essence of NOX4, its oxygen sensing ability supports hemostasis in aerobic organisms. Phagocyte-Type works as an oxygen sensor helping in the regulation of the synthesis of erythropoietin found in the renal cortex (Kawahara & Lambeth, 2007). It comes out that NOX4 and ROS have similar properties such that they work dependently.
3 Expression of NOX 4

3.1 Elevated NOX 4 Expression and Cancers

Just as discussed earlier, the gene of NOX4 conducts the encoding of enzymes that belong to the family of NOX that serves as the subunit within the NADPH oxidase complex. In such scenarios, the protein that NOX4 has encoded gets localized to non-phagocytic cells where it functions as an oxygen sensor. At the same time, it acts as a catalyst to the process of reducing molecular oxygen to different kinds of reactive oxygen species (ROS) (Amara et al., 2010; Li et al., 2006). The protein NOX4 (NADPH oxidase 4) generates many ROS that carries many biological functions such as cell differentiation, signal transduction and the growth of tumor cells (Han et al., 2016). Jayavelu et al. (2016) shows that NADPH oxidase 4 (NOX4) is a type of protein that is associated with membranes such that it is radioactive and it has the capability of contributing to genomic instability, radiation sensitivity, and redox signaling in human cancers because it is capable of generating H2O2. It appears complex to determine the prevalence of NOX4 expression across a wide range of solid tumors in the human body. Any study involving epithelial tumors reveals that high levels of NOX4 expression especially in carcinomas of the neck and head. The high levels of NOX 4 expression also come out in the carcinomas of the esophagus and the bladder (Kawahara et al., 2007). When low levels of TGF-β1 detect the up-regulation of NOX4, it shows how sensitive the probe is. Reports of immunofluorescence experiments indicate that the ovarian cells exhibit high levels of endogenous NOX4 expression in association with the perinuclear membranes. You et al. (2018) noted that the expression of NOX4 in the case of cancers appears up-regulated in comparison to normal tissues when considering a specific group of human carcinomas that is well-defined. On the other hand, the expression of NOX4 on intracellular membranes appears localized in a manner that can cause modulation of oxidative DNA damage.

3.2 Elevated NOX4 Expression and Tumorigenesis

NOX4 silencing in VHL-deficient renal cell carcinoma (RCC) cells revokes the branching and invasion of cells. It also abrogates the formation and growth of a colony in a murine xenograft model renal cell carcinoma (RCC) (Boltana et al., 2009). The treatment of superoxide scavenger or overexpression of manganese catalase or dimutase phenocopies the alterations. Superoxide scavenging or NOX4 silencing has the sufficient ability to block nuclear accumulations of HIF-2α in renal cell carcinoma cells (Tang, Gao & Ge 2018). This implies that NOX4 plays a critical role in renal tumorigenesis. VHL re-expression and NOX4 expression in VHL-deficient RCC cells exhibit genetic synonymy that supports the development of regimens that aims at NOX4 blockade (Kawahara & Lambeth, 2007). Considering the case of tumorigenic transformation of prostate epithelial cells, the production of reactive oxygen species and increased expression of NOX4 that produce ROS in cells transformed by arsenic confirms that oxidative stress is very vital in the whole process (O’Neill et al. 2018).

3.3 Elevated NOX4 Expression and Tumor Angiogenesis

Angiogenesis can be viewed as a fundamental development as well as the adult physiological process that require the coordinated action of different factors and adhesion of cell molecules in the mural and endothelial cells (Bruns et al. 2018). The activity of inhibiting angiogenesis in the company of other disorders like macular degeneration that relates to age is highly useful for treating cancer (Bedard, Lardy & Krause 2007). On the other hand, therapeutic angiogenesis promotes the growth of new vessel. As a result, it helps in treating ischemic disorders and comes out as a significant frontline of cardiovascular medicine. Based on the previous discussions, it is evident that NOX4 actively participates in the modulation of endothelial cell proliferation (Cho et al. 2018). The level of NOX4 found in endothelial cells is sufficiently high to support its critical role in the mediation of endothelial redox signaling (Vallet et al., 2005). This is functionally vital to the modulation of endothelial cell physiology.

3.4 Elevated NOX4 Expression and Cancer Development

NADPH oxidase 4 (NOX4) plays a vital role in the production of reactive oxygen species that incorporates itself in tumor progression (Liang et al. 2019). It comes out that there are high expressions of NOX4 in colorectal carcinoma (CRC) tissues. Chen et al. (2019) shows that there is a high correlation between NOX4 and T-classification distant metastasis, N-classification as well as poor prognosis of CRC patients. CRC cell lines alter the invasion, migration, cell-cycle and apoptosis, and cell proliferation when siRNAs change the expression of NOX4 (Vallet et al. 2005). In some cases, NOX4 facilitates the spread of cancer cells and apoptosis, migration and invasion through regulation of relevant genes.

4 NOX4 Expression and the Growth and Development of Specific Cancers

4.1 Renal Cell Carcinoma

Ljungberg et al. (2015) noted that Renal Cell Carcinoma is a type of kidney cancer, and it is responsible for approximately 85% of kidney cancers. Renal means kidney and carcinoma refer to cancer that starts in the cells that cover an organ. Its growth begins as a single tumor in one of the kidneys but given time it affects both kidneys (Hsieh et al. 2017). Renal cell cancer originates from the cells found in the outer layer of the kidney or the renal cortex. These cells are in line with the tiny tubes that form the structure nephrons in the kidney. Escudier et al. (2007) research shows that NOX4 encourages the growth of renal tumorigenesis by supporting its expression. However, the pathogenic contribution of NOX4 to renal cell carcinoma have not been examined and evaluated directly. NOX4 can be the
possible treatment of RCC by suppression or silencing superoxide that effectively blocks nuclear accumulation hypoxia-inducible factor (Shi et al. 2018). There are various types of renal cancer such as clear cell RCCs, Chromophobe cell RCC, and Papillary RCC and in all of them exists a direct relationship between their treatment and NOX4.

4.2 Urinary bladder carcinoma
O’toole et al. (1997) noted that bladder cancer is urologic cancer that exhibits the highest rate of malignancy, and it originates from tissues of the urinary bladder. It is caused by abnormal growth of Urothelial cells that can spread to other parts of the body. It exists in various types such as transitional cell carcinoma that have a high prevalence in North and South America and some parts on Asia (Pieters et al. 2017). Other examples include adenocarcinomas and squamous cell carcinoma. Most bladder cancers are diagnosed at an early stage when they are highly treatable. People with bladder cancers are advised to maintain periodic follow–up tests to prevent advancement to a higher stage. (Kamat et al. 2016) research shows that NOX4 produces reactive oxygen species, and they contribute to the development of urinary bladder carcinoma. Research links urothelial carcinoma to the pathological role of NOX4.

4.3 Endometriosis ovarian cancer
Moric et al. (2016) argued that the role of NOX4 in normal endometrium cancer has been linked to the implication of pathogenesis of diabetes and obesity which happens to be the primary risk factors of ovarian cancer. The number of studies determined that NOX4 is high in patients with high body mass index than those with low body mass index. It further noticed that expression of NOX4 splicing variants leads to suppression of breast and ovarian cancer. Vercellini et al. (1993) argued that there is a direct link between NOX4 and ovarian cancer; the presence of NOX4 decreases the invasion and spread of cancerous ovarian cells rendering NOX4 possible treatment for ovarian cancer. Endometriosis is a painful disorder that originates when tissues that line inside the uterus known as endometriosis grows outside the uterus (McAlpine, Temkin & Mackay 2016). It affects the fallopian tubes, ovaries, and fabrics that line the pelvis. The disorder is associated with an increased risk of epithelial ovarian cancer that involves clear cell subtypes (Leto & Geiszt 2006). The irons produced by endometriotic cysts catalyzes oxidative stress that leads to the malignant growth of ovarian cysts and gene mutation. Torre et al. (2018) study shows that 5 to 10 % of ovarian carcinoma are associated with endometriosis. Ovarian cancer occurs at a high rate in women than in men with children being at the lowest risk. Lifestyle is also an essential factor in causing ovarian cancer. NOX4 is a significant source of oxygen species that is involved in endometriosis tumor progression, but there are limited data to link NOX4 ovarian cancer (Fu et al. 2010).

4.4 Colorectal Cancer
The primary source of reactive oxygen species which catalyzes the tumorigenesis is NOX4. Oncomine database shows that there is a higher rate of production of NOX4 in the form of CRC tissues as compared to other usual controls (Kinzel & Vogelstein 1996). However, there are limited data to substantiate the role of NOX4 in colorectal carcinoma. Colorectal cancer originates from abnormal growth of cells from parts of the large intestine such as rectum or colon which later spreads out to other parts of the body. In most patients, it originates as small noncancerous clumps of cells known as adenomatous polyps that then develop to bowel cancer. The polyps may be limited in number, therefore, provides few symptoms making colon cancer hard to diagnose at early stages. Due to difficulty in colon cancer diagnosis physicians and doctors always recommend regular screening tests to help identify possible existence in the body (Bendell et al. 2016). When the polyps are diagnosed at an early stage, they can be removed before they turn into cancer. El-Deiry et al. (2015) study shows that NOX4 can stop the progression of CRC which in turn suppress the metastasis; therefore NOX4 can be used as a method of treatment of CRC.

4.5 Breast Cancer
Breast Cancer can affect both men and women, but women have a high probability of being infected than men. Breast cancer is formed when breast cells begin to grow abnormally as they divide rapidly than normal cells (Senkus et al. 2015). They accumulate in the breast and begin to form lumps or mass that metastasize from the chest to other body parts and lymph nodes. Cancer always originates from invasive ductal carcinoma which is a milk-producing duct or from cells in invasive lobular carcinoma. Other body cells and tissue may also produce breast cancer cells which spreads to other body parts. Medical scientist and researchers have associated breast cancer to lifestyle, hormonal changes and some environmental factors (Turner et al. 2015). Research also links breast cancer to gene mutations that are passed from one offspring to another during reproduction. There are different types such as inflammatory breast cancer, male breast cancer, Angiosarcoma, and many others. NOX4 expressions have been up-regulated in a various number of human tumors including breast cancer, and recent studies demonstrate that NOX4 supports urothelial and melanoma carcinogenesis by controlling cell cycle progression (Al-Hajj et al. 2003).

4.6 Hepatocellular Cancer
Meng et al. (2007) acknowledged that NOX4 active oxygen supports liver complications such as hepatocellular carcinoma. The correlation and prognostic relevance of NOX4 and NOX4 in an expression of hepatocellular carcinoma are still under study. Kanwal et al. (2017) researched shows that the examination of NOX4 protein by immunohistochemistry in tissue that contains tumor demonstrate that NOX4 is an essential predictor of short RFS and short OS in HCC patients.
Hepatocellular Cancer is a malignancy of the liver that is common in patients with chronic liver diseases and cirrhosis (Bruix et al. 2017). It is suggested that it originates from abnormal growth of hepatic stem cells, an argument that is still under investigation by various scientists. Hepatocellular cancer is the third leading cause of cancer globally with the highest affected being Asia and some parts of Africa. Its presence in these areas is linked to a high prevalence of hepatitis B and C which results in chronic liver diseases hence exposure to HCC (Amara et al. 2010). The risk factors include long-term liver complications, those who drink a large amount of alcohol have a high prevalence of HCC, and those who have a high accumulation of fat in their livers are highly exposed to HCC. Diagnosis includes various tests such as blood test, imaging tests, and liver biopsy.

4.7 Lung cancer
Lung cancer is a condition in which cells in the lung divide uncontrollably (Spanier et al. 2009). After some time the cells cause the growth of tumors that interfere with an individual's ability to breathe. Diagnosing lung cancer at early stages may be challenging, but its symptoms are almost similar to those of respiratory complications (Miller et al. 2016). Lung cancer is associated with lifestyle factors such as the use of alcohol and cigarettes, hormonal fluctuations and environmental factors such as breathing contaminated air. Paez et al. (2004) study shows that NOX4 has a crucial part in lung cancer. The suppression of NOX4 functions leads to noticeable inhibition of invasion and growth of cells that causes lung cancer. NOX4 activity is linked to lung cancer suppression by blocking lung cancer invasion and development.

4.8 Melanoma
Boia-Ferreira et al. (2018) shows that melanoma is a tumor that mostly affects the heart that involves a high rate of hematropic spread. It also associated with carcinomas of the lung and breast. The hematologic malignancies may result in heart complications such as stroke and paralysis. Wikstrom, Lundeberg, Frohm-Nilsson & Girnita (2018) noted that patients of acute myocardial infections suffer pulmonary osseous and cerebral complications. The condition is linked to abnormal growth of cardiovascular cells which results in tumors in the heart. The primary factors of exposure are the lifestyle of an individual. Patients of chronic heart diseases are also prone to melanoma. ROS has an essential role in melanoma development, but the source of ROS is not accurately determined (Garretson, Robertson & Earle 1987). Cellular ROS groups can originate from mitochondria, and NOX4 group of enzymes and recent studies provides that NOX4 is expressed in melanocytic lineage resulting in the high presence of NOX4 in metastatic melanoma tumors. Yang, Zhang, Ries & Key (2004) research noted that the existence of NOX4 in melanoma tumors activates NOX4 inhibitors that induce resistance to a subset of tumors. Furthermore, BRAF inhibitors enable identification and blockage of ROS; therefore, NOX4 can help in controlling Melanoma cancers (Su et al. 2012).

5 CONCLUSIONS
NADPH oxidase-4 (NOX4) is a vital enzyme that protects the body (Barret, Farhadi & Smith 2018). Its roles in the generation of reactive oxygen species are determined by its ability to release superoxide. The elevated expression of NOX4 depends on the nature of situation in the body that it combats. NOX4 was highly expressed in a lot of tumors such as renal cell carcinoma, bladder cancer, endometriosis ovarian cancer, colorectal cancer, breast cancer, hepatocellular carcinoma, lung cancer, melanoma, etc. Elevated levels of NOX4 are usually associated with poor prognosis in these solid tumors. Therefore, from this review, one can accept the claim that elevated NOX4 in gallbladder cancer and its stroma maybe predicts poor prognosis.

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