ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 11, pp. 64263-64267, November, 2023
https://doi.org/10.37118/ijdr.27396.11.2023

RESEARCH ARTICLE OPEN ACCESS

CHANGES IN THE KEAP1-NRF2-ARE PATHWAY AS A CHEMORESISTANCE TRIGGERING FACTOR AND AGGRESSIVE TUMORIGENIC ACTIVITY IN OVARIAN CARCINOMA

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ARTICLE INFO

Article History:
Received 27th August, 2023
Received in revised form
19th September, 2023
Accepted 13th October, 2023
Published online 27th November, 2023

Key Words:

Ovarian carcinoma;
Chemoresistance;
KEAP1-NRF2-ARE.

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ABSTRACT

Introduction: Cancer is understood as the term used to agglutinate the more than 100 types of malignant diseases that have as a common characteristic the disordered growth of cells, which can invade adjacent tissues or organs at a distance. There are many risk factors associated with a proliferation of neoplastic cells, and the Keap1-Nrf2-ARE signaling pathway (Kelch-like ECH-associated protein 1 - Nuclear factor- erythroid-2 related factor 2 - Antioxidant response element) is one of the main cellular sensors of oxidative stress, a factor that fits within the extensive list of genetic propensity to the appearance. ***Objective:*** To understand the KEAP1- NRF2-ARE pathway and analyze chemoresistance factors in the formation of ovarian tumors. ***Methodology:*** This is an integrative review of the literature, which uses an exploratory and descriptive methodology. Initially, studies were searched in the electronic databases: Latin American and Caribbean Literature in Health Sciences (Lilacs); Scientific Electronic Library Online (SciELO); Medical Literature Analysis and Retrieval System Online (Medline) and National Library of Medicine (PubMed). For research of such articles, the following descriptors were used: Ovarian carcinoma; Chemoresistance; KEAP1- NRF2-ARE. In the cataloging of these studies we used the Boolean operator "AND" in the descriptors of the health sciences (DECS). ***Results:*** The role of the KEAP1-NRF2-ARE pathway in the process of controlling cellular oxidative stress was understood, as well as its relevance in the treatment of ovarian neoplasms. Furthermore, the functioning of this mechanism was also understood and how its protective mechanism becomes favorable in the development and proliferation of neoplastic cells. Confirming that the study has full potential to serve as a vehicle for promoting scientific-based studies, as well as the implementation of evidence-based medicine. Making it of great value for understanding and studying effective therapies in the oncological scope of ovarian neoplasms.

Citation*: *João Gabriel Pimentel Soares; Eduardo de Sousa Lucena; Rodrigo Cruz de Carvalho and Luan Kelves Miranda de Souza. 2023. *"*Changes in the keap1-nrf2-are pathway as a chemoresistance triggering factor and aggressive tumorigenic activity in ovarian carcinoma*". International Journal of Development Research*, 13, (11), 64263-64267.

INTRODUCTION

Cancer is understood as the term used to agglutinate the more than 100 types of malignant diseases that have as a common characteristic the disordered growth of cells, which can invade adjacent tissues or organs at a distance. There are many risk factors associated with a proliferation of neoplastic cells, being the Keap1- Nrf2-ARE signaling pathway (Kelch-like ECH-associated protein 1 - Nuclear factor-erythroid-2 related factor 2 - Antioxidant response element) one of the main cellular sensors of oxidative stress, a factor that fits within the extensive list of genetic propensity to the appearance of malignant tumors.

Oxidative stress occurs as a result of an imbalance between the generation of oxidizing compounds and the action of antioxidant defense systems. The generation of free radicals, as well as non-radical reactive species are the result of this metabolic presentation. The NRF2 transcription factor is responsible for controlling the expression of antioxidant and detoxification genes. When cells are not in oxidative stress, Nrf2 is located sequestered in the cytoplasm due to the action of a complex called Keap1 - Cul3 (Culina 3), as a result of this action, Nrf2 is ubiquitinated and rapidly degraded by the proteosome. The repressive action of Nrf2 by Keap1 is then understood, as it reduces transcription via Nrf2, then lowering the basal levels of gene expression associated with it (LIU; ZHANG, 2022). With regard to the carcinogenic evolution, it is known that some classes of drugs are capable of stimulating the reversible and

short-term activation of NRF, which consists of a protein belonging to the cap'n'collar (CNC) family of transcription factors with a basic leucine zipper domain (bZIP) and so that it can perform its physiological role, needs a heterodimerization with Maf proteins. These proteins connect to the recognition element of MAF (MARE, Maf responsive element) regulating transcription, thus acquiring the ability to proge the individual for a limited period of time against exposure to chemical substances that can give rise to cancer. Associated with this process is the mechanism of permanent hyperactivation of NRF2, which is installed from somatic mutations in the gene that encodes NRF2, or in other genes that are associated with its degradation, this, finally, is observed in some types of cancers and are predictors of worse prognosis (LIU; ZHANG, 2022). Intracellular electrophilic and oxidative changes course with the disruption of the Keap1-Nrf2 complex, as they are capable of causing modifications in the cysteine residues (Cys273 and Cys288) of Keap1, causing the Nrf2 to be translocated to the nucleus instead of having its degradation in the proteasome. When it reaches the nuclear region, Nrf2 interacts with the ARE by stimulating the expression of cytoprotective genes, increasing cell survival. Normally, the activity of NRF2 is rigidly controlled in the cell and is continuously adjusted to ensure that these cells are protected against endogenous chemicals and environmental agents that disturb the intracellular antioxidant/pro-oxidant balance, which must be maintained so that they are able to grow and survive properly. This rigid control of NRF2 is achieved by a repressive protein called KEAP1 that aims to perpetuate the NRF2 protein for degradation under normal conditions, but is unable to do so when it encounters oxidizing substances or reactive chemicals (SILVA, 2022). Thus, the relevance of genomic medicine is observed for the delimitation of clinical and therapeutic conducts in cases of patients with diagnosis or risk factors predictors of neoplasms. Ovarian cancer is a gynecological neoplasm that affects the cells of the female reproductive tissue and is among the 10 most lethal types of cancers known today. It is then understood the importance of recognizing the risk factors associated with changes in the KEAP1-NRF2-ARE pathway because this represents a factor of great relevance in the process of chemoresistance and aggressive tumorigenic activity in this type of carcinoma.

METHODOLOGY

The present study is an integrative review of the literature, which uses an exploratory and descriptive methodology. Initially, studies were searched in the electronic databases: Latin American and Caribbean Literature in Health Sciences (Lilacs); Scientific Electronic Library Online (SciELO); Medical Literature Analysis and Retrieval System Online (Medline) and National Library of Medicine (PubMed). For research of such articles, the following descriptors were used: Ovarian carcinoma; Chemoresistance; KEAP1- NRF2-ARE. In the cataloging of these studies we used the Boolean operator "AND" in the descriptors of the health sciences (DECS). The data were organized during the literature review in order to list the studies related to the theme in question, the filtering of the articles found had as inclusion criteria, articles in the years 2016 to 2022, in addition to articles that served as the initial basis of the theme, within the languages: Portuguese and English, and as an exclusion criterion experimental articles, With children, in other languages and texts with only the abstract available. After this filter there were 15 articles left for review and literary basis.Although 15 articles and/or publications were analyzed regarding the aforementioned key words, the pathway studied, the affected organ, treatment resistance and the chemoresistance factor correlated with the pathway were taken into account. Therefore, from a perspective more linked to the topic at hand, only the 7 current articles in the table attached to our work are confirmed.

RESULTS AND DISCUSSION

Ovarian cancer is the fifth leading cause of cancer death in women and is estimated to be responsible for approximately 30% of all gynecological cancers in the world. In developed countries, this type of neoplasm has numbers similar to that of cancer of the cervix and uterine body of the uterus. In Brazil, its incidence is estimated at about 5.95 cases for every 100,000 women, and in capitals, this number reaches about 8.9 cases for every 100,000 women. Due to its insidious and little symptomatic evolution, it is usually detected late and this causes it to have a high mortality rate (ALVES, 2020). Some risk factors are associated with the development of this cancer, such as: advanced age, white race, obesity and nulliparity. It is also known that genetic factors may be related and in these cases it is necessary to monitor patients at risk of developing this neoplasm. Mutations in the BRCA1 and 2 genes are genetic characteristics that are directly associated with the risk of developing this disease, as well as oxidative stress among other factors. There are many histological types of this cancer, but the epithelial tumor stands out as the most frequent, representing about 90% of cases, followed by mucinous, endometrioid, clear cells, transitional, mixed and finally, undifferentiated tumors (DA SILVA OLIVEIRA, 2020).

When a patient has an established diagnosis of ovarian cancer, it is essential that she performs a genetic analysis to evaluate its hereditary character, because most cases come from mutations in the BRCA 1 and 2 genes, which characterize the Breast and Hereditary Ovarian Cancer Syndrome. After the diagnosis of genetic syndromes, the investigation of other neoplasms that may be synchronous or metachronic is continued. If there is confirmation of the genetic character, the patient's direct relatives should also undergo evaluations for early detection of the neoplasm or the risk factors associated with it. When there is genetic confirmation of heredity, a prophylactic salpingoophorectomy should be performed after they reach constituted offspring, between 35 and 40 years (ALVES, 2020). However, not only genetic mutations are factors that influence the development of ovarian neoplasms. Oxidative stress, which results from the inhibition of mitochondrial Complex I (IC), may also be related to the pathology. Reactive oxygen species (ROS) are the main compounds involved in this process. They are produced in mitochondria as by-products of the oxidative phosphorylation process. ROS are able to promote cell damage due to the oxidation of macromolecules Biological, such as lipid peroxidation, carbonylation and protein nitrosylation or even through the oxidation of DNA and RNA (TAGUCHI; YAMAMOTO, 2020). Oxidative stress in ovarian cells is a factor that contributes significantly to the development of the neoplastic process, as this results in an imbalance of the cellular redox state. In response to this redox imbalance, there is the activation of the Keap1-Nrf2-ARE cell signaling pathway (Kelch-like ECH associated protein 1 - nuclear factor-erythroid-2 related factor 2 - antioxidant response element), where the expression of the genes that encode the proteins of antioxidant action is regulated by the transcription factor Nrf2. In general, the Keap1 protein acts by endogenously repressing the Nrf2, causing it to be destroyed by the ubiquitin-proteosome pathway (DE FREITAS SILVA, *et al*., 2020). When the patient is in a state of oxidative stress, the dissociation of Nrf2 occurs causing it to be translocated to the nucleus, acting in a sensory way to the cellular redox environment. As a result of this translocation, Nrf2 stimulates the transcription of the enzymes that are responsible for phase I, II and III biotransformation reactions and in the antioxidant mechanisms. In this way it is perceived that the Keap1-Nrf2- ARE signaling pathway is an important mediator of the cellular antioxidant response, because it is due to the perception of this imbalance, through Keap1, that the nuclear action of Nrf2 is given so that it acts as a transcription factor of the ARE genes, which will subsequently perform the coding of the antioxidant enzymes, thus reducing Therefore, it is understood that the Keap1-Nrf2-ARE interaction maintains low basal levels of expression of genes regulated by Nrf2 (JIANG, *et al*., 2020). The genes that encode the set of enzymes that are involved in phase I, II and III biotransformation reactions and in the antioxidant mechanisms are part of a long polyndromic sequence of DNA that can be found in the regions responsible for cell regulation and are known as ARE. In its heterodimer form with Maf proteins, Nrf2 is associated with the ARE and then gains the ability to This modification mediated by a phosphorylation process changes the subcellular location in the Nrf2,

Table 1. Analyzed articles, authors' and their respective results

Article / Year / Journal	Authors	Objectives	Results
The Nrf2 Pathway in Liver Diseases/2022/ Front Cell Dev Biol.	Jiaming Zhou, Qiuxian Zheng and Zhi Chen.	Comprehensively summarize the relationships between oxidative stress and liver injury and the critical role of the Nrf2 pathway in multiple liver diseases.	Oxidative stress is non-disease-specific and a crucial factor in the occurrence and process of many liver diseases. The Keap-Nrf2 pathway is a critical pathway for organisms to resist oxidative stress. The expression of antioxidant protective genes and phase II detoxification enzyme genes induced by it can effectively reduce the sensitivity of liver cells to ROS and electrophiles, slow down the development of liver diseases, and prevent the occurrence and progress of liver fibrosis. However, the current clinical data of Nrf2 agonists are limited and there is no evidence-based basis. Multi-center, large-sample randomized controlled clinical studies are needed for further verification. Furthermore, most of Nrf2 agonists are Keap1 cysteine-targeting compounds. However, they can also interact with other cysteines around the body. It may affect the biological function and bring about drug side effects. Therefore, biopharmaceutical companies should develop drugs that only act on Keap1. Drugs that disrupt the Nrf2-Keap1 protein-protein interactions (PPI) are new targets for treating liver diseases. The advantage of Nrf2-Keap1 PPI inhibitors is improved target selectivity. Due to the extremely short half-life of Nrf2, drugs should be long-lasting, stable and easy to monitor. It is worth noting that the role of Nrf2 in liver cancer has two sides. It may promote tumor cell proliferation and produce drug resistance while anti-tumor. The safe therapeutic window of Nrf2 activators needs to be identified. However, the relevant mechanism is still unclear, and a large number of animal experiments and clinical trials are needed.
Potential Applications of NRF2 Inhibitors in Cancer Therapy/2019/Oxid MedCell Longev.	Panieri E and Sasso L.	Provide an overview of the NRF2/KEAP1 pathway, its biological impact on solid and hematologic malignancies, and the molecular mechanisms that cause NRF2 hyperactivation in cancer cells	It is becoming increasingly clear that NRF2 plays a crucial role in cancer malignancy and resistance to therapy by controlling intracellular redox homeostasis through activation of cytoprotective antioxidant genes. A growing number of studies suggest that suppression of NRF2-related antioxidant mechanisms may represent a viable and promising therapeutic approach to induce pro-oxidant conditions in the tumor microenvironment and trigger ROS-dependent cell death in various human malignancies. Despite the lack of specific and selective NRF2 inhibitors, convincing evidence indicates that the use of natural compounds or even the reuse of preexisting drugs with known pharmacokinetic and toxicity profiles can be successfully employed as single agents or chemosensitizing adjuvants in different types of tumors, 269, 341, 363, 364]. It is noteworthy that, given the functional location of NRF2 at the crossroads of several pathways, pharmacological manipulations of upstream regulators or downstream effectors of NRF2 signaling can also produce notable anticancer effects and synergy with already established drugs through mechanisms that converge almost invariably in the disruption of intracellular redox homeostasis [131, 363, 365, 366]. Therefore, it is expected that, in the near future, additional studies will explore other favorable combinations to hinder the pro-oncogenic functions of NRF2 and its biological effects, with the aim of discovering new and effective therapeutic alternatives against cancers with limited options and dependency on NRF2. On the other hand, it should also be noted that the discovery of new NRF2/ARE inhibitors with sufficient potency, specificity and safety profiles still represents a critical challenge in the field of cancer research that may lead to a breakthrough in the strenuous fight against cancer.
Potential Applications of NRF2 Modulators in Cancer Therapy/2020/ Antioxidants.	Panieri E, Buha A, Telkoparan-Akillilar P, Cevik D, Kouretas D, Veskoukis A, Skaperda Z, Tsatsakis A, Wallace D, Suzen S, Saso L.	Focus on the dual roles of the NRF2-KEAP1 pathway in cancer promotion and inhibition	Recent research suggests that suppression of antioxidant mechanisms involving NRF2 could potentially induce a pro-oxidative shift in the tumor microenvironment and promote ROS-dependent cell death in many types of cancer. Despite the absence of specific and selective NRF2 inhibitors, convincing indications show that the use of natural compounds with known therapeutic action can be effectively used in different types of tumors [351, 352]. NRF2 has been recognized as one of the critical factors that regulate a number of genes that protect cells against xenobiotics. NRF2-mediated transcriptional regulation is coordinated by a series of specific events within the cellular environment. Among them, the triggering stimulus, the cooperation with other activators and repressors, the interaction with different signaling pathways and the epigenetic landscape of the target gene promoters can be considered of extreme importance. Many approaches have been devised to target the NRF2 signaling pathway in cancer, such as regulating NRF2 expression at the transcriptional level, controlling NRF2 nuclear translocation, targeting KEAP1-NRF2 binding to modulate NRF2 protein stability, and regulating NRF2 binding. from NRF2 to its target gene promoters. Several small molecule NRF2 activators and inhibitors have been developed and used successfully in the treatment of cancer. Important disadvantages of targeted therapy include cancer cell resistance and difficulties in developing drugs for some specific tumor targets.191, 353]. Studies suggest that in tumors, high levels of NRF2 can occur in the absence of genomic alterations in the NRF2 and KEAP1 genes. Additional research will help increase the specificity of NRF2-based therapies.
NRF2 and the Ambiguous Consequences of Its Activation during Initiation and the Subsequent Stages of Tumourigenesis/2020/ Cancers.	Robertson H, Dinkova-Kostova AT, Hayes JD.	Provide a critical overview of the literature describing the seemingly ambiguous contributions that NRF2 makes to cancer development. In addition, we discuss how NRF2 upregulation may aid tumor growth and survival, whether NRF2 upregulation in certain cancers is associated with mutations in specific oncogenes, and at what stage of cancer development this is likely to occur. Finally, we discuss proposed therapeutic strategies that selectively target tumors in which NRF2 is permanently activated with the goal of overcoming NRF2-associated drug resistance.	Here, we describe the background to the discovery that NRF2 is responsible for intrinsic resistance to many chemical carcinogens and that, through its ability to mediate cellular adaptation to oxidative and electrophilic stress, it orchestrates the induction of cytoprotective detoxification genes by chemopreventive agents. of cancer, thereby inhibiting the initiation of carcinogenesis in the stomach, bladder, skin, GI tract, breast, lung, and liver. We also report events that led to the recognition that NRF2 is often up-regulated in tumor cells and describe a wide range of mechanisms that allow evasion of repression by KEAP1, with somatic mutations in NFE2L2, KEAP1 and CUL3 being the best characterized examples. From the screening work done using the TGCA, it was clear that NRF2 upregulation is a feature of many common cancers, including those of the lung, esophagus, liver, and head and neck. Although it might have been anticipated that the tissues in rodents in which chemopreventive agents protect against carcinogenesis would be the same ones in which NRF2 is permanently up-regulated in human tumors, because NRF2 function is required for adaptation in such tissues, it was discovered if that was only partially true. There are at least three reasons for this disparity: firstly, the NRF2-mediated mechanisms responsible for chemoprevention (increased detoxification) differ from those conferred by NRF2 during tumor progression (increased ROS clearance, NADPH generation, synthesis of serine and ribonucleotide synthesis); second, NFE2L2, KEAP1 and CUL3, the full extent to which NRF2 is constitutively activated in cancer is not known; Third, the demands made on NRF2 to support the growth and survival of cells that harbor mutations in genes that drive tumorigenesis are highly variable among different types of cancer.

Role of NRF2 in Lung Cancer/2021/MDPI Journal Cells	Miriam Sánchez-Ortega , Ana Clara Carrera and Antonio Garrido	Address the mechanisms of NRF2 activation, their implication in the progression of lung cancer and current therapeutic strategies aimed at blocking the action of NRF2.	Although NRF2 exerts cytoprotective effects in preventing malignant transformation in healthy tissues once some tumor types are generated, NRF2 is also important in maintaining the cancerous state by protecting cancer cells from environmental ROS and limiting chemotherapy-induced damage . This dual role of NRF2 discussed here in the context of NSCLC appears to be tumor stage dependent. NRF2 functions as a tumor suppressor usually in tumor initiation stages, while NRF2's prooncogenic functions are generally found in advanced tumor stages. Several reports have determined that lung tumor cells acquire a dependence on NRF2 overexpression to maintain their malignant phenotype, a process called NRF2 dependence. Tumor protection exerted by NRF2 supports cancer growth through multiple molecular mechanisms. More research into this dual role of NRF2 is needed to clarify its roles in each stage of cancer. The use of human samples, such as human biopsies or 3D cultures (organoids), can be helpful in this effort.
Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease/2015/ Free radical biology & medicine.	TEBAY, L. E. et al.	Discuss the basis of a putative U-shaped Nrf2 dose-response curve in terms of potentially concurrent processes relevant to different stages of tumorigenesis.	We provide an overview of processes such as redox status, cell differentiation, ER stress, mitochondrial function, drug metabolism, inflammation, tissue regeneration, and signal transduction that are altered in Nrf2-null mice and cells. we describe the mechanisms by which Nrf2 is regulated by CRL Keap1 and SCF β-TrCP with the aim of providing a better understanding of how redox status, growth factors, nutrient availability and energy levels modulate transcription factor activity and, thus, induction of their target genes. However, it is not clear how these two systems are integrated and if there is cross talk between them. More experiments are needed to determine whether CRL Keap1 and SCF β-TrCPprepress Nrf2 in different organs, cell types, or subcellular compartments, and whether they primarily control the magnitude or duration of Nrf2 activation. It is also not known whether the β-TrCP1 and β-TrCP2 isoforms regulate Nrf2 differently, nor is it clear why Nrf2 contains two binding sites for β-TrCP1/2. There is evidence that certain xenobiotics activate Nrf2 by antagonizing GSK-3 [299, 306], but more work is needed to establish the spectrum of chemicals that work through this mechanism and how they compare to those that activate Nrf2 by inhibiting Keap1 . Furthermore, there is a complex signal transduction network upstream of GSK-3, including Akt, PI3K and mTORC2, which allows growth factors and nutrients to enhance Nrf2 activity. Additional studies are needed to establish the extent to which xenobiotics and endobiotics control Nrf2 through this network.
Role of NRF2 in Ovarian Cancer/2020/ Antioxidants.	TOSSETTA, G. et al.	In this review, we report evidence from the literature describing the effect of NRF2 on ovarian cancer, with a focus on its function in drug resistance, NRF2 natural and synthetic modulators and its protective function in normal ovarian preservation.	Recent studies show that the NRF2/KEAP1/ARE pathway plays a fundamental role in many processes involved in regulating ovarian cancer progression, proliferation and chemoresistance. It is clear that NQO1 and NRF2 are highly expressed in ovarian carcinoma compared with normal tissues and that NRF2 expression increases with advancing stage of ovarian carcinoma. Furthermore, low KEAP1 expression is associated with disease recurrence and death, whereas high KEAP1 expression is predictive of better disease-free and overall survival. Interestingly, it has been reported that both low nuclear expression of NRF2 and high expression of KEAP1 depend on the age of patients, suggesting that the efficiency in combating ROS decreases with aging and is associated with an increased risk of carcinogenesis. Furthermore, NRF2 can regulate the expressions of ERα and PGR in ovarian cancer cells, Table 1 and Table 3). Several lines of research have demonstrated that NRF2 signaling can be modulated indirectly by non-coding RNA, such as miR-181d and Lin-H19, and that these can modulate drug response in ovarian cancer. Furthermore, p62 can activate NRF2, protecting cancer cells from chemotherapeutic agents that induce autophagy. Furthermore, the direct action of NRF2 on proteins involved in chemoresistance, such as AKR1C1-3, ABCF2, SLC40A1, is known, as well as the modulation of important growth factor receptors, such as c-MET, ErbB2 and EGFR, which regulate growth. tumor. Unfortunately, chemotherapy causes cytotoxic effects on both cancer cells and normal cells. Every year, thousands of young women are exposed to chemotherapy, with serious consequences on fertility and ovarian tissue [87]. To date, cryopreservation of ovarian tissues and gametes is the only way to give these women the chance to become pregnant [89]. It has been reported that GSK-3 inhibitors, resveratrol, melatonin, epigallocatechin gallate, and theaflavins can protect ovarian tissues exposed to chemotherapeutic agents or cryopreservation by activating NRF2 signaling to preserve female fertility (see Table 4).

then creating three pathways in response to oxidative stress: the protein kinase C pathway (PKC), the mitogen-activated protein kinase cascade pathway (MAPK) and the phosphatidylinositol 3-kinase/protein kinase B pathway (PI3K/AKT) (DA SILVA OLIVEIRA, 2020). Despite the reported antioxidant effects, the KEAP1-NRF2-ARE pathway may present changes suggestive of a tumorigenic process since cancer cells are Capable of producing large amounts of reactive oxygen species during their proliferation, to the point that they need to be able to withstand high levels of oxidative stress during the metastatic process. In this case, there is a positive regulation through the Nrf2, causing it to act benefiting the growth and carcinogenic evolution while the overexpression of antioxidant genes prevents cell death that is stimulated by ROS (JIANG, *et al*., 2020). In addition to the positive regulation in relation to gene expression capable of encoding enzymes that sequester ROS, NRF2 is also responsible for controlling the expression of PPP genes in the oxidative (G6PDePGD) and non-oxidative (TALDO1eTKT) pathways, and the overexpression of these pathways can favor the survival and proliferation of cancer cells, Associated with this, we highlight the effective ability that cancer cells have to multiply quickly using the non-oxidative arm of PPP to generate ribonucleotides, thus favoring the biosynthesis of nucleic acids. In this way, tumor cells that can overcome the oxidative stress barrier caused by oncogene inhibition are able to reprogram themselves metabolically, with the help of NRF2 promoting a genetic superexpression for oxidative enzymes PPP and TXN1, TXN2 and TXNRD1, And excluding the synthesis of GSH, leading to the conclusion that NRF2 helps in the formation and growth of recurrent tumors (TAGUCHI; YAMAMOTO, 2020).

Recent studies show that the NRF2/KEAP1/ARE pathway plays a fundamental role in many processes involved in regulating ovarian cancer progression, proliferation and chemoresistance. It is clear that NQO1 and NRF2 are highly expressed in ovarian carcinoma compared with normal tissues and that NRF2 expression increases with advancing stage of ovarian carcinoma.

Furthermore, low KEAP1 expression is associated with disease recurrence and death, whereas high KEAP1 expression is predictive of better disease-free and overall survival. Interestingly, it has been reported that both low nuclear expression of NRF2 and high expression of KEAP1 depend on the age of patients, suggesting that the efficiency in combating ROS decreases with aging and is associated with an increased risk of carcinogenesis (TOSSETTA, G. *et al*. 2022).

CONCLUSION

One of the biggest challenges in the search for new therapies that favor the cure of cancer is to understand the mechanisms that are capable of promoting the emergence and growth of a tumor, as well as those that can help in its regression. Due to the high prevalence of ovarian neoplasms in Brazil and around the world, as well as because it is a pathology that often has a late diagnosis, it is necessary to know the factors that predispose it as well as to know how to conduct them effectively, in order to promote a greater chance of cure for patients affected by it. In this way, the genetic analysis of organic components that influence carcinogenesis is relevant as well as it is of paramount importance to evaluate the systemic interactions that can lead to an antioxidant protective factor such as the KEAP1- NRF2-ARE pathway, to promote the formation or accentuate the growth of a malignant ovarian tumor according to the possible cellular responses for these cases.

REFERENCES

ALVES, Joana Filipa Martins. Via de sinalização Keap1-Nrf2-ARE como alvo terapêuticonamodulaçãodostr essoxidativonasdoen çasneurodegenerativas. 2020.Tesede Doutorado.

DA SILVA OLIVEIRA, Rafaela *et al*. Ação Quimiopreventiva dos Fitoquímicos por meio da Regulaçãodo Fatorde Transcrição Nrf2: Revisão Integrativada Literatura. *Revista Brasileirade Cancerologia,* v. 66, n. 1, 2020.

DE FREITAS SILVA, Matheus *et al*. The Keap1/Nrf2-ARE pathway as a pharmacologicaltar get for chalcones. Molecules, v. 23, n. 7, p. 1803, 2018.

HASSANEIN, Emad HM *et al*. Coumarins as modulators of the Keap1/Nrf2/ARE signaling pathway. Oxidativemedicine and cellular longevity, v. 2020, 2020.

Institutos Nacionais de Saúde (EUA); Estudo Curricular de Ciências Biológicas. Série de suplementos curriculares do NIH [Internet]. Bethesda (MD): Institutos Nacionais de Saúde (EUA); 2007. Compreendendo o câncer. Disponível em: https://www.ncbi.nlm. nih.gov/books/NBK20362/

JIANG, Ganggang *et al*. p62 promotes proliferation, apoptosis-resistance and invasion ofprostate cancer cells through the Keap1/Nrf2/ARE axis. *Oncology Reports,* v. 43, n. 5, p.1547-1557, 2020.

LI, Hui-xian *et al*. Role of Keap1-Nrf2/ARE signal transduction pathway in protection ofdexmedetomidine preconditioning against myocardial ischemia/reperfusion injury. *Bioscience Reports,* v. 42, n. 9, p. BSR20221306, 2022.

LIU, Shengnan; PI, Jingbo; ZHANG, Qiang. Signal amplification in the KEAP1-NRF2-AR Eantioxidantresponse pathway.Redox Biology, p. 102389, 2022.

Panieri E, Buha A, Telkoparan-Akillilar P, Cevik D, Kouretas D, Veskoukis A, Skaperda Z, Tsatsakis A, Wallace D, Suzen S, Saso L. Potential Applications of NRF2 Modulators in Cancer Therapy. Antioxidants (Basel). 2020 Feb 25; 9(3):193. doi: 10.3390/ antiox9030193. PMID: 32106613; PMCID: PMC7139512.

Panieri E, Saso L. Potential Applications of NRF2 Inhibitors in Cancer Therapy. Oxid Med Cell Longev. 2019 Apr 11; 2019: 8592348. doi: 10.1155/2019/8592348. PMID: 31097977; PMCID: PMC6487091.

Robertson H, Dinkova-Kostova AT, Hayes JD. NRF2 and the Ambiguous Consequences of Its Activation during Initiation and the Subsequent Stages of Tumourigenesis. Cancers (Basel). 2020 Dec 2;12(12):3609. doi: 10.3390/cancers12123609. PMID: 33276631; PMCID: PMC7761610.

SÁNCHEZ-ORTEGA, M.; CARRERA, A. C.; GARRIDO, A. Role of NRF2 in Lung Cancer. Cells, v. 10, n. 8, p. 1879, 24 jul. 2021.

SILVA, Rafaeletal. Albumin Inhibits Heme-Induced Inflammation, Reactive Oxygen Species and Enables Heme-LPS Inflammatory Synergism in a TLR4 Independent Way. Reactive Oxygen Species and Enables Heme-LPS Inflammatory Synergism in aTLR4 Independent Way (August 9, 2022), 2022.

TAGUCHI, Keiko; YAMAMOTO, Masayuki. The KEAP1–NRF2 system as a moleculartarget of cancer treatment. Cancers, v. 13, n. 1, p.46, 2020.

TEBAY, L. E. *et al*. Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease. Free radical biology & medicine, v. 88, n. 0 0, p. 108–146, 1 nov. 2015.

TOSSETTA, G. *et al*. Role of NRF2 in Ovarian Cancer. Antioxidants, v. 11, n. 4, p. 663, 30 mar. 2022.

TU, Wenjun et al. The anti-inflammatory andanti-oxidantmechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. Aging and disease, v. 10, n. 3, p.637, 2019.

ZHOU, J.; ZHENG, Q.; CHEN, Z. The Nrf2 Pathway in Liver Diseases. *Frontiers in Cell and Developmental Biology*, v. 10, 10 fev. 2022.

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