e-ISSN 2544-1620

Medical Science Pulse 2022 (16) 3

Reviews

Published online: 25 July 2022

DOI: 10.5604/01.3001.0015.9645

PROPERTIES AND FUNCTIONS OF MYELOPEROXIDASE AND ITS ROLE IN OVARIAN CANCER

Beata Gąsowska-Bajger[1 A,B,D-F]
• ORCID: 0000-0003-0831-383X

Agnieszka Gąsowska-Bodnar[2 B,D-F]
• ORCID: 0000-0003-2930-8116

Lubomir Bodnar[3 B,D-F]
• ORCID: 0000-0001-8548-8778

1 Institute of Chemistry, University of Opole, Poland
2 Faculty of Medicine, Lazarski University, Warsaw, Poland
3 Faculty of Medical and Health Sciences, University of Natural Sciences and Humanities, Siedlce, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Elevated levels of myeloperoxidase in body fluids are increasingly being used as an indicator for the diagnosis of cancer.

Aim of the study: The aim of this study was to review the literature on the physical and chemical properties of myeloperoxidase, its role in carcinogenesis, the role of tumor-associated neutrophils in cancer, and the role of myeloperoxidase in ovarian cancer.

Material and methods: The research literature published between January 1999 and December 2019 was reviewed. The properties and role of myeloperoxidase in the development of ovarian cancer were selected from publications available in selected online databases, including MEDLINE, PubMed, Scopus, and Web of Science. Searches were performed using the following word combinations: "myeloperoxidase", "ovarian cancer", "reactive oxygen species", "expression", "polymorphism", and "tumor-associated neutrophils".

Results: Thirty-five scientific articles were included in the final review. Of the 35 articles, 11 discussed the role of myeloperoxidase in carcinogenesis, and five discussed its role in the development of ovarian cancer.

Conclusions: Elevated myeloperoxidase levels are associated with many types of cancer, including ovarian cancer. In the studied group of invasive ovarian tumors, up to 65% exhibited elevated levels of myeloperoxidase. Continued research on myeloperoxidase expression in ovarian cancer cells is vital and warranted.

KEYWORDS: myeloperoxidase, ovarian cancer, polymorphism, G-463A polymorphism

Background

Epithelial ovarian cancer (EOC) is one of the most deadly and insidious gynecological cancers in women because it does not present with specific symptoms until late in its course. Approximately 230,000 women are diagnosed with ovarian cancer each year worldwide, and over 150,000 die as a result of this terrible disease. EOC belongs to the group of the seven most diagnosed cancers among women in the world. Its 5-year survival rate is 46% [1]. Risk factors for EOC include, but are not limited to, lifelong ovulation (no pregnancy, early menstrual age, late menopause), family history of EOC, smoking, mild gynecological diseases (including endometriosis, polycystic ovary syndrome, and pelvic inflammatory disease), and, possibly, talcum powder use [2]. The last factor is particularly controversial. The use of talcum powder on the genitals can induce significant changes in key redox enzymes and improve the status of prooxidants in normal and EOC cells. Studies have shown a significant, dose-dependent increase in iNOS prooxidant, nitrate/nitrite, and myeloperoxidase in cells exposed to talcum powder [3].

Myeloperoxidase (an enzyme belonging to the peroxidase group) is a protein that plays a crucial role

in the nonspecific antibacterial defense system. This enzyme is released in the process of phagocytosis and catalyzes oxidation reactions in the presence of hydrogen peroxide, halide, or thiocyanate to appropriate acids, which are strong and effective antimicrobial substances. As myeloperoxidase produces these compounds, various inflammatory reactions occur, and tissue damage ensues [4]. Patients with gynecological cancers have elevated plasma myeloperoxidase levels and tissue expression [5].

Currently, attempts to improve methods of treating ovarian cancer are heavily focused on overcoming resistance to platinum analogues, hyperthermic intraperitoneal chemotherapy, immunotherapy, and personalized medicine. Efforts are constantly being made to discover new and better therapeutic goals based on personalized medicine (adapting the medicine to a given patient). In this article, we review the literature on the role of myeloperoxidase in the carcinogenesis of ovarian cancer.

Aim of the study

The aim of this study was to investigate and present the importance of myeloperoxidase, its expression, and its polymorphisms in ovarian cancer.

Material and methods

Search strategy and study selection

The research literature published between January 1999 and December 2019 was reviewed using the electronic databases MEDLINE, PubMed, Scopus, and Web of Science. The search was conducted using the following words: "myeloperoxidase", "ovarian cancer", "reactive oxygen species", "expression", "polymorphism", and "tumour-associated neutrophils".

The following inclusion criteria were used: (I) articles written in English; (II) articles published between January 1999 and December 2019; (III) articles about the properties of myeloperoxidase and its significance in ovarian cancer; (IV) original and review articles; and (V) articles based on human studies. Articles involving animal studies and studies published as conference reports or letters to the editor were excluded from this review.

Data extraction

To minimize bias, three independent reviewers (BGB, AGB, and LB) assessed the articles based on abstracts during the search. If a study was deemed "relevant", the entire manuscript was assessed; the study was considered "relevant" if it met the inclusion criteria and was not excluded for the reasons mentioned above. When analyzing the article, the completeness of the following data was noted: first author's name, reference, year of publication, type of publication, country, and aim of the study.

A total of 3,375 articles were identified in the search. Thirty-five articles published from 1999 to 2019 and one published in 1989 (describing the isolation of myeloperoxidase) were included in the final review.

Results

A total of 3,375 articles were identified through the search of MEDLINE, PubMed, Scopus, and Web of Science. After excluding duplicate articles, 2261 were included for review. After careful analysis of these articles, some were excluded because they did not meet the inclusion criteria. The remaining 1,085 articles were further reviewed and analyzed. Of these, 998 were excluded because they were commentaries on articles and conference papers that did not contain the data required for this review; at this point, 87 articles remained. Fifty-three more articles were then excluded, leaving 34 articles published from 1999 to 2019 that were ultimately included in the review. One article from 1989 was focused on the isolation of myeloperoxidase (Figure 1).

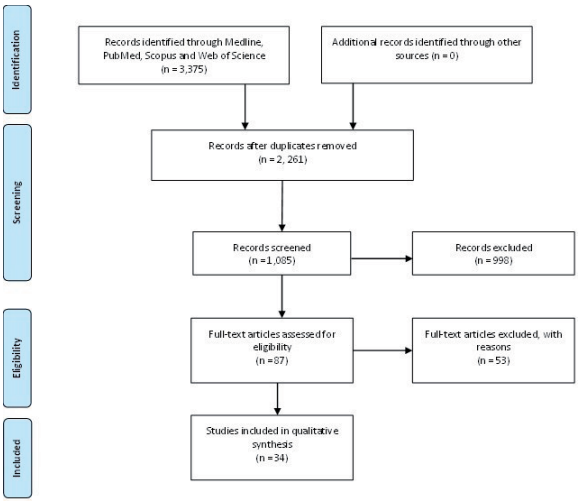

Figure 1. Flowchart of study selection

As a result, 34 articles published between 1999 and 2019 met the criteria for inclusion in this review paper. A summary and description of these articles are presented in Table 1.

Myeloperoxidase

Malle et al. demonstrated that myeloperoxidase (MPO EC 1.11.1.7) is an enzyme belonging to the per-

Table. 1. Characteristics of the included articles

Authors	Reference	Year of publication	Type of publication	Country	Aim of the study
Malle E et al.	[6]	2007	Review	Austria	Physico-chemical properties of MPO
Davies MJ	[7]	2010	Review	Australia	Physico-chemical properties of MPO
Nauseef WM	[8]	2014	Review	USA	Physico-chemical properties of MPO
Furtmüller PG et al.	[9]	2006	Review	Austria	Structure and properties of MPO
But PG et al.	[10]	2003	Review	Russia	Structure and properties of MPO
Ikeda-Saito M et al.	[11]	1989	Research Article	USA	Properties and isolation of MPO
Kettle AJ et al.	[12]	2001	Research Article	New Zealand	Properties and activity of MPO
Klebanoff SJ	[13]	2005	Review	USA	Structure, properties, and importance of MPO
Khan AA et al.	[14]	2018	Review	Saudi Arabia	Structure, properties, and importance of MPO; Role of MPO in different diseases
Atwal M et al.	[15]	2017	Research Article	UK	Hypochloric acid and its importance
Ikwegbue PC et al.	[16]	2019	Review	Africa	Hypochloric acid and its importance
Zhu H et al.	[17]	2006	Research Article	China	MPO G-463A polymorphism in various types of neoplasms
Qin X et al.	[18]	2013	Meta-analysis	China	MPO G-463A polymorphism in various types of neoplasms
Cascorbi I et al.	[19]	2000	Research Article	Germany	MPO G-463A polymorphism in various types of neoplasms
Feyler A et al.	[20]	2002	Research Article	France	Myeloperoxidase (MPO) polymorphism
Stevens JF et al.	[21]	2008	Review	USA	The role of acrolein in carcinogenesis
Tang M et al.	[22]	2011	Review	USA	Acrolein and DNA damage
Tsou HH et al.	[23]	2019	Research Article	Taiwan	Acrolein and DNA damage
Fridlender ZG et al.	[24]	2012	Review	USA	Tumor-associated neutrophils
Ghatalia P et al.	[25]	2019	Research Article	USA	Tumor-associated neutrophils
Wang J et al.	[26]	2019	Research Article	China	Tumor-associated neutrophils
Trellakis S et al.	[27]	2011	Research Article	Germany	Tumor-associated neutrophils and head and neck cancer
Banat GA et al.	[28]	2015	Research Article	Germany	Tumor-associated neutrophils and lung cancer
Fossati G et al.	[29]	1999	Research Article	Italy/UK	Neutrophil infiltration into human gliomas
Reid MD et al.	[30]	2011	Research Article	USA	Tumor-infiltrating neutrophils in pancreatic neoplasia
Shen M et al.	[31]	2014	Meta-analysis	China/Denmark	Tumor-associated neutrophils as a new prognostic factor in cancer
Fridlender ZG et al.	[32]	2009	Research Article	USA	Tumor-associated neutrophils
Mishalian I et al.	[33]	2013	Research Article	Israel	Tumor-associated neutrophils
Zeindler J et al.	[34]	2019	Research Article	Switzerland	Tumor-associated neutrophils and MPO
Mayer C et al.	[35]	2016	Research Article	Germany	Neutrophil granulocytes in ovarian cancer
Fletcher NM et al.	[36]	2012	Research Article	USA	MPO and free iron levels
Olson SH et al.	[37]	2004	Research Article	USA	Polymorphisms of the MPO gene in patients with ovarian cancer
Castillo-Tong DA et al.	[38]	2014	Research Article	Austria/Germany/ USA	Myeloperoxidase and ovarian cancer
Droeser RA et al.	[39]	2016	Research Article	Switzerland	Myeloperoxidase and ovarian cancer
Dai Y et al.	[40]	2018	Research Article	China/USA	The MPO encapsulation process by metal phenolic nanoparticles

oxidase group that is stored in the azurophilic granules of neutrophils. It constitutes 2% to 5% of all proteins in these cells. Myeloperoxidase is also present in monocytes, Kupffer cells, and glial cells. It plays a vital role in defending the body against pathogens and microorganisms [6]. Davies et al. reported that, during inflammation, activated neutrophils secrete myeloperoxidase into the phagosomes and intercellular spaces of infected sites. Activation of these cells is the result of the production of hydrogen peroxide

during NADPH oxidation in aerobic respiration. Myeloperoxidase uses hydrogen peroxide to oxidize halide (Cl^-, Br^-, I^-) and pseudohalide (SCN^-) ions to generate hypochlorous (HOCl), hypobromous (HOBr), hypoiodous (HOI), and hypothiocyanous (HOSCN) acids. All of these acids are strong and effective antimicrobial molecules [7]. The most rapid and complete antimicrobial action by human neutrophils against many organisms relies on the combined efforts of the azurophilic granule protein myeloperoxidase and hydrogen peroxide from the NADPH oxidase to oxidize chloride, thereby generating HOCl and a host of downstream reaction products [8].

Physical and chemical properties of myeloperoxidase

Myeloperoxidase is a cationic glycoprotein with a molecular weight of 146 kDa composed of two symmetrically arranged dimers (73 kDa) joined by a disulphide bridge formed by Cys153 residues [1,6]. Each dimer consists of a 14.5 kDa light subunit of 108 amino acids and contains one intra-disulphide chain linkage. The 58.5 kDa heavy subunit is made up of 466 amino acids, and its structure is stabilized by five intra-disulphide bonds [4,6]. Five glycosyl asparagine residues are located in the heavy subunit: Asn157, Asn189, Asn225, Asn317, and Asn565. Asn317-related sugar residues are found in the space between dimers and play a large role in their formation [9].

Each myeloperoxidase dimer consists of 19 α-helices, a small number of β-turns, an iron ion covalently bound to a heme molecule, and a calcium ion [9]. The heme molecule found in every myeloperoxidase dimer is located in a special pocket shaped by a core consisting of five α-helices, one of which comes from the light subunit. All peroxidases in which the chemical group is a prosthetic group contain in their active center an iron ion (Fe^{3+}) coordinated with a macrocyclic tetrapyrrole ring of protoporphyrin IX. In myeloperoxidase, the methyl groups of the A and C heme pyrrole rings are modified and form ester bonds with the Glu242 heavy subunit and the Asp94 light subunit carboxyl groups. The calcium ion binding site has the characteristic shape of a pentagonal bipyramid. This ion is bound by the oxygen atom of the Ser174 hydroxyl group and the oxygen atom of the Phe170 carbonyl group, which are arranged in the axis of the bipyramid, and by five other ligands that are in one plane [9,10].

The calcium ion in myeloperoxidase affects the position of the distal histidine relative to the heme group iron and thus affects the microenvironment and catalytic activity of the enzyme. The oxygen atom of the hydroxyl group of the Ser174 residue and the oxygen atom of the Phe170 carboxyl group of the polypeptide chain are axial ligands, while the residues Asp96 (carboxyl oxygen and peptide carbonyl oxygen), Thr168 (hydroxyl and peptide carbonyl oxygen) and Asp172 (carbonyl oxygen) are arranged approximately co-planar. Of these ligands, only Asp96, near the distal histidine (His95), is derived from a light polypeptide chain. The histidine 95α-light subunit helix is distal and regulates enzyme activity. The distal histidine plays an essential role as an acid-base catalyst that is involved in oxygen–oxygen (O–O) bond heterolysis in a hydrogen peroxide molecule by regulating deprotonation of peroxide and protonation of the resulting water molecule. The presence of calcium ions that maintain the correct orientation of the distal histidine and play a role in the interaction between the light and heavy dimer subunits is a characteristic of all mammalian peroxidases [9,10].

Properties of myeloperoxidase

The myeloperoxidase enzyme has two activities: chlorinating and peroxidative (Figure 2).

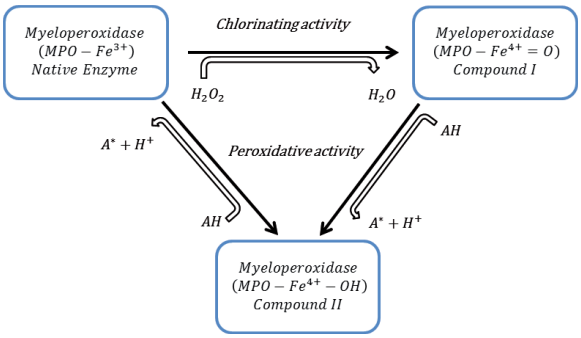

Figure 2. Enzymatic cycle of myeloperoxidase

This chlorinating activity has been very well described and reported in four of the scientific articles (Malle et al., Davies et al., Ikeda-Saito et al., and Kettle et al.) included in this review. This activity is based on the catalytic oxidation by myeloperoxidase of chloride (Cl^-), bromide (Br^-), or thiocyanate (SCN^-) ions to the appropriate halide (HXO, HOCl, or HOBr) or thiocyanate (HOSCN) in the presence of hydrogen peroxide.

$$H_2O_2 + X^- \longrightarrow HOX + H_2O$$

The appropriate halide acids or thiocyanic acid (HXO/HOSCN) formed during these reactions can then participate in further non-enzymatic reactions, such as oxidation and chlorination of chemical compounds present in their immediate environment. The most important task that arises during the acid chlorination reaction is protection of the body against the action of microorganisms because these compounds

are highly toxic to bacterial cells. Normally, to measure chlorinating activity, a reaction using chlorination of monochlorodimedone to dichlorodimedone, or reaction with taurine, in which taurine chloramine is formed, is used (Figure 3). During these reactions, product formation or substrate consumption can be monitored with a spectrophotometer [6,7,11,12].

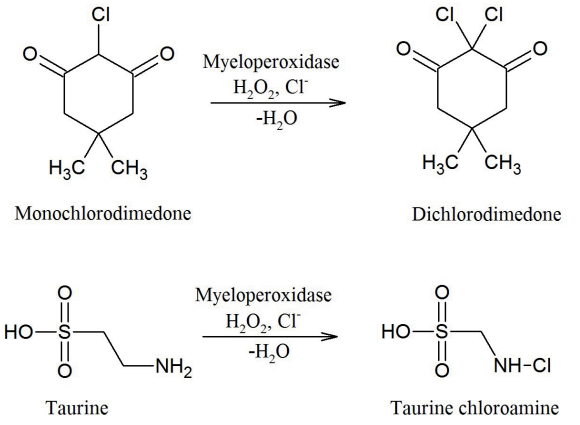

Figure 3. Oxidation of monochlorodimedone and taurine by myeloperoxidase

Peroxidative activity was described in three of the scientific articles (Malle et al. 2007, Davies et al. 2010, and Furtmüller et al. 2006) included in this review. This activity consists of myeloperoxidase catalysis of a one-electron oxidation reaction of a typical AH_2 peroxidase substrate with hydrogen peroxide to the appropriate radical (AH*).

$$H_2O_2 + 2AH_2 \longrightarrow 2AH^* + 2H_2O$$

During the reaction of the native form of the enzyme (*Por* – Fe^{3+}), the iron ion in myeloperoxidase is in the third degree of oxidation. In the resulting Complex I, the iron is in the fourth degree of oxidation and contains the cationic porphyrin radical ($Por^{\bullet+}$ – Fe^{4+} = 0). Complex I myeloperoxidase is a powerful oxidant that oxidizes both mono- and bi-electron reactions. This complex can oxidize many different substrates, including tyrosine, tryptophan, phenol, indole derivatives, hydrogen peroxide, and xenobiotics. Complex I can be reduced to the native form of the enzyme by reaction with halide ions (chlorination activity) to the corresponding halide acids or form Complex II (*Por* – Fe^{4+} – OH). Complex II iron is in oxidation state 4, and the bond between iron and oxygen is extended. This complex is formed as a result of the first one-electron reaction with the first substrate molecule (AH_2) and the substrate radical cation (AH*). Complex II can be reduced by the second substrate molecule back to the native form of myeloperoxidase or may form Complex III, with the iron ion in oxidation state 3 ($Por^{\bullet+}$ – Fe^{3+} – $O_2^{\bullet}$). This complex is formed as a result of the reaction of Complex II with an excess of hydrogen peroxide or by the reaction of Complex I with a superoxide ion [6,7,9]. Normally, to measure peroxidative activity, the reaction of o-dianisidine to oxidized o-dianisidine is used (Figure 4).

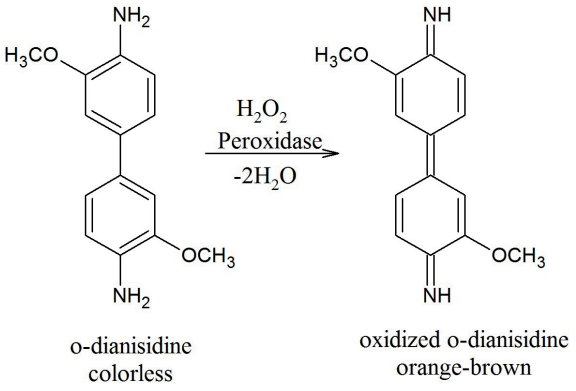

Figure 4. Oxidation of o-dianisidine by myeloperoxidase

Role of myeloperoxidase in carcinogenesis

Malle et al. reported that myeloperoxidase is a cytotoxic and bactericidal protein secreted by neutrophils at inflammatory sites that protects the body against various pathogens by generating HOCl (Figure 5) [6].

Klebanoff characterized myeloperoxidase as one of the main enzymes secreted by neutrophils as a result of phagocytosis during an inflammatory reaction; thus, it serves as an immunohistochemical marker for neutrophils [13]. Khan et al. submitted that an increase in the concentration of myeloperoxidase in plasma and other body fluids in humans may be useful as a marker during several inflammatory diseases, including rheumatoid arthritis, septic shock, atherosclerosis, renal disease, lung injury, and multiple sclerosis [14].

On the other hand, Atwal et al. and Ikwegbue et al. determined that HOCl (a powerful antimicrobial agent) can damage DNA, proteins, and fats and can oxidize fats by generating chloramine, nitrating agents, and free radicals. Myeloperoxidase catalyzes the production of HOCl, which causes damage to the DNA (Figure 5) molecule and can lead to mutations in oncogenes. The identification of defects in the DNA of 5-chlorocytosine (5-CIC) caused by secreted HOCl to inactivate or kill microorganisms through toll-like receptor 4 (TLR4) can cause chronic inflammation in the intestines, becoming evidence linking inflammation directly to cancer [15,16].

The work of Zhu et al., Qin et al., and Cascorbi indicates that myeloperoxidase expression disorders and an increased risk of various cancers may be directly related to myeloperoxidase gene polymorphisms. Many epidemiological studies have shown

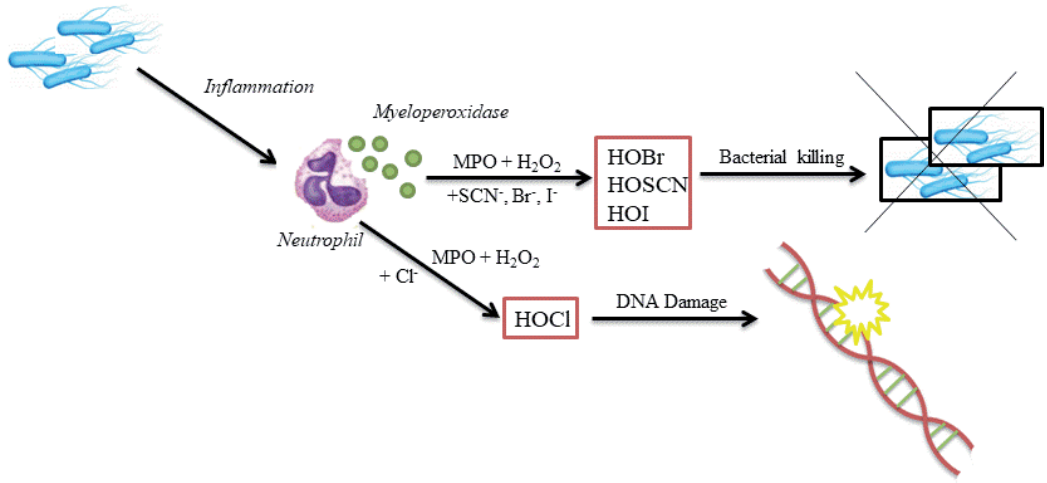

Figure 5. The role of myeloperoxidase in damage of the DNA molecule as a result of inflammation, leading to mutations

that the MPO G-463A polymorphism has an impact on the risk of many cancers, including lung cancer, breast cancer, bladder cancer, lymphoma, esophageal cancer, hepatocellular carcinoma, and laryngeal cancer [17–19]. Feyler et al. revealed that single nucleotide polymorphisms in the myeloperoxidase gene promoter region can affect protein transcription and expression [20]. Nauseef demonstrated that the replacement of thymidine with cytosine in codon 569 results in the substitution of an amino acid from arginine to tryptophan, which can cause functional defects in myeloperoxidase [8].

One of the studies in the review (Stevens et al.) showed that myeloperoxidase can also induce cancer indirectly by activating genotoxic intermediates and procarcinogens. As a result of the metabolism of certain unsaturated fats and amino acids (e.g., serine and threonine), it can form by-products, such as acrolein, which in turn form protein acrolein adducts. The main endogenous sources of acrolein are myeloperoxidase-mediated degradation of threonine and amine oxidase-mediated degradation of spermine and spermidine. In situations of oxidative stress and inflammation, they may be a significant source of acrolein. The biological effects of acrolein are a consequence of its reactivity toward biological nucleophiles, such as guanine in DNA and histidine, arginine, lysine, and cysteine residues in critical regions of proteases, nuclear factors, and other proteins. The resulting acrolein adducts may impair the function of these macromolecules, which can cause mutations, lesions in the transcriptome, and apoptosis modulation [21]. Tang et al. reported that the free form of acrolein induces α- and γ-hydroxy-1,N2-cyclic propano-2′-deoxyguanosine (α-OH-Acr-dG and γ-OH- Acr-dG) adducts in human cells. It was found that both types of Acr-dG adducts could be mutagenic and that they may induce G to T and G to A mutations [22]. For example, Tsou et al. introduced the concept that the mapping of the Acr-dG adduct distribution at the nucleotide level in acrolein-treated normal human bronchial epithelial cells determined that the acrolein-DNA binding spectrum in the p53 gene coincides with the p53 mutational spectrum in cigarette smoking-related lung cancer [23].

Role of tumor-associated neutrophils in cancers

According to Fridlender et al., tumor-associated neutrophils (TANs) are defined as neutrophils that have migrated into tumors [24]. TANs were found to be independent prognostic factors for overall survival, recurrence-free survival, and cancer-specific survival in localized clear cell renal carcinoma [25]. TANs had a predominantly immunosuppressive function in renal cell carcinoma, and the presence of TANs was an independent, unfavorable prognostic factor in patients treated with immunotherapy and tyrosine kinase inhibitors [26]. TANs were also found to be a prognostic factor in head and neck squamous cell carcinoma [27] and lung cancer [28]. Infiltration of neutrophils was found to correlate with tumor grade in human gliomas [29] and to be related to more aggressive types of pancreatic tumors [30].

A meta-analysis (Shen et al.) of 20 studies (including 3,946 patients with various solid tumors) investigating the presence of TANs in different cancer types found that a high density of tumor-infiltrating neutrophils was associated with unfavorable survival, recurrence-free survival/disease-free survival, cancer-specific survival, and overall survival. Conversely, peritumoral and stromal neutrophils were not statistically significantly associated with survival [31].

In analyzing the results of studies regarding the significance of TANs, two existing phenotypes of these cells present in tumors should be considered.

Under the influence of cytokines, TANs undergo polarization into either a protumorigenic (N2) phenotype or a proinflammatory/antitumorigenic (N1) phenotype. Polarization toward the N2 phenotype depends on transforming growth factor β (TGF-β), while TGF-β blockade leads to the recruitment and activation of the antitumorigenic N1 phenotype [32]. Antitumorigenic (N1) inflammatory neutrophils produce more reactive oxygen species (ROS) and higher levels of nitric oxide, hydrogen peroxide, and tumor necrosis factor alpha (TNF-α) than N2 TANs [33]. The N1 TAN phenotype can also recruit and activate CD8+ T cells, which are key contributors to any tumor immune response, while N2 TANs inhibit the function of CD8+ T cells [32].

In subset univariate analyses, infiltration by MPO-positive cells was associated with significantly longer overall survival in the triple-negative breast cancer subtype, the HER2-enriched subtype, and the luminal B/HER2-negative subtype. The expression of MPO-positive neutrophils in tumors showed that it is an independent prognostic factor for improved overall survival in multivariate analysis [34].

A study of a population of 334 patients attempted to explain the role of TANS in ovarian cancer. Analysis of this group of patients determined that neutrophils infiltrating tumors were found in 72% of cases. Co-cultivation of ovarian cancer cells with either neutrophils or neutrophil lysate can cause a change in the polygonal epithelial phenotype of these cells to the spindle morphology, resulting in cribriform cell growth. The reason for these changes in the shape of cells caused by neutrophils may be elastase, which is one of the most important proteases released by these cells. The change in shape induced by elastase is most likely due to degradation of membranous E-cadherin, which leads to loss of cell contact and polarization [35]. Moreover, in response to elastase, epithelial cytokeratins were downmodulated in parallel with nuclear translocation of β-catenin. These neutrophil elastase-induced alterations in cancer cells were compatible with the epithelial-to-mesenchymal transition (EMT) phenomenon. Following EMT, the cells displayed a more migratory phenotype. Neutrophil infiltrates were detected preferentially in areas with low E-cadherin expression. These *in vitro* data established a link between neutrophil-derived elastase, loss of E-cadherin, and EMT, which may explain why ovarian cancer patients with increased levels of neutrophils in tumors have a poorer prognosis [35].

Myeloperoxidase in ovarian cancer

We included five studies in this review to present the importance of myeloperoxidase in ovarian cancer [36–40].

In experimental studies by Saed et al., myeloperoxidase was expressed in ovarian cancer cell lines. In addition, it was observed in invasive ovarian cancer cases but not in normal ovarian epithelium. By causing caspase-3 nitrosylation, myeloperoxidase may inhibit apoptosis and increase ovarian cancer cell survival. In turn, silencing myeloperoxidase can significantly induce apoptosis, which underlines its role as a redox switch that regulates apoptosis in ovarian cancer [5]. Myeloperoxidase expression was evaluated in a study by Fletcher et al., who found significantly higher levels of myeloperoxidase expression in ovarian cancer tissues compared with benign and inflammatory lesions. International Federation of Gynecology and Obstetrics (FIGO) stages II–IV ovarian cancers manifested higher levels of tissue myeloperoxidase than FIGO stage I ovarian cancers ($p<0.05$). Also, ovarian cancer stages II–IV had significantly higher levels of serum myeloperoxidase compared with early-stage ovarian cancer, control, benign, and inflammatory groups. Serum myeloperoxidase levels assessed in FIGO stage I ovarian cancer and gynecological inflammation disorders did not differ significantly from each other but were significantly different from the control group and benign ovarian lesions [36].

One of the first studies (Olson et al.) assessing polymorphisms of the MPO gene in patients with ovarian cancer found that lower expression of the A allele (GA/AA) genotypes was associated with a small reduction in risk (OR=0.72); however, this trend did not reach statistical significance. The authors postulated the hypothesis that for myeloperoxidase, the slightly reduced risk for women with the AA genotype at position –463 in the promoter region could be protective, because this leads to weakening of the binding site [37]. Another study assessing myeloperoxidase polymorphisms by Castillo-Tong et al. showed that the higher expressing -463GG genotype was more frequent in FIGO I early-stage carcinoma. This suggests that the G allele increases the risk of ovarian cancer. Together, these studies suggest that atypical expression of this normally myeloid-specific MPO gene can cause oxidative damage and accumulation of potentially pathogenic mutations in ovarian epithelial cells that increase the risk of cancer. The GG genotype usually leading to higher expression of myeloperoxidase was not overrepresented in more advanced FIGO stages II–IV of ovarian carcinoma. A possible explanation for these findings is that myeloperoxidase expression in early-stage GG genotype carcinomas causes oxidative damage that shortens cell survival so that fewer GG genotype cancer cells survive to advanced stages. Another possibility is that higher levels of myeloperoxidase in infiltrating cancer cells with the GG genotype by neutrophils and monocytes/macrophages could enhance the killing of

cancer cells at an early stage of development, which could reduce the number of GG genotype cases detected in FIGO stages II–IV [38].

An investigation of the predictive role of myeloperoxidase and interleukin (IL)-17 in chemotherapy in ovarian cancer patients conducted by Droeser et al. revealed that IL-17- and MPO-positive immune cells correlated with each other in the tissues of both primary and recurrent carcinomas. Myeloperoxidase expression in multivariate Cox regression analysis combined categorized IL-17 and myeloperoxidase cell densities in ovarian cancer primary tumor tissues, indicating that the combination of these two immunological biomarkers was an independent prognostic factor for relapse-free survival. In the subgroup of IL-17- and MPO-positive biopsies of primary and recurrent cancer patients, there were no chemoresistant patients [39].

Dai et al. stated that myeloperoxidase has been used to produce modern nanoparticles to improve the effectiveness of platinum analogues, which are crucial in the treatment of ovarian cancer patients. In order to improve the therapeutic efficacy of platinum analogues, the idea of HOCl production *in situ* was used in experimental studies. Modern nanoparticles have been developed in which the phagocytic enzyme myeloperoxidase is coated with two functional polyphenol derivatives (PEG polyphenols and platinum prodrug polyphenols) and a ferric ion by metal phenolic coordination, which can shield myeloperoxidase from degradation by other compounds in the blood. Additionally, in cells, the platinum prodrug may be reduced to cisplatin and produce hydrogen peroxide. In the intercellular environment, myeloperoxidase may catalyze the conversion of hydrogen peroxide to HOCl. The preparation of MPO Pt PEG nanoparticles (MPP NPs) may be employed as an ROS cascade bioreaction to enhance platinum analogue therapy. It was found that treatment with MPP NPs caused significantly higher antitumor activity than free cisplatin at the same dose. Mice treated with MPP NPs exhibited much longer survival. Moreover, hematoxylin and eosin staining of tumor sections from MPP NPs showed the most significant tumor cell apoptosis and necrosis compared with the control groups. It was evidenced by ^{89}Zr-based positron emission tomography imaging that MPP NPs could circulate for a prolonged time in the blood and showed high accumulation in tumors. No change in body weight was observed during any treatment. Furthermore, analysis of the major organs (lung, liver, spleen, heart, and kidneys) determined that there were no significant histological changes [40].

Conclusions

Since ovarian cancer is one of the most common cancers in women, it is imperative to refine methods to detect it earlier. Because myeloperoxidase oxidizes many different compounds, including halogenated ones, it causes DNA damage, thus increasing the risk of mutations that cause an increase in ovarian cancer. Therefore, continuous research on the expression of myeloperoxidase in ovarian cells is vital and warranted.

References

1. Doherty JA, Peres LC, Wang C, Way GP, Greene CS, Schildkraut JM. Challenges and opportunities in studying the epidemiology of ovarian cancer subtypes. Curr Epidemiol Rep 2017; 4(3): 211–220.
2. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. The Lancet 2019; 393(10177): 1240–1253.
3. Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM, et al. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. Reprod Sci 2019; 26(12): 1603-1612.
4. Zederbauer M, Jantschko W, Neugschwandtner K, Jakopitsch Ch, Moguilevsky N, Obinger Ch, et al. Role of the covalent glutamic acid 242–heme linkage in the formation and reactivity of redox intermediates of human myeloperoxidase. Biochemistry 2005; 44(17): 6482–6491.
5. Saed GM, Ali-Fehmi R, Jiang ZL, Flechter NM, Diamond MP, Abu-Soud HM, et al. Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer. Gynecol Oncol 2010; 116(2): 276–281.
6. Malle E, Furtmüller PG, Sattler W, Obinger C. Myeloperoxidase: a target for new drug development? Br J Pharmacol 2007; 152(6): 838–854.
7. Davies MJ. Myeloperoxidase-derived oxidation: mechanisms of biological damage and its prevention. J Clin Biochem Nutr 2010; 48(1): 8–19.
8. Nauseef WM. Myeloperoxidase in human neutrophil host defence. Cell Microbiol 2014; 16(8): 1146–1155.
9. Furtmüller PG, Zederbauer M, Jantschko W, Helm J, Bogner M, Jakopitsch Ch, et al. Active site structure and catalytic mechanisms of human peroxidases. Arch Biochem Biophys 2006; 445(2): 199–213.
10. But PG, Fomina VA, Murav'ev RA, Rogovin VV. Myeloperoxidase from neutrophil peroxisomes. Biol Bull 2003; 30(3): 207-211.
11. Ikeda-Saito M, Lee H, Adachi K, Eck HS, Prince RC, Booth KS, et al. Demonstration that spleen green hemeprotein is identical to granulocyte myeloperoxidase. J Biol Chem 1989; 264(8): 4559–63.
12. Kettle AJ, Winterbourn CC. A kinetic analysis of the catalase activity of myeloperoxidase. Biochemistry 2001; 40(34): 10204–10212.
13. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol 2005; 77(5): 598–625.

14. Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. Med Sci 2018; 6(2): 33.

15. Atwal M, Lishman EL, Austin CA, Cowell IG. Myeloperoxidase enhances etoposide and mitoxantrone-mediated DNA damage: a target for myeloprotection in cancer chemotherapy. Mol Pharmacol 2017; 91(1): 49–57.

16. Ikwegbue PC, Masamba P, Mbatha LS, Oyinloye BE, Kappo AP. Interplay between heat shock proteins, inflammation and cancer: a potential cancer therapeutic target. Am J Cancer Res 2019; 9(2): 242–249.

17. Zhu H, Yang L, Zhou B, Yu R, Tang N, Wang B. Myeloperoxidase G–463A polymorphism and the risk of gastric cancer: a case–control study. Carcinogenesis 2006; 27(12): 2491–2496.

18. Qin X, Deng Y, Zeng ZY, Peng QL, Huang XL, Mo CJ, et al. Myeloperoxidase polymorphism, menopausal status, and breast cancer risk: an update meta-analysis. PloS One 2013; 8(8): e72583.

19. Cascorbi I, Henning S, Brockmöller J, Gephart J, Meisel Ch, Müller JM, et al. Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant-463A of the myeloperoxidase gene. Cancer Res 2000; 60(3): 644–649.

20. Feyler A, Voho A, Bouchardy C, Kuokkanen K, Dayer P, Hirvonen A, et al. Point: myeloperoxidase –463G --> a polymorphism and lung cancer risk. Cancer Epidemiol Prev Biomark 2002; 11(12): 1550–1554.

21. Stevens JF, Maier CS. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. Mol Nutr Food Res 2008; 52(1): 7–25.

22. Tang M, Wang H, Hu Y, Chen WS, Akao M, Feng Z, et al. Acrolein induced DNA damage, mutagenicity and effect on DNA repair. Mol Nutr Food Res 2011; 55(9): 1291–1300.

23. Tsou HH, Hu CH, Liu JH, Liu ChJ, Lee ChH, Liu TY, et al. Acrolein is involved in the synergistic potential of cigarette smoking– and betel quid chewing–related human oral cancer. Cancer Epidemiol Prev Biomark 2019; 28(5): 954–962.

24. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis 2012; 33(5): 949–955.

25. Ghatalia P, Gordetsky J, Kuo F, Dulaimi E, Cai KQ, Devarajan K, et al. Prognostic impact of immune gene expression signature and tumor infiltrating immune cells in localized clear cell renal cell carcinoma. J Immunother Cancer 2019; 7(1): 139.

26. Wang J, Liu L, Bai Q, Ou Ch, Xiong Y, Qu Y, et al. Tumor-infiltrating neutrophils predict therapeutic benefit of tyrosine kinase inhibitors in metastatic renal cell carcinoma. OncoImmunology 2019; 8(1): e1515611.

27. Trellakis S, Farjah H, Bruderek K, Dumitru CA, Hoffmann TK, Lang S, et al. Peripheral blood neutrophil granulocytes from patients with head and neck squamous cell carcinoma functionally differ from their counterparts in healthy donors. Int J Immunopathol Pharmacol 2011; 24(3): 683–693.

28. Banat GA, Tretyn A, Pullamsetti SS, Wilhelm J, Weigert A, Olesch C, et al. Immune and inflammatory cell composition of human lung cancer stroma. PloS One 2015; 10(9): e0139073.

29. Fossati G, Ricevuti G, Edwards SW, Walker C, Dalton A, Rossi ML. Neutrophil infiltration into human gliomas. Acta Neuropathol (Berl) 1999; 98(4): 349–354.

30. Reid MD, Basturk O, Thirabanjasak D, Hruban RH, Klimstra DS, Bagci P, et al. Tumor-infiltrating neutrophils in pancreatic neoplasia. Mod Pathol 2011; 24(12): 1612–1619.

31. Shen M, Hu P, Donskov F, Wang G, Liu Q, Jiajun D. Tumor-associated neutrophils as a new prognostic factor in cancer: a systematic review and meta-analysis. PloS One 2014; 9(6): e98259.

32. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-β: "N1" versus "N2" TAN. Cancer Cell 2009; 16(3): 183–194.

33. Mishalian I, Bayuh R, Levy L, Zolotarov L, Michaeli J, Fridlender G. Tumor-associated neutrophils (TAN) develop protumorigenic properties during tumor progression. Cancer Immunol Immunother 2013; 62(11): 1745–1756.

34. Zeindler J, Angehrn F, Droeser R, Däster S, Piscuoglio S, Ng CKY, et al. Infiltration by myeloperoxidase-positive neutrophils is an independent prognostic factor in breast cancer. Breast Cancer Res Treat 2019; 177(1): 581–589.

35. Mayer C, Darb-Esfahani S, Meyer AS, Hübner K, Rom J, Sohn Ch, et al. Neutrophil granulocytes in ovarian cancer - induction of epithelial-to-mesenchymal-transition and tumor cell migration. J Cancer 2016; 7(5): 546–554.

36. Fletcher NM, Jiang Z, Ali-Fehmi R, Levin NK, Belotte J, Tainsky MA, et al. Myeloperoxidase and free iron levels: potential biomarkers for early detection and prognosis of ovarian cancer. Cancer Biomark 2012; 10(6): 267–275.

37. Olson SH, Carlson MDA, Ostrer H, Harlap S, Stone A, Winters M, et al. Genetic variants in SOD2, MPO, and NQO1, and risk of ovarian cancer. Gynecol Oncol 2004; 93(3): 615–620.

38. Castillo-Tong DA, Pils D, Heinze G, Braicu I, Sehouli J, Reinthaller A, et al. Association of myeloperoxidase with ovarian cancer. Tumor Biol 2014; 35(1): 141–148.

39. Droeser RA, Mechera R, Däster S, Weixler B, Kraljević M, Delko T, et al. MPO density in primary cancer biopsies of ovarian carcinoma enhances the indicative value of IL-17 for chemosensitivity. BMC Cancer 2016; 16(1): 639.

40. Dai Y, Cheng S, Wang Z, Zhang R, Yang Z, Wang J, et al. Hypochlorous acid promoted platinum drug chemotherapy by meloperoxidase-encapsulated therapeutic metal phenolic nanoparticles. ACS Nano 2018; 12(1): 455–463.

Word count: 4436 • Tables: 1 • Figures: 5 • References: 40

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Gąsowska-Bajger B, Gąsowska-Bodnar A, Bodnar L.
Properties and functions of myeloperoxidase and its role in ovarian cancer.
Med Sci Pulse 2022;16(3): 23–32. DOI: 10.5604/01.3001.0015.9645.

Correspondence address:
Beata Gąsowska-Bajger
Institute of Chemistry,
University of Opole,
Oleska 48, 45-052 Opole,
Poland
E-mail: bgasowska@uni.opole.pl

Received: 22.04.2022
Reviewed: 20.07.2022
Accepted: 25.07.2022