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Review

Possible Roles of Mitochondrial Dynamics and the Effects of Pharmacological Interventions in Chemoresistant Ovarian Cancer

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ABSTRACT

Ovarian cancer is the major cause of death out of all the gynecologic cancers. The prognosis of this cancer is quite poor since patients only seek treatment when it is at an advanced stage. Any early biomarkers for this cancer are still unknown. Dysregulation of mitochondrial dynamics with associated resistance to apoptosis plays a crucial role in several types of human carcinogenesis, including ovarian cancers. Previous studies showed that increased mitochondrial fission occurred in ovarian cancer cells. However, several pharmacological interventions and therapeutic strategies, which modify the mitochondrial dynamics through the promotion of mitochondrial fission and apoptosis of cancer cells, have been shown to potentially provide beneficial effects in ovarian cancer treatment. Therefore the aim of the present review is to summarize and discuss the current findings from in vitro, in vivo and *clinical studies* associated with the alteration of mitochondrial dynamics and ovarian cancers with and without interventions.

Contents

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1. Introduction

Ovarian cancer remains the leading cause of gynecologic cancer death in the United States [1]. The 5-year relative survival rate is low since most of patients only seek treatment in advanced stages of the disease [1]. The majority of histological subtypes of ovarian cancers are epithelial cancers [2]. Recently, ovarian cancers have been subdivided into low-grade and high-grade cancers based on underlying molecular biological differences [3]. The primary treatment for ovarian cancer is surgical removal followed by systemic platinum-based chemotherapy [4]. The prognosis of ovarian cancers can be classified as poor when no clinical benefit or refractory condition occurs after two consecutive chemotherapy regimens, or when cancer recurs within 6 months after completion of treatment with chemotherapy or called platinum resistant condition [4]. On the contrary, the condition in which the cancer relapses after 6 months of initial chemotherapy is classified as the platinum sensitive condition [4]. Although many patients respond well to the first-line chemotherapy, some patients with an advanced stage ovarian cancer ultimately develop recurrent diseases with the platinum resistant condition [2]. Therefore, research into the identification of an early biomarker of ovarian cancers and into alternative strategies to treat patients with ovarian cancer is still needed.

Mitochondria are mobile organelles, undergoing consistent transformation, a process known as "mitochondrial dynamics" [5]. Mitochondrial dynamics consists of two processes, mitochondrial fusion and fission. Mitochondria can continuously join together by the process of fusion and divide into two mitochondria by the process of fission. The process of fission creates small and fragmented mitochondria, which can generate reactive oxygen species (ROS), cause mitophagy, or accelerate cell proliferation in response to nutrient excess and cellular dysfunction. An increase in mitochondrial fission has been observed in several human diseases including several types of cancer cells [6–12]. In contrast to mitochondrial fission, mitochondrial fusion results in a tubular or hyperfused mitochondrial network that allows diffusion of matrix content among mitochondria, diluting the accumulated mitochondrial DNA mutations and oxidized proteins [5,13]. Previous studies have reported an association between an increased mitochondrial fusion and chemoresistance in several cancer types, including breast, cervical and ovarian cancer [14,15]. An essential step in mitochondrial membrane fission is the recruitment of dynamin-related protein-1 (Drp1) to mitochondria and interaction with its outer mitochondrial membrane receptors, where membrane constriction fueled by GTPase activity is initiated [5]. With regards to mitochondrial fusion, the mitofusins, Mfn-1 and Mfn-2, along with optic atrophy protein 1 (Opa1), have been shown to mediate mitochondrial fusion [5]. Several previous studies have shown an imbalance of mitochondrial fission and fusion in several types of cancer [6–12]. Those studies demonstrated that increased fission activity and/or decreased fusion leading to a fragmented mitochondrial network have been observed in cancer cells [6–12].

Recent studies have demonstrated that ovarian cancer cells had an increase in mitochondrial fragmentation, Drp1 protein and mRNA levels, indicating a potential role of Drp1, a mitochondrial fission mediator in tumorigenesis in ovarian cancer [10,16]. In addition, a previous study reported the relationship between mitochondrial fusion and chemoresistance in ovarian cancer [15]. Furthermore, the mitogen-activated protein kinase/ extracellular signal-regulated (MAPK/ERK) pathway and estrogen-related receptor (ERR)-α (a co-transcription factor for gene expressions associated with mitochondrial fusion) have been shown to be associated with invasion, migration and aggressiveness in human ovarian cancer cells [17,18]. Hou and colleagues demonstrated that the inhibition of the MAPK/ERK pathway with a MEK inhibitor (MEKi) caused an increase in ERR-α positive ovarian cancer cells, resulting in weak tumor suppression activity [19]. However, the tumor suppression effect was enhanced when the treatment was combined with fulvestrant (a synthetic estrogen receptor (ER) antagonist) [19]. In addition, Wang and colleagues observed that an increase in ERR-α was associated with an elevation in Mfn-1 and Mfn-2 mRNA expression, leading to an epithelial-mesenchymal transition (EMT), and finally resulting in increased ovarian cancer cell migration [18]. All of these findings suggest that alterations in mitochondrial dynamics with increased mitochondrial fusion could be a possible underlying mechanism responsible for the aggressiveness of ovarian cancers.

Moreover, increased Drp1 expression is associated with a hypoxia-driven migratory phenotype in multiple cancer types, and several studies have emphasized the important role of mitochondrial dynamics in cancer metastasis [12,20,21]. Therefore, the aim of this review is to summarize the existing evidence regarding the connection between mitochondrial dynamics and ovarian cancers and the effects of various pharmacological interventions on mitochondrial dynamics of ovarian cancers.

1.1. Search Strategy and Selection Criteria

The PubMed database was searched using the keywords: "ovarian cancers", and "mitochondrial dynamics" from August 2013 to September 2017. The search was limited to research articles published in the English language.

2. Mitochondrial Dynamics under Physiological and Pathological Conditions

Mitochondria are dynamic organelles that have their own genome and process of protein synthesis [22]. Mitochondrial morphology varies across cell types and tissues through the regulatory process of mitochondrial dynamics: fusion and fission. In addition, mitochondria play a central role in many biochemical, fundamental cellular and physiological processes such as the generation of ATP and reactive oxygen species (ROS), calcium homeostasis, cell-cycle progression, apoptosis, mitophagy and oxygen sensing [5]. During their life cycle, mitochondria start with growth and division of pre-existing mitochondria (known as biogenesis) and end with degradation of damaged mitochondria by mitophagy (a process called turnover) [23]. Both fusion and fission enable the cells to create multiple heterogeneous mitochondria or interconnected mitochondrial networks, depending on the physiological conditions. Fission plays roles in the maternal inheritance and separation of organelles during cell division, the release of pro-apoptotic factors, the intracellular distribution, and the elimination of impaired organelles by mitophagy [23,24]. Fused mitochondrial networks are essential for the dissipation of metabolic energy and for the complementation of mitochondrial DNA (mtDNA) gene products in heteroplasmic cells to defend against aging [23]. The balance of these processes is essential for cell life and death.

Unopposed fusion leads to a hyperfused network and serves to counteract metabolic insults, maintain cellular integrity, and guard against autophagy. However, unopposed fission causes mitochondrial fragmentation, which can create greater ROS production, enable mitophagy, and accelerate cell proliferation. Not surprisingly, therefore, mitochondrial dysfunction or deregulation of mitochondrial dynamics have been found in conditions associated with aging and several diseases including obesity, cardiovascular, endocrine, neurodegenerative and neoplastic diseases or cancers [5,25,26].

3. Role of Mitochondrial Dynamics in Ovarian Cancer

Among six hallmarks proposed by Hanahan and Weinberg to characterize a cancer cell, resistance of cell death is involved in mitochondrial dynamics [27]. Alterations in mitochondrial dynamics that promote mitochondrial fission or impaired fusion have been observed in several types of cancer [6–12]. Previous studies demonstrated the role of Drp1 on tumorigenic cell proliferation in ovarian cancer [10,16]. Those studies found that ovarian cancer cells had increased

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