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Editorial

Targeting mitochondrial dynamics to overcome therapeutic resistance

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Mitochondria are frequently described as the powerhouse of the cell for apparent reasons. However, these organelles are dynamic was not known until recently. Scientists have found that mitochondria must undergo well-organized cycles of fragmentation/fission and fusion to maintain structural integrity, size, and distribution. These fission and fusion events are collectively called "mitochondrial dynamics" and are considered crucial for regulating organelle function. Mitochondrial fission accounts for the division of one mitochondrion into two. It is regulated by GTPase dynamin-related protein 1 (DRP1) and its adaptor proteins such as mitochondrial fission protein 1 (FIS1), mitochondrial fission factor (MFF), and mitochondrial dynamics protein of 49 and 51 kDa (Mid49, Mid51). DRP1, a cytosolic protein, is recruited to mitochondria to cause fragmentation upon activation through upregulation of serine 616 and downregulation of serine 637 phosphorylation. In contrast, mitochondrial fusion involves the fusion of two separate small mitochondria into one large mitochondrion, thereby generating a network of elongated or tubular mitochondria. These fusion events are regulated by GTPase dynamin-like proteins located on the outer (Mitofusin 1, MFN1 and mitofusin 2, MFN2) and inner (optic atrophy protein 1, OPA1) mitochondrial membrane. Fission is generally coupled with apoptosis, while fusion is associated with pro-survival signals. However, cancer cells can utilize mitochondrial dynamics, depending on their cellular state; this is reflected in the current conflicting literature explaining mitochondrial fission or fusion influencing tumor progression. Nonetheless, alterations in mitochondrial dynamics have been implicated as one of the key factors in tumor progression and therapeutic resistance across a wide spectrum of cancers. As a result, targeting mitochondrial dynamics is emerging as a potential strategy for solid tumors.

One of the key features leading to therapeutic resistance exhibited by a wide variety of tumors is their ability to induce the expression of the PIM family of serine-threonine kinases. Chauhan et al. tested the hypothesis that PIM kinase could drive therapeutic resistance through mitochondrial dynamics [1]. PIM1 kinase expression is dramatically increased in lung cancer, and overexpression studies have shown that these cells exhibit hyper-fused mitochondria, causing a shift in the effectiveness of chemotherapeutic drugs such as docetaxel or cisplatin to higher doses. In contrast, PIM inhibitors significantly induce mitochondrial fission and retard tumor growth when combined with a low dose of chemotherapeutic drugs, suggesting that PIM1 triggers therapeutic resistance by regulating mitochondrial dynamics. The effects of PIM1 kinase on mitochondrial dynamics are primarily mediated through DRP1. An inverse relationship exists between PIM1 and DRP1 expression levels in lung cancer dictated by the severity or stage of the disease progression. In addition, PIM1 kinase also controls DRP1 activation and mitochondrial recruitment through serine phosphorylation at sites 616 and 637. The use of specific inhibitors targeting PIM family kinases enhance DRP1 expression and mitochondrial localization to induce fission events accompanied by elevated mitochondrial superoxide production, total cellular ROS accumulation, and the activation of apoptotic cell death pathways [1]. Thus, targeting mitochondrial dynamics through the PIM1-DRP1 signaling axis provides a critical approach to overcoming therapeutic resistance in lung cancer (Figure 1).

Mitochondria change their morphology and function to maintain cellular energy homeostasis. Interestingly, cancer cells can utilize these features to support high metabolism, proliferation, and survival requirements. One of the recent developments in finding new treatments for triple-negative breast cancer (TNBC) is understanding the mitochondrial morphological changes. TNBC is an aggressive form of breast cancer often described by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). During stress, the extent of mitochondrial fragmentation dictates the fate of TNBC cells. Under moderate stress, a low level of mitochondrial fragmentation is utilized by TNBC cells to

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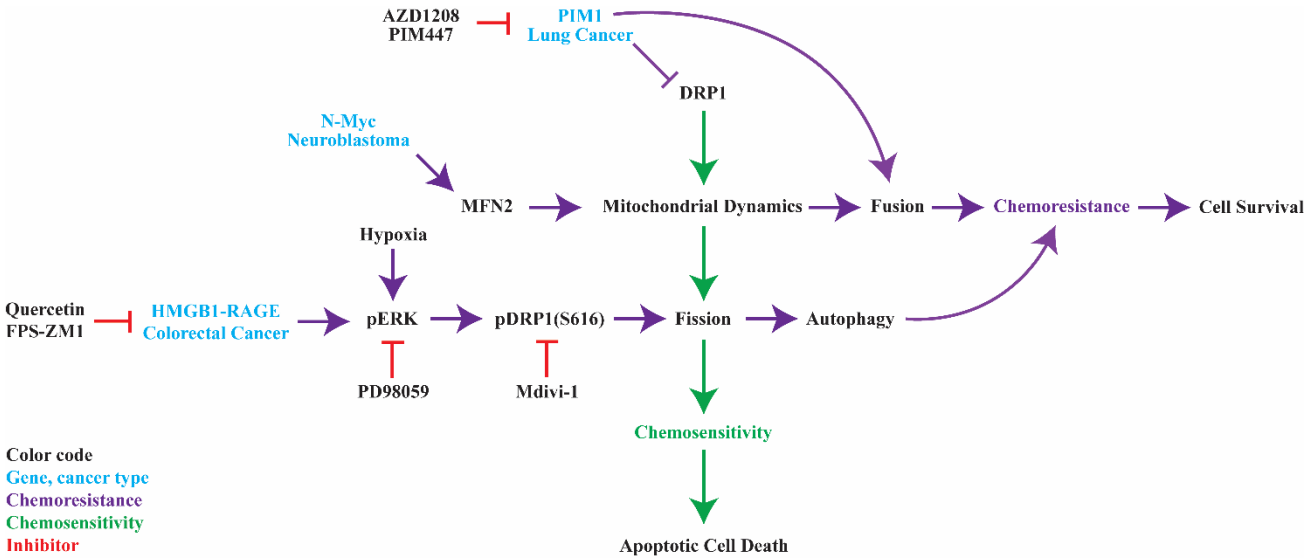

Figure 1: Overview of mitochondrial dynamics leading to chemoresistance in representative cancers [1, 5, 7].

promote survival or aggressiveness. In contrast, a severe stress signal amplifies mitochondrial fragmentation to the level that can cause excessive ROS production and apoptosis. In TNBC, the induction and suppression of metastatic events are strongly coupled with fused and fragmented mitochondria. Mitochondrial dynamics have become a suitable new target for TNBC. As a result, present breast cancer research mainly focuses on chemotherapeutic drugs targeting mitochondrial dynamics instead of investigating mitochondrial dynamics for drug resistance. However, tamoxifen resistance in breast cancer cells has been linked to fragmented mitochondrial phenotype [2]. It is also known that DRP-1 mediated mitochondrial fragmentation can sensitize breast cancer cells to cisplatin besides controlling cell migration under hypoxia. Thus, targeting mitochondrial dynamics could be a novel approach to suppressing metastasis and overcoming chemoresistance in breast cancer.

Although patients with ovarian cancer respond to cisplatin initially, they develop chemoresistance when therapy is continued over a long period. Zou et al. recently investigated cisplatin chemoresistance using a human ovarian cancer cell line model ($SKOV_3$) and reported that the observed chemoresistance could be attributed to the regulation of mitochondrial dynamics involving DRP1 and MFN2 [3]. The authors further claim that cells uptake cisplatin through copper influx transporters or organic cation transporters and target mitochondria to augment ROS production, alter mitochondrial membrane potential, and activate an intrinsic apoptotic pathway by upregulating BAX and cleaved caspase 3/9. However, when cells acquire cisplatin resistance, there is a reduction in DRP1 levels and enhanced expression of MFN2, leading to increased mitochondrial fusion, which prevents ROS production, changes in mitochondrial membrane potential, and suppresses activation of apoptotic cell death pathways. Thus, targeting mitochondrial dynamics in ovarian cancer could be beneficial in overcoming cisplatin chemoresistance.

Venetoclax is approved for the treatment of acute myeloid leukemia (AML). However, patients develop drug resistance when therapy is continued for an extended period. Uncovering resistance mechanisms becomes crucial for the effective treatment or successful response to the drug. It was found that the drug resistance is caused due to mitochondrial dynamics resulting from CLPB (mitochondrial chaperonin) and OPA1 (mitochondrial dynamics regulator) interaction. Consequently, CLPB depletion sensitizes AML cells to Venetoclax-induced apoptosis. Another study attributed Jurkat leukemia cell survival following doxorubicin treatment to mitochondrial fusion mediated through upregulation of MFN2 [4]. Thus, targeting mitochondrial dynamics could be beneficial in overcoming Venetoclax or doxorubicin resistance in leukemia patients.

The induction in N-Myc expression has been associated with tumorigenesis of pediatric cancer called neuroblastoma. Casinelli et al. reported that N-Myc amplification causes aberrant transcriptional and posttranslational regulation to facilitate enhanced mitochondrial fusion resulting in apoptotic resistance and altered bioenergetics. In addition, the authors found that cisplatin resistance exhibited with N-Myc overexpression is due to increased mitochondrial fusion [5], indicating that the cisplatin resistance in neuroblastoma can be overcome by targeting mitochondrial dynamics (Figure 1).

While chemoresistance has been majorly associated with fused mitochondria, there is increasing evidence linking it to mitochondrial fission. In nasopharyngeal carcinoma (NPC), LMP1 (latent membrane protein1) regulates DRP1 through AMPK and cyclin B1/Cdk1 signaling to induce mitochondrial fission, causing increased survival and cisplatin resistance. Interestingly, targeting DRP1 by

metformin or cucurbitacin E has sensitized NPC cells to cisplatin [6]. One of the most frequent changes in the tumor microenvironment is hypoxia. Hypoxia has been linked to cisplatin resistance in ovarian cancer through induction in DRP1-dependent mitochondrial fission. Treating these cells with DRP-1 inhibitor, Mdivi-1, was sufficient to counteract drug resistance. T-cell acute leukemia cells exhibit bone marrow-derived mesenchymal stem cell-induced drug resistance due to mitochondrial fission promoted through ERK/DRP1 signaling. Another study on colorectal cancer reported that ERK-mediated DRP1 phosphorylation through the HMGB1-RAGE signaling axis contributes to oxaliplatin resistance [7] (Figure 1).

In response to metabolic requirements, cancer cells undergo fusion or fission in a context-specific manner which may differ in the mechanisms regulating mitochondrial dynamics. This could be instrumental in framing new strategies to combat chemoresistance for different contexts. All these findings highlight the importance of mitochondrial dynamics as a central mechanism of chemoresistance. Although fusion and fission are seemingly opposite processes, they both could be promoting chemoresistance in a context-specific manner. Thus, targeting mitochondrial dynamics sounds promising to overcome therapeutic resistance. However, it warrants further studies to generate valuable insights into chemoresistance associated with fusion or fission in an altered tumor microenvironment.

Declarations

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