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The Role of Heme Oxygenase 1 in Drug-Resistance in Hematoloigcal Malignancies

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Abstract

Heme oxygenase-1(HO-1) is well-known as its strong capacity of oxidative stress decreasing, inflammatory response attenuating and anti-apoptosis. Recent reports indicate the promotive efficacy of HO-1 on drug-insensitivity in hematological malignancies. Herein, we conduct this article to review the anti-apoptotic activities and the mechanism involved in chemo-resistance induced by abnormal expression of HO-1. In conclusion, these research progresses provide an insight into knowing properties of HO-1 and disclose a new strategy to reversing drug-resistance in hematological malignancies.

Keywords: Heme oxygenase-1; Hematological maliganancies; Drug-resistance; Mechanism

Introduction

More recent studies, including our discoveries, reported that over expression of HO-1 can lead to resistance to anti-cancer agents in hematological maglinancies [1-4]. It depends on the special characteristic of HO-1, which could decrease cellular oxidative stress to the acceptable level with ease in malignant cells underwent with stimulation [5-6]. Otherwise, HO-1 was also proven as a crucial regulator to chemo-resistance mediated by bone marrow environments [7-8]. In this review, we'll concisely describe the mechanism of drug-resistance inducted by HO-1 and the reversing strategy from various aspects.

Protection of malignant cells against damaging by reducing oxidative stress

Reactive Oxygen Specis (ROS) is a main production of oxidative stress [9]. As it was accumulated to the maximum limit, the mitochondrial respiratory chain would be damaged and cell death was triggered directly. HO-1 was reported to reduce the oxidation level to protect cells from damage [10]. Silencing HO-1 activated the endoplasmic reticulum apoptotic pathway by releasing Ca2+ and activating caspase-12. Meanwhile, HO-1 down regulation increased ROS generation and reduced MTP by undermining the steady state of oxidation reduction system, thus releasing Cyto C and increasing caspase-9 to activate the mitochondrial apoptotic pathway in acute myeloid leukemia [11].

Activation of anti-apoptosis signaling pathway

Up to now, most studies concerning the role of HO-1 in the signaling pathways of AML apoptosis have focused on the correlation between HO-1 and tumor suppressing pathway [12-14]. The high level of HO-1 exerts an anti-apoptotic effects on AML cells by JNK/c-JUN signaling pathway which probably suppresses P53 or releases reactive oxygen species (ROS) [15,16]. In addition, the characteristic over expression of HO-1 is mediated by constitutively activated NF-κB in ABC-DLBCL. HO-1 expression inhibits apoptosis in ABC-DLBCL, whereas HO-1 silencing promotes apoptosis. Increasing the expression of HO-1 in GCB-DLBCL-derived OCI-ly19 cells can lead to drug resistance. Furthermore, the combination of NF-κB and HO-1 may provide a new target for the therapy of ABC-DLBCL [17]. Moreover, we also found that HO-1 had anti-apoptotic effects on Imatinib (IM)-resistant CML cells through hyperfunction of NHE1, which may promotes tumor resistance by increasing pHi through the PKC-β-p38/MAPK-Nrf2 pathway [18].

Increasing resistance to demethylation agents in MDS

Myelodysplastic syndrome (MDS), as a heterogeneous group of related clonal diseases. It has been associated with aberrant methylation of relevant gene promoters that can facilitate tumor onset by silencing anti-oncogenes and by changing the

expressions of tumor-related genes [19,20]. These epigenetic changes can be reverted by drugs such as DNA methyl-transferase inhibitor 5-azacytidine (AZA) and decitabine (DAC). HO-1overexpression may regulate the proliferation and survival of MDS cell line SKM-1 that thus escaped decitabine-induced apoptosis. The expression level of HO-1 was related with the risk stratification of MDS.

With DAC treatment in vitro, HO-1 over expression was blocked in SKM-1 cells, and the apoptotic rate significantly elevated by demethylation of p15INK4B and up regulation of p15INK4B protein expression, which activated the caspase dependent apoptotic pathway [21]. In the other study, we found that silencing HO-1 sensitized SKM-1 cells to AZA in vitro and in vivo. After being treated with AZA, SKM-1 cells expressed more HO-1, and the bone marrow MNCs from high-risk and very high-risk MDS patients had higher HO-1 expression than those from low-risk and very low-risk patients. With HO-1 silenced, AZA began to inhibit the proliferation of SKM-1 cells more potently, accompanied by raised apoptotic rate and dominant arrest in the G0/G1 phase. The changes were related with increases in the expressions of p16, cleaved caspase-3 and -9 as well as decrease in BCL-2/Bax ratio [22].

Promoting cells proliferation by cytokines regulated by HO-1

The growth and survival of leukemic cells are highly dependent on growth-promoting cytokines in the bone marrow microenvironment [23]. Recent studies indicated HO-1 played a critical role in the IL-6 paracrine and autocrine loop, and it might be a potential diagnostic marker or a therapeutic target for MM. Paracrine IL-6 regulated the cellular expression of HO-1 via the JAK2–STAT3 signaling pathway, and HO-1 regulated autocrine IL-6 production via the p38MAPK pathway [24]. Moreover, our data confirmed previous results of high expression of HIF-1a in human AML cell lines. We propose that inhibition of HIF-1a by 2ME2 has a potent anti leukemia activity through activation of the mitochondrial apoptotic pathway mediated by ROS, and is not cytotoxic to normal cells [25].

Autophagy induced by HO-1 reduced sensitivity of CML cells to IM

Autophagy is a catabolic process involved in the degradation of intracellular aggregated or misfolded proteins and damaged organelles through lysosomal machinery in response to stress or starvation [26,27]. Autophagy induces both survival and death of tumor cells during the initiation, progression, maturation and maintenance of cancer depending on the type and stage [28]. It reported that expressions of HO-1 and LC3I/II in IM-resistant CML patients surpassed those in healthy donors. After Znpp treatment, however, such expressions decreased, and IC50 values, as evidenced by MTT assay, also dropped significantly. Hence, for IM-resistant CML patients, inhibiting HO-1 expressionwas capable of increasing IM sensitivity by hindering autophagy. Hence, chemotherapy-induced HO-1 overexpression in leukemia cells promoted autophagy, which in turn inhibited apoptosis and increased IM resistance, indicating that HO-1 is an important regulator of autophagy. Moreover, suppressing HO-1 expression significantly increased IM sensitivity of leukemia cells [29].

Conclusion

The abnormal expression of HO-1 plays a key role in drug-resistance in hematological maglinancies. In this article, we summarized five points to demonstrate the relative mechanism, including oxidative stress reduction, anti-apoptotic signaling pathway activation, demethylation inhibition, cytokines regulation and autophagy induction. All points indicated that HO-1 might be a potent factor to prognosis of drug-resistance in hematology. On the contrary, inhibition of HO-1 could significantly increase sensitivity of malignant cells to anti-cancer agents. Therefore, the therapeutic usefulness of inhibitors of HO-1, especially in combination with conventional anti neoplastic therapies, may well represent a potential and promising approach in the fight against hematological malignancies.

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