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

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Submission: February 16, 2017; Published: February 21, 2017

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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 chemoresistance 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 malignancies; 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 malignancies [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 cheemo-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 Speics (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 pH 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 methyltransferase inhibitor 5-azacytidine (AZA) and decitabine (DAC). HO-1 overexpression may regulate the proliferation and survival of MDS cell line SKM-1 and thus escape 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 LC3II/II in IM-resistant CML patients surpassed those in healthy donors. After Znpp treatment, however, such expressions decreased, and p105 values, as evidenced by MTT assay, also dropped significantly. Hence, for IM-resistant CML patients, inhibiting HO-1 expression was 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 malignancies. 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.

Acknowledgments

This study was supported, in part, by the National Natural Science Foundation of China (nos. 81270636, 813605011, 81470006 and 81670006), Science Fund of Guiyang City Technology Bureau (no. 2012103) and Guizhou Province Technology Bureau Union Fund (no. UnionLH-2015-7386).

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