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Mini-Review

Targeting Nucleolar GTP-Binding Protein Nucleostemin for Improving Treatment Options in Leukemia

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Abstract

Leukemia stem cells (LSC) are the root of leukemia and known as the major cause of the relapse in leukemia patients. It is believed that therapeutic strategies based on targeting these drug resistance LSCs may ultimately result in eradication of leukemia and curing this disease. Here, we highlight the fundamental roles of nucleolar proteins, with a focus on nucleolar GTP-binding protein nucleostemin (NS), in controlling cell fate and maintaining genome and telomere integrity of normal and cancer stem cells. Then, we provide evidence to propose that new therapeutic approaches based on NS targeting might be utilized for sensitizing cancerous cells to chemotherapy, and consequently for improving current therapeutic options available to treat leukemia.

Introduction

Leukemia is a hematological disease that caused by genetic alterations in normal hematopoietic stem or progenitor cells. These mutations lead to uncontrolled self-renewal, unlimited proliferation, blocked differentiation and disregulation of cell death pathways such as apoptosis and autophagy in population of leukemia initiation cells [1-4]. These so-called leukemia stem cells (LSCs) have unique phenotypes, such as resistant to chemotherapeutic agents, and are considered as the major cause of the relapse in patients with leukemia [1,4]. Although new generation of drugs and combination therapy protocols have been introduced over the past several years, long term survival in the leukemia patients is poor and this disease still remains as a challenge in medicine [1,4,5].

The nucleolus is the largest structure in the nucleus of eukaryotic cells that typically known as an organelle dedicated to ribosome biogenesis, but earlier it was evidence other roles in controlling cell cycle, proliferation, differentiation and cell death pathways [6-8]. Recent findings suggest that the nucleolus is connected to initiation and progression of cancers so that nucleolar proteins have been proposed as new therapeutic targets in different types of malignancies [9-12]. Among nucleolar proteins, nucleostemin (NS), also known as guanine-nucleotide binding protein-like 3 (GNL3), is of particular interest due to its fundamental roles in controlling cell fate of normal and cancer stem cells [13-15]. This GTP-binding protein, which has been recently discovered by Tsai and Mckay, is enriched in neural stem cells, embryonic stem cells, hematopoietic stem cells, and also several cancer cells but not in the normal or differentiated counterpart cells [15-17]. NS initially defined to regulate cell cycle progression and proliferation directly through binding and regulating p53 protein or indirectly via modulating stability of p53 protein [17]. These crucial roles of NS are mostly mediated through shuttling between the nucleolus and the nucleoplasm in a GTP-dependent manner [16]. Importantly, emerging evidence uncovered new recognized roles of NS in controlling cell fate and also in maintaining genome and telomere integrity of the cells through p53-dependent and/or independent signaling pathways [10,13]. In fact, recent reports suggest that NS can operate different cell fate outcomes, including proliferation, self-renewal, differentiation, apoptosis and autophagy in cancer stem cells [5,14].

It has been reported that NS is highly expressed in several human diseases and various types of cancers [2,5,15]. For example, NS is abundantly detected in LSCs as well as bone marrow and blood samples of leukemia patients [18]. The association of NS with poor prognosis and undifferentiated status of leukemia points to its importance as a molecular prognosis/diagnostic marker or even a potent therapeutic target for cancer management [2]. In this context, NS gene silencing could inhibit proliferation and induce cell cycle arrest, differentiation and/or apoptosis in K562, MOLT-4 and HL-60 leukemia cell lines [9,11,19]. NS knocking down in chronic myelogenous leukemia K562 cells inhibited proliferation followed with apoptosis induction at long times (48-72 h) [11]. In addition, NS depletion triggered post-G1 arrest apoptosis in human T-cell leukemia MOLT-4 cells through upregulation of p53 and p21Waf1/Cip1 proteins [9]. Moreover, NS is also an important regulator of proliferation and differentiation in HL-60 and NB4 leukemia cells, and this closely depends on autophagy pathway [3, 19]. Depletion of NS induced autophagy-dependent differentiation and promted all-*trans* retinoic acid (ATRA)-based differentiation therapy in NB4 cells [3]. All these evidence point to the therapeutic importance of NS as a valuable target to be tested in other leukemia models and the clinical protocols. Several strategies can be used for targeting NS as a therapeutic approach for cancer treatment [7]. RNA interference (RNAi) is one the successful strategies with a solid

results at least in *in vitro* cancer models [9,11,19]. Most above reports confirmed efficacy of siRNA technology for NS targeting in normal and cancerous cells. The other approach is based on designing and discovering new drugs with capability of targeting different domains of NS. A recent study on the predictive model of NS revealed that GTP-binding motif 4 (G4) is more druggable than other domains/motifs of NS [7]. These GTP-binding motifs are critical for controlling function of NS because they are responsible for shuttling of NS between nucleolus and nucleoplasm [16].

In conclusion, nucleolar proteins such as NS can manage different signaling pathways including, proliferation, self-renewal, differentiation, cell death and DNA and telomere integrity in cancer stem cells [5,14]. Owing to these fundamental roles, targeting NS or other related nucleolar proteins [12] is supposed to be promising for cancer therapy. We propose that NS inhibition in conjugation with other therapies may aid targeting cancer stem cells, which in turn may improve the current treatment options for cancer patients, especially for the patients with leukemia.

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