Review Article

Potential effects of CRM1 inhibition in mantle cell lymphoma

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Abstract: Mantle cell lymphoma (MCL) is an aggressive histotype of B-cell non-Hodgkin lymphoma. The disease has no known cure, which prompts the urgent need for novel therapeutic agents. Chromosomal region maintenance 1 (CRM1) may play a role in human neoplasia and serve as a novel target of cancer treatment. This study summarizes MCL pathogenesis and determines the involvement of CRM1 in the regulation of several vital signaling pathways contributing to MCL pathogenesis, including the pathways of cell cycle progression, DNA damage response, phosphoinositide kinase-3, nuclear factor-κB activation, and chromosomal stability. A preclinical study is also presented to compare the CRM1 status in MCL cell lines and primary MCL cells with normal B cells, as well as the therapeutic efficiency of CRM1 inhibition in MCL *in vitro* and *in vivo*, which make these agents potential targets of novel MCL treatments.

Key Words: Chromosomal region maintenance 1 (CRM1); CRM1 inhibitor; mantle cell lymphoma

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Introduction

Mantle cell lymphoma (MCL) is an aggressive disease that has been recognized as a histotype of B-cell non-Hodgkin lymphoma (NHL), a heterogeneous group of human lymphoid neoplasms with significantly increased incidence in the United States over the past three decades (1,2). Conventional chemotherapy induces MCL remission in many previously untreated patients. However, within a few years after chemotheraphy treatment, these patients experience relapse that often leads to death with a relatively short median survival duration of 5 to 7 years (3,4). Therefore, the discovery of novel therapeutic agents for MCL with low toxicity and better treatment outcomes remains a challenge.

In MCL, the non-random t[11,14][q13;32] translocation leads to cyclin D1 overexpression, which is believed to be associated with oncogenesis. However, the overexpression of cyclin D1 alone is not sufficient for MCL development, which suggests that additional genetic events are necessary for oncogenesis (5), such as the chromosomal region maintenance/exportin1/Xpo1 (*CRM1*) gene. *CRM1* gene was first identified in the fission yeast *Schizosaccharomyces pombe* through genetic screening, and was determined to be involved in chromosomal structural control (6). CRM1 overexpression has been detected in several cancers (glioblastoma, ovarian, and cervical cancer) and has been associated with worse outcome (7-9).

The nucleocytoplasmic exchange of proteins (macromolecules larger than 40 kDa) is a spatially and temporally regulated process that involves several nucleocytoplasmic shuttling proteins. CRM1 is a nuclear protein export receptor belonging to the karyopherin β family of transport receptors, which transports target proteins across a guanosine triphosphate (GTP)-bound rat sarcoma (Ras)-related nuclear protein (RanGTP) gradient (10-13). CRM1 has a broad substrate range and mediates the export of leucine-rich nuclear export signal (NES)-bearing proteins through the nuclear pore complexes (NPCs) and the transfer of messenger RNAs (mRNAs) (14-18) (*Figure 1*).

Mechanistic studies have demonstrated the importance of the CRM1 nuclear export pathway to many NES-containing signaling molecules, including P53 (19), histone deacetylase 5 (20), protein kinase 1 (21), epidermal growth factor

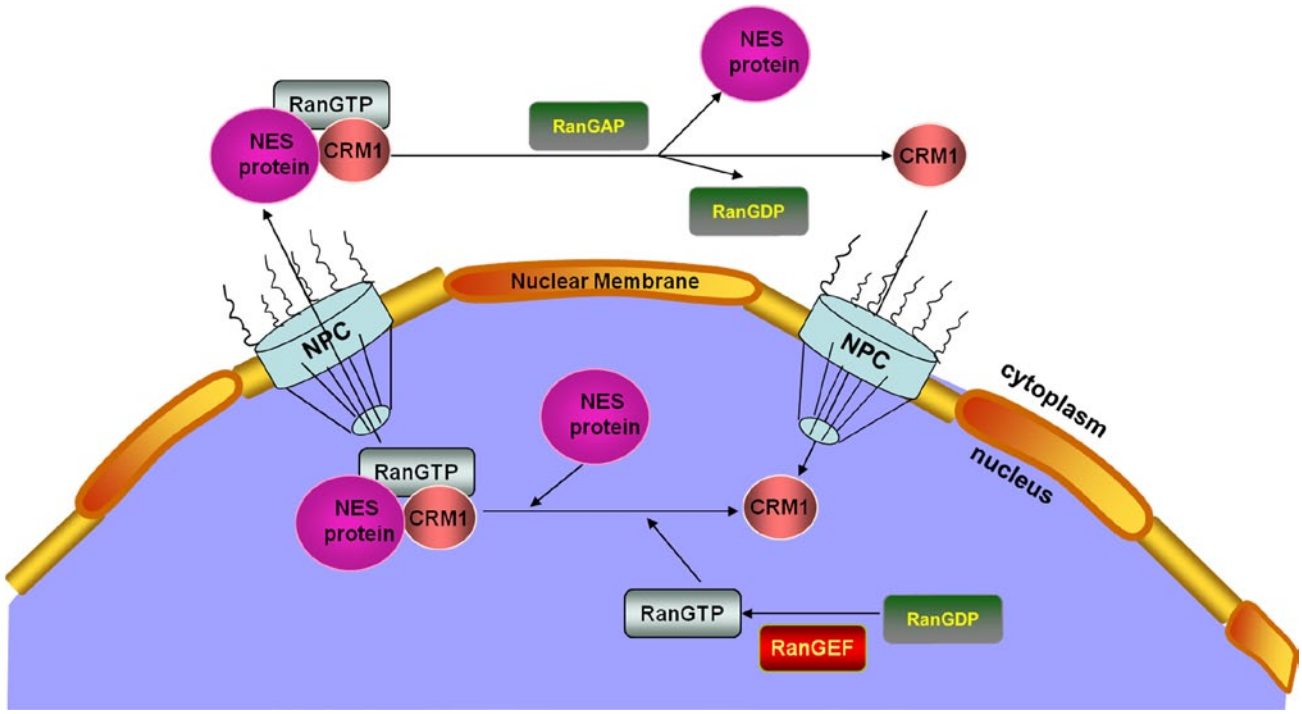

Figure 1 Nuclear export of proteins. Cargo proteins containing a nuclear export signal (NES) bind to chromosome maintenance protein 1 (CRM1) and rat sarcoma (Ras)-related nuclear protein (RanGTP) before they are exported from the nucleus through the nuclear pore complex (NPC). In the cytoplasm, the hydrolysis of guanosine triphosphate (GTP)-bound Ran (RanGTP) to guanosine diphosphate (GDP)-bound Ran (RanGDP) by a Ran GTPase activating protein promotes complex dissociation. In the nucleus, the phosphorylation of RanGDP to RanGTP by a guanine nucleotide exchange factor for Ran (Ran-GEF) allows it to reassociate with a NES-containing protein and CRM1 to restart the nuclear export process

receptor (22), and others (23,24). Given the key roles of these exported molecules in the proliferation and survival of cancer cells, including MCL cells, CRM1 could represent a new therapeutic target in MCL treatment (25-28). In this study, we summarize MCL pathogenesis and CRM1 involvement in the regulation of several vital signaling pathways contributing to MCL pathogenesis. A preclinical study is also presented to compare the CRM1 status in MCL cell lines and primary MCL cells with normal B cells, as well as the therapeutic efficiency of CRM1 inhibition in MCL *in vitro* and *in vivo*.

MCL pathogenesis

A brief overview of the relevant pathways and pathogenic mechanisms in MCL is shown in *Figure 2*. Cyclin D1 overexpression is the diagnostic hallmark in the majority of MCL patients (29). The aberrant B-cell receptor (BCR) (30) and B-cell activating factor signaling (31) both activate MCL cells. Furthermore, phosphoinositide kinase-3 (PI3K), Wnt, and transforming growth factor-β (TGF-β) signaling are also altered in MCL cells (32). Mutations in tumor suppressors such as P53 and ataxia telangiectasia-mutated (ATM) attenuate the DNA damage response in MCL cells (33). Disordered protein homeostasis and pro-apoptotic and anti-apoptotic protein imbalances also occur in MCL. Epigenomic changes in DNA methylation and histone modifications can cause genomic instability, resulting in the aberrant expression of oncogenes and/or tumor suppressor genes, thereby contributing to MCL pathogenesis (34,35).

Regulatory roles of CRM1

Subcellular localization and function of cyclin D1

Although cyclin D1 is responsible for MCL pathogenesis, cyclin D1 overexpression does not lead to the transformation of normal lymphocytes into lymphoid malignancy in nude mice (5), whereas cyclin D1 overexpression in the nucleus induces mature B-cell lymphoma in transgenic mice (36) and

