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AML-associated mutation of nucleophosmin compromises its interaction with nucleolin

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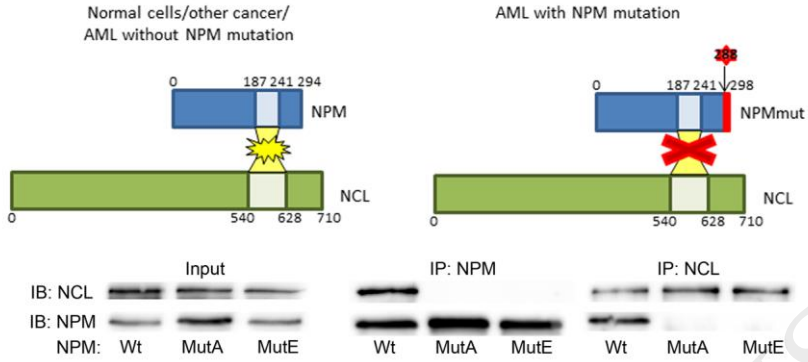
Graphical abstract



Highlights

- Leukemia-related mutation of nucleophosmin disrupts its interaction with nucleolin
- Stability of nucleophosmin oligomers is attenuated by C-terminal mutation
- All-trans retinoic acid stabilizes nucleophosmin oligomers
- Nucleolin/nucleophosmin ratio is enhanced in patients with nucleophosmin mutation

Abstract

C-terminal mutations of the nucleolar protein nucleophosmin (NPM) are the most frequent genetic aberration detected in acute myeloid leukemia (AML) with normal karyotype. The mutations cause aberrant cytoplasmic localization of NPM and lead to loss of functions associated with NPM nucleolar localization, e.g. in ribosome biogenesis or DNA-damage repair. NPM has many interaction partners and some of them were proved to interact also with the mutated form (NPMmut) and due to this interaction thereby to be withdrawn from their site of action. We analyzed the impact of the mutation on NPM interaction with nucleolin (NCL) which is also prevalently localized into the nucleolus and cooperates with wild-type NPM (NPMwt) in many cellular processes. We revealed that the NCL-NPM complex formation is completely abolished by the mutation and that the presence/absence of the interaction is not affected by drugs causing genotoxic stress or differentiation. Deregulation resulting from changes of NCL/NPMwt ratio may contribute to leukemogenesis.

Key words: nucleophosmin, AML, mutation, nucleolin, interaction, oligomerization

1. Introduction

Nucleolin (NCL, C23) and nucleophosmin (NPM, B23) are abundant nucleolar phosphoproteins whose roles in ribosomal biogenesis, cell cycle, DNA-damage repair or apoptosis were widely reported (Leary and Huang, 2001, Scott and Oeffinger, 2016, Yang, Maiguel and Carrier, 2002). NPM is localized mainly in the nucleolus due to nucleolar localization signal (NoLS) at its C-terminus (Falini et al, 2007) as well as to multiple interactions of its N-terminus with arginine-rich motifs in ribosomal proteins, which are produced in the granular component (GC) of the nucleolus (Mitrea et al, 2016). NCL probably uses a bipartite nuclear localization signal (NLS) to enter the nucleus and then