The Acute Myeloid Leukemia-associated *Nucleophosmin 1* gene mutations dictate amyloidogenicity of the C-terminal domain.

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ABSTRACT: Nucleophosmin 1 (NPM1) is a nucleus-cytoplasm shuttling protein ubiquitously expressed and highly conserved. It is involved into many basic cellular processes and its gene is mutated in approximately 50-60% of Acute Myeloid Leukemia (AML) patients. These mutations cause its cytoplasmic mislocation and accumulation (NPM1c+) and open the door to rational targeted therapy for AML diseases with mutated *NPM1*. Currently, there is limited knowledge on the mechanism of action of NPM1c+ and on structural determinants of the leukemogenic potential of AML mutations. Several previous studies outlined an unexpected amyloid-like aggregation tendency of several regions located in the C-terminal domain that, in wild-type form, folds as a three-helical-bundle. Here, using a combination of different techniques including ThTfluorescence, Congo Red absorbance, Circular Dichroism spectroscopy, Scanning Electron Microscopy (SEM) and Wide-Angle X-ray Scattering (WAXS) on a series of peptides bearing mutations we evidence that the amyloidogenicity is directly linked to AML. Noticeably AML point mutations strongly affect the amyloid cytotoxic effects in neuroblastoma cells and the morphologies of deriving fibrils. Since structural studies are crucial in drug discovery process focused on NPM1c+/AML, this study paves the way in deepen molecular basis of NPM1/AML that could help to break innovative grounds for the identification of new drugs targeting NPMc+.