MedicalXpress

Scientists discover new cellular mechanism for potential target protein for acute myeloid leukemia

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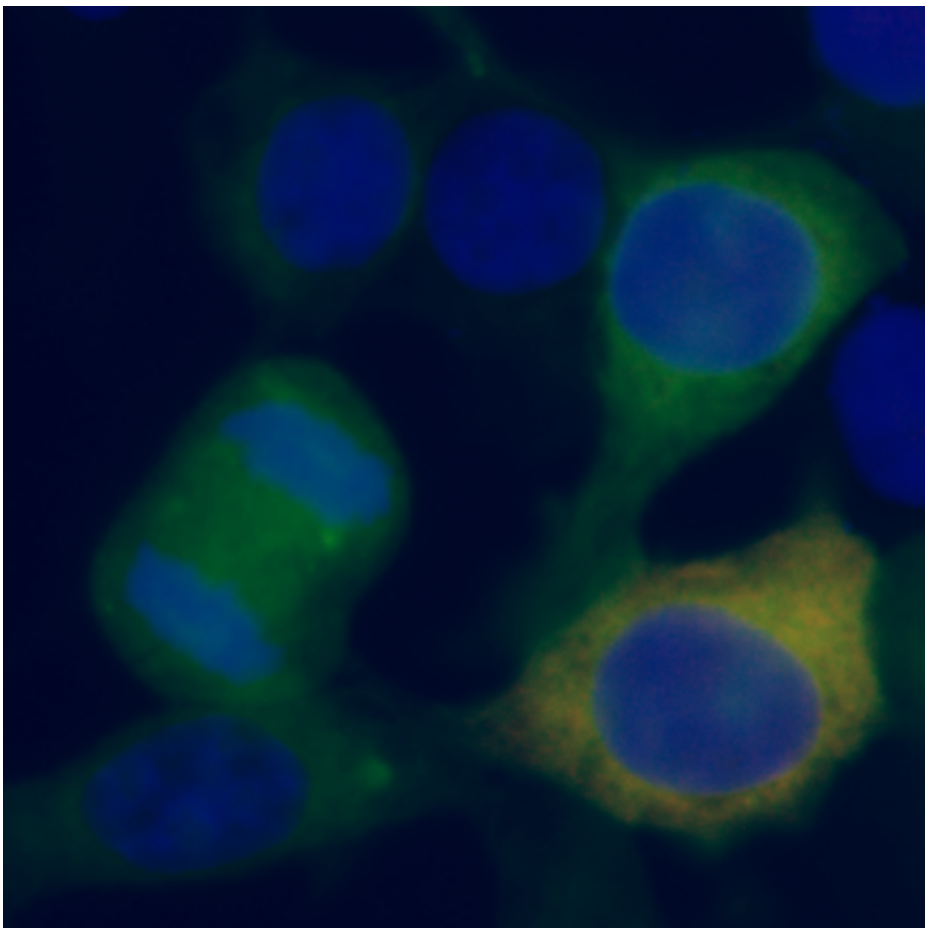

Mutant NPM (green), which contributes to a significant portion of AML cells to possess normal-looking chromosomes, resides outside of the nucleus (blue) and is phosphorylated/modified (orange) when the nucleus is intact. Credit: National University of Singapore

A team of researchers from the National University of Singapore (NUS) has found a new significant correlation between the protein nucleophosmin (NPM) and the development of an aggressive form of blood cancer called acute myeloid leukemia (AML).

Specifically, the team, led by Professor Lim Tit Meng from the Department of Biological Sciences at the NUS Faculty of Science, explained the puzzling phenomenon of AML cells appearing like normal cells even though they are cancerous. While about 50 to 60 per cent of AML cells show abnormal chromosomes which contribute to genomic instability as a hallmark of cancer, a significant portion of AML cells (about 40 to 50 per cent) possess normal-looking chromosomes. The team discovered that the mutated form of NPM – called NPMc – which is found in about one-third of AML cases, is associated with a novel cellular mechanism that develops AML cells containing normal chromosomes. The landmark findings were published in the journal *Scientific Reports* on 30 June 2015.

Earlier studies by the team have shown that NPMc inhibits programmed cell death, and this latest study further highlights the importance of NPMc in the development of AML and as a potential target for AML diagnosis and treatment. Greater understanding in this area may possibly lead to AML diagnostic applications and drug screening exploration.

AML – aggressive form of blood cancer

AML is a cancer of the bone marrow and blood, in which abnormal blood cells are created. Red blood cells are responsible for carrying oxygen to tissues in the body, white blood cells fight infection and platelets stop bleeding by clotting the blood. Any abnormality in these cells can have devastating effects on these critical processes. AML is the most common form of blood cancer in adults and progresses very rapidly if left untreated.

While NPM has long been known as an important housekeeping gene that regulates various cellular functions in the body, its association with AML was only established in the last decade.

In earlier studies led by Prof Lim, it was established that NPM is vital for normal cell death and cell differentiation, and it was observed that mutated NPM actually inhibits programmed cell death (which is a normal process regulated in the human body).

While conducting further studies on the novel functions of the protein, Prof Lim and NUS PhD candidate, Ms Narisa Chan, learned that there was a prevalence of normal-looking chromosomes in AML cells when viewed under a microscope. The team then conducted further studies to explain the observation.

Mutation of NPM protein inhibits normal cell division

The recent study by the NUS team described how the NPM is involved in a process called centrosome duplication in the cell. Centrosomes are responsible for the separation of chromosomes during cell division, a vital process for cellular and tissue development. Each human cell has 23 pairs or 46 chromosomes and when they divide, the resulting daughter cells must also contain the same number of chromosomes. Centrosomes are responsible for ensuring proper cell division and the separation of chromosomes.

The experimental results showed that the presence of NPMc could suppress centrosome reduplication which would otherwise result in unequal segregation of chromosomes during cell division and lead to genomic instability. The findings from this study therefore explained the prevalence of normal-looking chromosomes in AML cancer cells in

about a third of AML cases.

With this new knowledge discovery, NPM may potentially become a target protein for future cancer therapy drug development. Prof Lim and his team are currently looking to collaborate with clinician scientists to expand research into clinical sample investigations to further understand the cell biology involving NPM and NPMc.

More information: Narisa Chan et al. Cytoplasmic nucleophosmin has elevated T199 phosphorylation upon which G2/M phase progression is dependent, *Scientific Reports* (2015). DOI: 10.1038/srep11777

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