The role of noncoding 5S rRNA in protecting the p53 tumor suppressor gene

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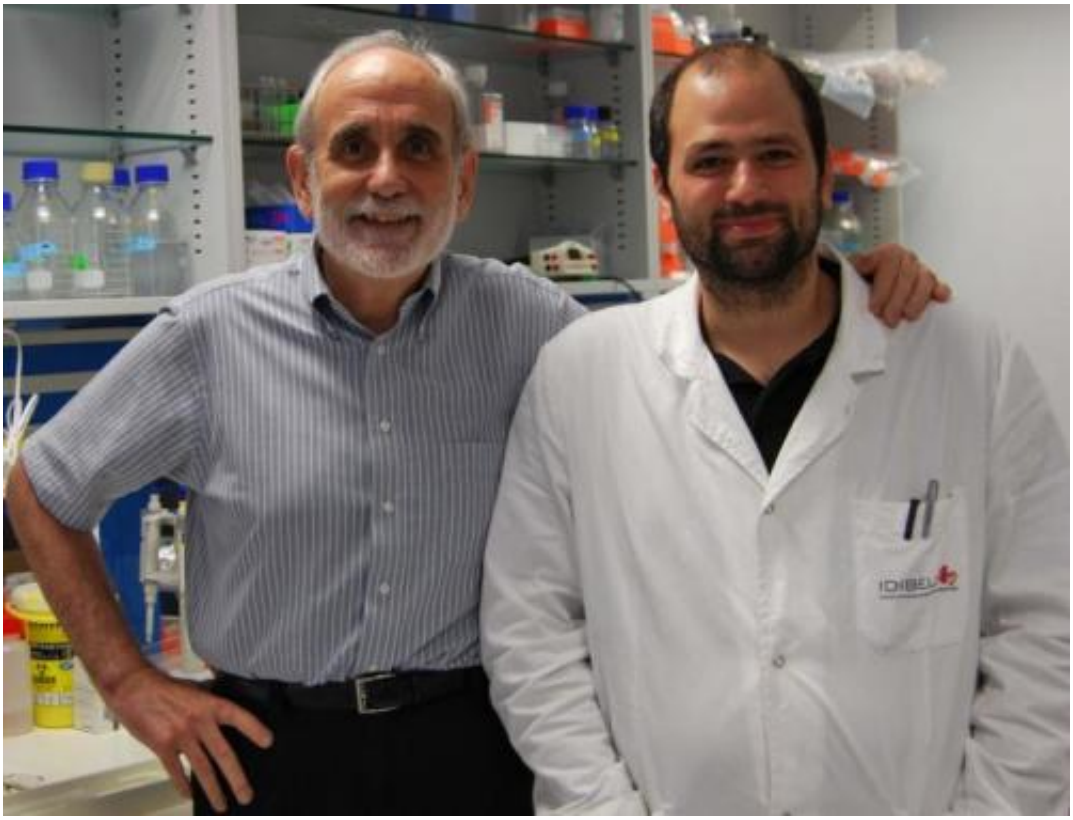

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The results have been published in the online edition of *Cell Reports*.

Cell growth

The ability of cells to grow is directly related to the amount of protein synthesized by ribosomes, the intracellular machinery responsible for translating messenger RNA transcribed from DNA into amino acids containing proteins. Misregulation of ribosome biogenesis is associated with extreme forms of aberrant cell growth including anemia and cancer.

Activation of p53 leads to the induction of a cell death program, preventing aberrantly growing cells from initiating tumor development. In normal conditions, p53 is kept at low levels to avoid damaging healthy cells. The chief enzyme that maintains low levels of p53 is Hdm2, which under normal growth conditions degrades p53.

Ribosomes themselves are composed of two subunits termed 40S and 60S. The formation of the 60S involves many molecular constituents, including L5, L11 and 5S rRNA, which form a pre-ribosomal complex before being incorporated into the mature 60S subunit. The Thomas team have shown that when there is damage to ribosomes, or potentially when ribosome biogenesis is hyperactivated, the L5/L11/5S rRNA pre-ribosomal complex is redirected from nascent ribosomes to the binding and inhibition of Hdm2, allowing p53 to rise, leading to cell death.

Recently, the Thomas team showed that L5 and L11 regulate Hdm2 in a mutually dependent manner. Now, Giulio Donati, the first author of these studies, has demonstrated the existence of the L5/L11/5S rRNA pre-ribosomal complex and its role as a tumor suppressor. Strikingly, they also show that the same 5S rRNA species that regulates Hdm2 is also a positive effector of Hdm4, a negative regulator of p53. These findings point to an ancient evolutionary link between ribosome biogenesis and cancer.

Over 50% of tumors

Thomas explained that understanding how p53 is regulated and functions is critical as "more than 50% of tumors have mutations in p53 or overexpress Hdm2 or Hdm4, which blocks the activity of p53". Thomas adds that "we are currently working on the design of a clinical trial, with the Ramon Salazar team (ICO) based on activating Hdm2-p53 checkpoint to kill tumor cells".

More information: Donati G., Peddigari S., Mercer C.A. and Thomas G. 5S rRNA is an essential component of a nascent ribosomal precursor complex that regulates the Hdm2-p53 checkpoint. Cell Reports.

Provided by IDIBELL-Bellvitge Biomedical Research Institute