

Design Of Compound That Stabilizes The Main Natural Suppressor Of Tumours IRB Barcelona

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An interdisciplinary team of researchers, headed by Ernest Giralt at the Institute for Research in Biomedicine (IRB Barcelona) and Javier de Mendoza at the "Institut Català d'Investigació Química" (ICIQ, Tarragona), have discovered a substance with the capacity to maintain protein p53 stable even when it presents certain mutations that promote the appearance of cancer. Giralt, head of the Chemistry and Molecular Pharmacology programme and senior professor at the University of Barcelona, explains that, "tentatively, this could be the starting point to develop a new approach for anti-tumour treatments". The study will be published this week in the journal Proceedings of the National Academy of Sciences (PNAS) in an advanced edition.

Protein p53 is considered the most important tumour suppressor and it is at the centre of the machinery that regulates cell cycle arrest and the death of cells with damaged DNA. In its active form, p53 protein is a tetramer, that is to say it is formed by four identical copies of proteins bound together, which has four domains with differentiated functions: activation of transcription, DNA binding, tetramerization and regulation. The tetramerization domain is responsible for stabilizing the tetrameric structure.

More than 50% of cancer patients have mutations in the p53 gene. Although most of these are located in the DNA binding domain, several mutations are found in the tetramerization domain, thereby causing destabilization of the entire protein with the consequent loss of activity. Two well documented examples of this kind of congenital predisposition are pediatric adrenocortical carcinoma and Li-Fraumeni syndrome. Therefore, the design of compounds with the capacity to stabilize the tetramerization domain of p53 represents a new and attractive strategy for the development of anti-tumour drugs.

The article describes the design, synthesis and study of a compound with the capacity to interact with the p53 tetramerization domain. Javier de Mendoza, group leader at ICIQ and senior professor at the "Universidad Autónoma de Madrid", explains, "it is a conical shaped molecule with four positive charges prepared to recognize and stabilize four negative charges of the protein". To obtain results in the design and study of new molecules, it is necessary to have an in-depth knowledge of the language that proteins use to communicate with each other, to recognise each other and to bind to exert their function. From this perspective, more associated with basic science, Giralt emphasizes that "the study demonstrates the high level of maturity" that has been reached in the field of molecular recognition.

Drugs that act as tethers

The first author of the article, Susana Gordo, researcher with Giralt's team, explains that "this work also opens up a new avenue for the design of drugs based on the use of small molecules that act as moulds or tethers to preserve the active form of proteins". Among these possible applications of synthetic binding compounds, the researchers point out the stabilization of native forms of proteins or the recovery and rescue of mutated proteins. "The anti-tumoural factor p53, because of its fundamental role in the appearance of cancer, provides a magnificent opportunity for this kind of study", concludes Giralt.

Through the combination of several techniques, including nuclear magnetic resonance, the researchers have been able to describe in detail the interaction of the new compound with the tetramerization domain. Furthermore, computer simulations and in vitro experiments have allowed the scientists to demonstrate the functionality of the complex.

The design and analysis of the compound has also involved the collaboration of the biologist Vera Martos, Javier de Mendoza's team, and the researcher Margarita Menéndez at the "Consejo Superior de Investigaciones Científicas". The computational chemistry part of the study was directed by Carles Bó at ICIQ, with the help of Eva Santos, from the same institute.

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