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The Discovery of p53 Protein [1]

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The p53 protein acts as a pivotal suppressor of inappropriate cell proliferation. By initiating suppressive effects through induction [5] of apoptosis [6], cell senescence [7], or transient cell-cycle arrest, p53 plays an important role in cancer suppression, developmental regulation [8], and aging. Its discovery in 1979 was a product of research into viral etiology and the immunology of cancer. The p53 protein was first identified in a study of the role of viruses in cancer through its ability to form a complex with viral tumor antigens. In the same year, an immunological study of cancer also found p53 due to its immunoreactivity with tumor antisera. Although a series of studies found p53 through various routes, and various researchers called it different names, it was eventually confirmed that they had all encountered the same protein, p53.

In the 1970s, cancer researchers made substantial efforts to study how tumor viruses transform normal cells into cancer cells to gain knowledge about how malignant tumors form. It was clear that some RNA tumor viruses package mutated copies (oncogenes) of certain host genes [9], which enable the viruses to induce abnormal proliferations in host cells. The mechanism through which DNA tumor viruses cause cancer, however, was still an enigma, since unlike RNA tumor viruses, DNA tumor viruses encode their own genes [9] that are not homologous to mammalian genes [9]. The proteins expressed from the DNA tumor viral genome [10] in the inoculated host animals are called tumor antigens, because they are recognized as foreign by the immune system, resulting in antiserum production. Exploring how DNA tumor virus induces cancer, researchers concentrated on a small DNA tumor virus, Simian Virus 40 (SV40), that codes for two tumor antigens, small t antigen and large T antigen. Pinpointing interactions between tumor antigens, cellular proteins, and antisera, several studies converged to demonstrate the existence of p53 protein in a variety of cancer cells.

In molecular biology, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was often used to study proteins. In SDS-PAGE, proteins with different sizes were electrified with identical amount of charge per unit mass, and travel through a jelly-like gel under an electric field. Proteins with different sizes separate on the gel, and are visualized after staining. Researchers often use a marker containing proteins of known sizes to help them identify the size of the proteins in the sample. The mass of a protein is expressed in daltons (Da). This measure helps the researchers to classify, and sometimes even name proteins. The p53 protein was so named because it is a protein weighing 53,000 daltons. In the late 1970s, researchers often optimized their SDS-PAGE experimental settings differently from each other, and thus achieved different levels of accuracy in measuring protein size. These variations in technique may explain why there were discrepancies in the molecular weight reported for p53 when it was first discovered.

The story of the discovery of p53, however, begins several years before its identification in 1979. The first hints suggesting the existence of the protein can be found in studies in the mid-

1970s by Peter Tegtmeyer and his colleagues on the modification and regulation [8] of SV40 large T antigen, which they called A protein. Tegtmeyer and his team at the State University of New York, Stony Brook, used antisera against SV40-transformed cell extracts to immunoprecipitate proteins from SV40-infected cells. Proteins of various sizes appeared on their protein gels, including a protein with molecular weight 50 kDa. Probably because smaller proteins were unlikely to be forms of large T antigen (94 kDa and 84 kDa), Tegtmeyer?s team did not address questions about the 50 kDa protein. The similarity of Tegtmeyer?s method to those used in some later reports about p53, and the size of the small protein as recorded in Tegtmeyer?s papers in 1975 and 1977, however, strongly suggest that the 50 kDa protein he saw was indeed what later was identified as p53.

Cancer researchers soon observed more evidence of the existence of this mystery protein, leading to a flurry of papers reporting this molecule in 1979. Most of the researchers, much like Tegtmeyer?s team, had based their research on SV40-mediated viral transformation of cells. The exception was one serological study on the tumor-induced immune response, which not only detected the protein, but also gave it its name p53.

In 1976, David Philip Lane, a newly graduated PhD from University College [11], London, arrived at Lionel V. Crawford?s laboratory at Imperial College, London to start his postdoctoral research. Their research eventually led them to report explicitly for the first time about the existence of p53 protein. Lane first worked with the technician Alan K. Robbins to resolve a technical issue in making more specific antiserum against large T antigen. By producing anti-T sera from immunopurified large T antigens, they greatly reduced unspecific precipitants in immunoreactions between anti-T sera and cell extracts. Lane and Crawford then applied the improved anti-T sera to cell extracts from a SV40-transformed mouse [12] cell line and found that two proteins were immunoprecipitated: the large T antigen, and a protein with a molecular weight of 53 kDa. They reasoned that the 53 kDa protein was likely to be of a cellular origin due to several factors: its antigenic properties, its absence from lytically infected cells, and its large size which made it unlikely to be coded as a third antigen by the compact SV 40 genome [10]. They also verified that the 53 kDa protein could not precipitate alone with anti-T sera without the presence of the large T antigen, concluding that the cell coded protein must form an oligomeric complex with the large T antigen. After some revision, their report about a large-T-binding host protein (p53) was published in *Nature* in March 1979.

Only two months later, *Cell* published a paper describing a 54 kDa cellular protein in both SV40-transformed cells and uninfected teratocarcinoma cells, which was later confirmed as p53 as well. The authors, Daniel I. H. Linzer and Arnold J. Levine, working at the Department of Biochemical Sciences at Princeton University [13], made independent observations about a protein similar to what Lane and Crawford had reported. They found that a 54 kDa protein was immunoprecipitated from both SV40-infected cells and teratocarcinoma cells by interacting with antisera generated from animals bearing SV40-induced tumors. To confirm that the 54 kDa protein was not homologous to the large T antigen, its partial peptide map was prepared and shown to display a different pattern from that generated from the large T antigen.

Two more papers were published in the *Journal of Virology* in August 1979, reporting similar results about the existence of a protein of around 55 kDa that bound to large T antigen in various types of cancerous cells. These independent discoveries were carried out at the National Cancer Institute [14] and the *Institut de Recherches Scientifiques sur le Cancer*, France.

Although major cancer research efforts were devoted to viral etiology in the 1970s, studies on immune responses to tumors continued, and these two areas converged with the discovery of p53. Studying serological responses of animals to transplanted tumor tissues, Albert B. DeLeo and his colleague at the Memorial Sloan-Kettering Cancer Center [15], New York, found that the antisera against chemical-induced tumors immunoprecipitated a 53 kDa protein in chemical-transformed cells. In the paper published in *PNAS* in May 1979, DeLeo et al. designated this protein as p53.

Although some of the discoverers expressed much excitement about finding p53, the protein was actually regarded as a commonplace oncogene [16] by many molecular biologists at the time. It would take researchers a decade of elaborate investigations to reveal that p53 is actually not an oncogene [16] product, but a tumor suppressor. Further identifications of the roles of p53 in cancer, development, and other physiological processes demonstrated that p53 is crucial in coordinating complex cell cycle responses to DNA damage and other stress signals. Consequently, in the 1990s, p53 attracted much research. In 1993, Levine and Lane were awarded the Charles Rodolphe Brupbacher Prize for Cancer Research for their independent discoveries of p53.

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Subject

Tumor Suppressor Protein p53 [18]

Topic

Experiments [19]

Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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Format

Articles [20]

Last Modified

Wednesday, September 25, 2013 - 15:53

DC Date Accessioned

Friday, May 25, 2012 - 15:48

DC Date Available

Friday, May 25, 2012 - 15:48

DC Date Created

2011-01-21

DC Date Issued

Friday, May 25, 2012

DC Date Created Standard

Friday, January 21, 2011 - 08:00

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