

# The Ras Gene and Cancer

*The following is an excerpt taken from a talk given by Dr. Maxine Singer at the "Winding Your Way through DNA" symposium at the University of California, San Francisco in 1992. Dr. Singer's research career has been prolific, and she is widely recognized as a leader in the effort to promote science education. At the time of the talk, she was President of the Carnegie Institution in Washington and an active researcher at the National Institutes of Health.*

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During the 1960s and 1970s, a great deal of research was done on a class of viruses that affects rodents and birds and causes tumors in those species. The motivation for a lot of this research was the idea that similar viruses might cause tumors in humans, but in fact it's turned out that there are very few viruses that cause tumors in humans. Nevertheless, the study of these rodent viruses has been enormously fruitful in helping us to understand human cancer, and that's the basis of this story.

One of the viruses that was studied in those years had two peculiarities. One was that it had lost most of the genes that it needed to reproduce itself. It could only reproduce if a helper virus was present in the same cell to supply the missing functions. The second peculiarity was that in place of the genes that were required for reproduction of the virus was another gene that had actually been picked up at some point in the history of this virus when it went through rats, and it picked up a rat gene and incorporated it into its own genome.

At the same time that a lot of work was going on on these viruses, other scientists were studying other aspects of tumor formation, in particular, the action of carcinogenic agents, chemicals and X-rays and ultraviolet light. As you all know, human cells can turn into tumor cells under the influence of such agents. The tumor-like properties of those cells are inherited by all the daughter cells through many generations and, moreover, almost all chemicals that turn out to be carcinogens are also able to cause mutations.

Another observation was that in tumor cells, many of the chromosomes seemed to have altered structures. So, all of these observations and others certainly suggested that changes in DNA might be involved in the development of tumor cells. By about 1980, it became possible to test that hypothesis directly.

If you have human tumor cells produced in laboratory dishes or isolated from the tumor itself, then perhaps they have a gene or genes in them which is responsible for the fact that they're tumor cells. If you isolate the DNA from the cells and cut it up into more or less gene-sized pieces and then put it on top of mouse cells growing in a dish, the mouse cells can take up pieces of this DNA, and any mouse cell that picks up a piece of DNA that carries on it a gene that can cause a tumor will begin to grow like tumor cells, and its progeny will grow rapidly and form a tight little cluster on the cell.

Now it's possible to pick such cells off and isolate the DNA from them and also separate the human DNA sequence that might have caused the tumor-like property from the bulk of the mouse sequences and to clone that DNA. And when you do that and put that DNA, which is now pure sequence, back in mouse cells, many of the cells become tumor-like rather than just a rare few. And such a gene, such a DNA sequence, bears the name of an **oncogene**.

When such DNA segments are cloned, the DNA can also be used to probe, to find out whether matching DNA sequences occur only in tumor cells or whether there are similar DNA sequences in normal cells. And the answer has been for a whole group of oncogenes, that very similar DNA sequences are present in normal cells. To find out just how similar, the sequences of the normal genes were compared with those from the genes that were isolated from these tumor cells.

The first such oncogene isolated was from a human bladder tumor, and everyone was surprised by the results. First of all, the gene isolated from the bladder tumor was almost identical to the normal human gene and almost identical to the gene that was present in the tumor virus that infected rodents that I told you about before. This gene has become known as "ras," because it was originally isolated from rats with sarcoma, and it caused sarcomas and it's called that, and its protein is called that. And the only really significant difference between the normal human gene, the bladder tumor gene, and the rodent virus gene was a change in one codon, Codon XII, and therefore a change in amino acids.

So the normal human gene has a sequence GGC, encodes the amino acid glycine, and does not cause tumors. But the bladder tumor gene has GTC; it encodes valine. The rodent virus has AGA; it encodes arginine, and both of these cause tumors. In fact, any change that leads to a loss of the glycine at Codon XII can change this normal gene, ras, into a gene that would cause tumors. So there were two different ways in which the ras gene turned up. First, as a rat gene in a tumor virus and second of all as the gene that could account for the tumor-like properties of the bladder tumor.

Well by now, many of the questions that occurred to the scientists working on this have occurred to you. What is the ras protein normally (if anything), and what does the altered ras protein do that differently, and how can a change in one amino acid in a protein change cells from normal to tumor cells?

It turns out that the ras gene and the ras protein are important for a lot of

things, but more particularly for regulating the growth of cells. Normal cells need to have a good ras gene in order to grow, in order to make new DNA, to time it all right so they don't grow out of control. Moreover, the ras gene occurs in virtually all living things. For example, yeast cells also have two ras genes. If either one of them is knocked out, the yeast cells can still grow very well and multiply. But if both ras genes are knocked out, the yeast cells cannot multiply, and they die. Astonishingly, if a human ras gene is applied to these yeast cells, it completely takes the place of the yeast's own ras genes. So we know from this that the ras gene is very important to all living cells and that it's probably been around for a couple billion years, ever since the very first cells were formed on the planet.

So ras does something important and the question is, what does it do? David Golde told you before about receptors that span cell membranes that bind molecules outside the cell and provide a signal inside the cell, and it turns out that what the ras protein does is to help convey that signal from the receptor at the surface down into the cell and into the gene where it results in a change in gene expression. The ras protein itself actually sits right under the cell membrane, very well positioned to do this.

Well, how can it do that? To tell you about that I need to tell you a couple of things about the ras protein and what it does. First of all, ras combines two small molecules called GDP and GTP, and they differ only in the presence of one more phosphate, three in GTP and two in GDP. This G is related; it's in fact the same kind of molecule as the G that occurs in DNA. Moreover, ras protein can catalyze the removal of one phosphate, so you go from ras GTP to ras GDP and a phosphate is lost. Furthermore, the ras GDP can lose the GDP and pick up the GTP, and there are extra proteins in the cell that foster either this exchange, back to GTP or this loss of the phosphate to GDP. And the whole trick is the ratio of the GTP to the GDP. So if you have ras GTP, it's active and it stimulates growth, but if you have ras GDP, then it's inactive and you don't stimulate growth.

In fact, the change in Codon XII from a glycine results in a change in the amount of ras GTP, so that there's more ras GTP collecting in the cell than the ras GDP, and therefore the cell is constantly under pressure to make DNA and grow and divide. And this is the critical reason for this change, this oncogenic change in those versions of ras that cause tumors or are related to tumor formation as opposed to the natural protein.

How can that happen, a small change like that? You've heard a little bit about the importance of shapes of proteins. If one looks closely at the atoms in the proteins then you see that the whole shape of the protein changes as you go from GTP to GDP.

Now one ras gene and protein all by itself would be interesting, but it turns out that there's a whole family of ras genes and ras proteins. Two of them are specially similar to the type that I've been describing, and mutations in those genes are associated with a whole variety of human tumors including some that are believed to be the result of the reaction to environmental agents.

A mutant in one of those two related genes, which was also first discovered in a tumor virus, is very frequently associated with human tumors of the colon and rectum. And again, it's Codon XII in that similar gene that is altered in the oncogenic form of this kind of ras. Tumors of the colon and rectum are the third most common human malignancy worldwide, and surgical removal of the tumors can actually cure the disease in many cases, but only if the tumor is detected very, very early. Recent work has shown that you can, in fact, detect the change in the gene even by looking at the DNA in the stool of people who are suspected of having the colon tumor.

Even though the mutant DNA only occurs in a very small percentage of the cells in the stool, namely the cells that come from the tumor, not from all the normal cells or all the bacterial cells that are there, it is possible to amplify the amount of a possible abnormal ras gene and test directly for it. So, for example in this test, DNA from the stool of patient #1 matched a probe for the normal ras gene, but DNA isolated from the stool of patient #2 matched a probe not only from a normal ras gene but also from a ras gene with a mutation at Codon XII, thereby permitting a very early diagnosis of a colon tumor and thereby providing real hope that such tumors can be detected early, when the tumor is small enough to be removed surgically with a successful cure.

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