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EDITORIAL

Molecule of the Year

Some molecules are good guys, some are bad guys, and some become bad because they fail in their functions. The molecule p53 is a good guy when it is functioning correctly. The specific cellular roles of p53 appear to be varied. It has a role in transcription (the first biochemical step in "reading" DNA), in cell cycle control (the steps leading to cell growth), and in many other metabolic functions. It is a tumor suppressor in that it halts abnormal growth in normal cells and thus prevents cancer. However, a small change in p53, a mutation of one of its 393 amino acids, can eliminate the surveillance capability of the protein and allow a cancer to grow. So a mutated p53 is frequently as bad as no p53 at all.

As in most practical outcomes derived from basic research, the implications of tumor suppressors gradually permeated the consciousness of researchers in cell metabolism. Thus, the realization that p53 was one of those molecules was a seed that fell on fertile soil. The excitement generated by it and its fellow tumor suppressors is reaching a crescendo with exhilarating possibilities for prevention and cure of cancer. Therefore, we have chosen p53 as Molecule of the Year for 1993. (The nine runners-up for Molecule of the Year are described on page 1959 in this issue; p53 is described further there and in a Perspective on page 1978.)

About 50 percent of all human cancers contain a mutation in p53, so hopes are high that the molecule will provide new insights into treating the disease. Curing cancer and curing a bacterial disease are very different problems. A bacterium has a different metabolism from that of a human cell, so scientists can target a metabolic pathway that kills the bacterium but has no human counterpart. Because cancer cells are simply human cells that grow too well, a drug that kills cancer cells usually kills or weakens normal cells. We need to find the pathway in cancer cells that's gone wrong and try to target it. The p53 protein is part of a fundamental pathway in human cell growth, and finding p53's function allows scientists to develop strategies for the diagnosis, prevention, and cure of cancers resulting from p53 deficiencies. For example, in the future, misshapen molecules caused by mutations in the gene may be brought back to the right shape by a drug that binds to the mutant p53 and pushes the mutant back into the shape of the normal molecule. Another possible approach is genetically engineering the correct p53 molecule back into the cells in which a deficient p53 is unable to act in its tumor suppressor role. Identification of mutations in oncogenes may also have prognostic value. Not all tumors contain a p53 mutation, but those that do are associated with a less favorable prognosis. Knowledge of a patient's p53 status could help determine which treatments would be most beneficial. The p53 protein is also identified with a process of programmed cell death that may be important in killing cancer cells, and further understanding of this process provides hope for cancer therapy.

The great excitement in this field and the understanding that has already been obtained are typical of basic research. A rather innocuous molecule is shown to play a key role in a basic body function. No possible clarification of its important role could have been obtained without the background knowledge of biochemistry, cell biology, and genetics that was also the product of basic research. "Basic" research does not mean "no practical value" research, nor does it mean research with no goal in mind. The basic approach proceeds from an understanding that cancer results from uncontrolled growth, and therefore an understanding of what controls cell growth will ultimately lead to clues on ways to control cancer. Soon the diagnostic opportunities that basic research has made available will enable clinicians to diagnose certain cancers at a stage early enough for effective intervention to take place. Therapeutic drugs are likely to follow. The finding of p53 and genetic markers for cancer means that early detection can save lives now by known methods such as surgery and by providing the opportunity for new drugs in the future.

Thus, p53 and its fellow tumor suppressors are generating an excitement that suggests prevention now and hope for a cure of a terrible killer in the not-too-distant future. In this endeavor the 1993 Molecule of the Year is certain to play a major role.

Daniel E. Koshland Jr.

Molecule of the Year

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Science **262** (5142), . DOI: 10.1126/science.8266084