Beyond the Genome, Cancer’s Secrets Come Into Sharper Focus – NYTimes.com

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For the last decade cancer research has been guided by a common vision of how a single cell, outcompeting its neighbors, evolves into a malignant tumor.

Through a series of random mutations, genes that encourage cellular division are pushed into overdrive, while genes that normally send growth-restraining signals are taken offline.

With the accelerator floored and the brake lines cut, the cell and its progeny are free to rapidly multiply. More mutations accumulate, allowing the cancer cells to elude other safeguards and to invade neighboring tissue and metastasize.

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These basic principles — laid out 11 years ago in a landmark paper, “The Hallmarks of Cancer,” by Douglas Hanahan and Robert A. Weinberg, and revisited in a follow-up article this year — still serve as the reigning paradigm, a kind of Big Bang theory for the field.

But recent discoveries have been complicating the picture with tangles of new detail. Cancer appears to be even more willful and calculating than previously imagined.

Most DNA, for example, was long considered junk — a netherworld of detritus that had no important role in cancer or anything else. Only about 2 percent of the human genome carries the code for making enzymes and other proteins, the cogs and scaffolding of the machinery that a cancer cell turns to its own devices.

These days “junk” DNA is referred to more respectfully as “noncoding” DNA, and researchers are finding clues that “pseudogenes” lurking within this dark region may play a role in cancer.

“We’ve been obsessively focusing our attention on 2 percent of the genome,” said Dr. Pier Paolo Pandolfi, a professor of medicine and pathology at Harvard Medical School. This spring, at the annual meeting of the American Association for Cancer Research in Orlando, Fla., he described a new “biological dimension” in which signals coming from both regions of the genome participate in the delicate balance between normal cellular behavior and malignancy.

As they look beyond the genome, cancer researchers are also awakening to the fact that some 90 percent of the protein-encoding cells in our body are microbes. We evolved with them in a symbiotic relationship, which raises the question of just who is occupying whom.

“We are massively outnumbered,” said Jeremy K. Nicholson, chairman of biological chemistry and head of the department of surgery and cancer at Imperial College London. Altogether, he said, 99 percent of the functional genes in the body are microbial.

In Orlando, he and other researchers described how genes in this microbiome — exchanging messages with genes inside human cells — may be involved with cancers of the colon, stomach, esophagus and other organs.

These shifts in perspective, occurring throughout cellular biology, can seem as dizzying as what happened in cosmology with the discovery that dark matter and dark energy make up most of the universe: Background suddenly becomes foreground and issues once thought settled are up in the air. In cosmology the Big Bang theory emerged from the confusion in a stronger but more convoluted form. The same may be happening with the science of cancer.

**Exotic Players**

According to the central dogma of molecular biology, information encoded in the DNA of the genome is copied by messenger RNA and then carried to subcellular structures called ribosomes, where the instructions are used to assemble proteins. Lurking behind the scenes, snippets called microRNAs once seemed like little more than molecular noise. But they have been appearing with increasing prominence in theories about cancer.

By binding to a gene’s messenger RNA, microRNA can prevent the instructions from...
reaching their target — essentially silencing the gene — and may also modulate the signal in other ways. One presentation after another at the Orlando meeting explored how microRNAs are involved in the fine-tuning that distinguishes a healthy cell from a malignant one.

Ratcheting the complexity a notch higher, Dr. Pandolfi, the Harvard Medical School researcher, laid out an elaborate theory involving microRNAs and pseudogenes. For every pseudogene there is a regular, protein-encoding gene. (Both are believed to be derived from a common ancestral gene, the pseudogene shunted aside in the evolutionary past when it became dysfunctional.) While normal genes express their will by sending signals of messenger RNA, the damaged pseudogenes either are mute or speak in gibberish.