LOS ANGELES

COLON AND RECTAL SURGICAL ASSOCIATES

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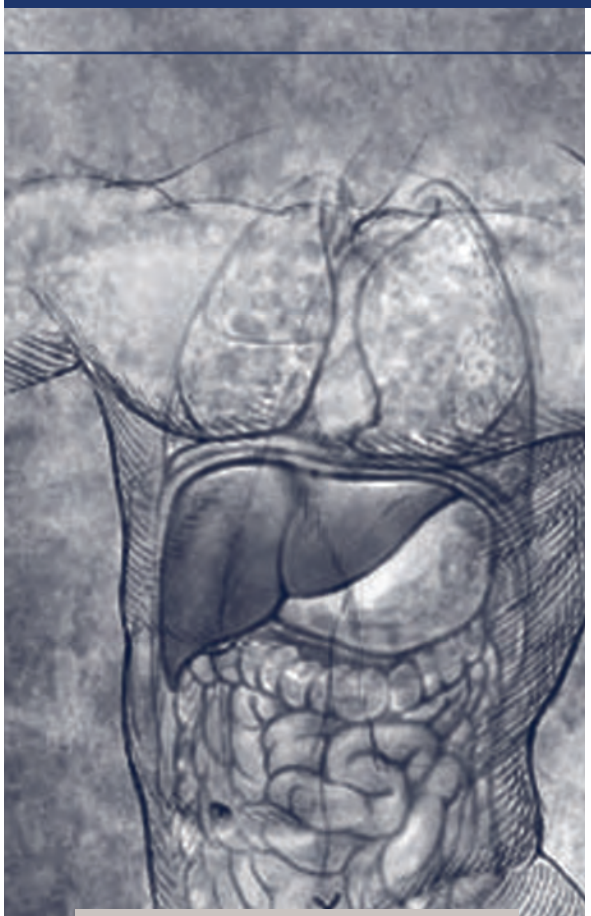

Designer proteins might be able to stop or reverse the malignant process. Perhaps, incisionless cures will follow soon.

PROTEOMICS

The Incisionless Cure May Be Closer Than You Think

Is this science fiction fodder or is it food for the working surgeon?

LENGTH MATTERS. SHORTER IS BETTER.

Finishing a robotic colon resection recently, and admiring the 8 mm incisions on the abdomen, the following question was raised: "What could possibly be more elegant than this?" Of course, the surgical resident, always quick with the demonstration of wit and genius, laughed and quipped, "No incision at all. Shorter is better." Pressed for an elaboration, it was stated that genetic engineering and curative protein therapy would allow for "incisionless" surgery, by replacing the surgeon's scalpel with the surgeon's medicine.

For this enlightening demonstration of surgical wisdom, the resident was allowed to close the skin. But, was the resident on to something? Could the scalpel be replaced by the intravenous line?

FIRST, DNA AND RNA. NEXT, PROTEINS.

This much is known and trusted: **DNA makes RNA. RNA makes protein.** This is the central dogma of genetics.

This too is known: Proteins form the physical backbone of every living animal and form the enzymatic machinery that drives our bodily functions. Proteins also perform cell signaling functions, controlling the pace of all bodily things much like the conductor signaling the woodwinds to sing, the horns to shout, the tympani to blast and the strings to soothe and caress. When functioning perfectly, the orchestra sings; the body hums.

Things become garbled at this point. The orchestra becomes strident. The unknown has been breached. When proteins bind to cells, how do they cause the cellular apparatus in turn on and act? How do proteins "know" to become the strong structures whose job is to form the strong physical blocks of our bodies? Or, how does a protein "know" that it is time to signal cell death (apoptosis) or cellular division? How does a protein "know" what to do? Who knows?

Back to the known: Healthy, intact DNA usually produces healthy functioning protein. Corrupted, mutant DNA makes corrupted proteins. Corrupted DNA may bring a halt to the production of protein, depriving the body of important functioning machinery. Or, to complicate matters, this same corrupted DNA and genes may produce normal proteins. Why? How? Back to the unknown.

GOOD DNA. BAD PROTEINS. WHY?

At this stage of our understanding and technical expertise, clinicians are in a position to understand the genetic defects that may lead

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to the production of malignant tissue changes and gradual development of cancerous tissue. It seems as if each passing day/month/year, advances are made in our understanding of genetic mutations and their roles in the generation of malignancies.

Not so clear is how a researcher or clinician might understand exactly which proteins are abnormal and may do the work of the malignant cells. Which proteins are involved in malignant cellular signaling or in facilitating the development or perpetuation of cancer? If we can isolate those proteins, have we then found the protein "signature" of mutant genes? Exciting stuff.

PROTEOMICS, AT LAST.

Our **genome** is the entire set of our genes, the study of which is termed **genetics**. Our genome produces all of our proteins. A **proteome** is our entire set of bodily **proteins**. ***Proteomics*** is a hybrid term describing the study and analysis of the structure and functions of all of our proteins. Proteomics is a combination of the words ***prote***in and gen***ome***. **Proteome**. Our proteome can be studied using mass spectrometry (a technique measuring the mass to charge ratio).

Researchers began with the premise that understanding the abnormal genotype of cancers does not always or reliably lead to an understanding of the abnormal cancer phenotype. Beginning in 2005, researchers began cataloging the genetic mutations of those tumors responsible for many of the common cancers. These were published in The Cancer Genome Atlas (TCGA). Samples of malignant tumors were collected and their DNA was sequenced, yielding a vast library of tumor DNA genetic sequences. It was noted that while many of the genetic mutations of cancer had previously been identified (at the DNA level), the analysis of the structure and function of their corresponding proteins had been more difficult to analyze. It was thought that it is these proteins that actually perform cancer's "work".

Recently, researchers at Vanderbilt University and six other institutions identified five colorectal cancer protein subtypes (based on their protein content), in the TCGA group, two of which overlapped with the TCGA microsatellite instability phenotype of inherited colorectal cancer. Patients with these proteins had poorer clinical outcomes. The work was done using mass spectrometry on 95 colorectal tumor samples with known DNA characterizations in the The Cancer Genome Atlas. Genomic data was then compared and integrated with proteomic data.

It was observed that some of the DNA in the tumor samples did correlate with amplified and abnormal proteins in the very same tumor. This suggested that further studies using proteomics might yield clues to the most important and common genetic abnormalities, which might be targeted by new "designer" drugs or other therapeutic interventions.

WORKING BACKWARDS. REVERSE ENGINEERING.

Working backwards, researchers identified a single chromosome which they thought might contain the responsible colon cancer "driver" genes. For purists, chromosome 20q (chromosome 20, long arm) seemed to be associated with three abnormal protein quantities and also associated with corresponding abnormal mRNA. The genes on chromosome 20q thought to be "driver" gene candidates are: HNF4A (hepatocyte nuclear factor 4, alpha), TOMM34 (translocase of mitochondrial membrane 34), and SRC (SRC proto-oncogene, non-receptor tyrosine kinase). Chromosome 20q has 63 million base pairs and represents about 2% of the human genome. It contains approximately 25,000 genes. Studies have shown that 20q aberrations do not exist in normal colonic mucosa, appear in some (but not all) benign adenomas, become more prevalent as colorectal cancer advances, and are present in almost all samples of metastatic colorectal cancers.

WORKING BACKWARDS TOWARD TOMORROW.

The hope is that understanding the structure and functioning of these abnormal proteins will help researchers work backward to find the exact piece of mutated gene responsible for the protein malfunction, and possibly repair the faulty DNA in patient's and their at-risk family members. Or baring identification at the DNA level, these proteins might allow for early identification of the dysfunction of our colorectal cancer mismatch repair genes (MMR genes), or might facilitate the early identification of malignant disease. Hereditary colorectal cancer lends itself well to study. However, sporadic, non-hereditary colorectal cancer is also a study target. Colorectal cancer is common worldwide, and tissue samples are readily available. The same may be said for many other hereditary or sporadic cancers.

In essence, proteomics might soon help clinicians in the early diagnosis of colorectal cancer, and in the early and rapid incisionless treatment of colorectal cancer.

DESIGNER DRUGS?

When isolated, abnormal proteins can serve as markers, whose detection would indicate a serious and profound malignant DNA degeneration. These proteins have mass to charge characteristic signatures, making them ideal to find using mass spectrometry. Identifying these signatures might serve as a window into a patient's faulty DNA and allow for early detection of mutated DNA.

If researchers can identify and isolate an abnormal protein or abnormal DNA, then clinicians might be able to determine:

- Which chromosome and gene caused the malignant transformation.
- If a "bad" (mutant) gene can be repaired, or silenced.
- If there are drugs which could block the harmful effects of these "malignant" proteins.
- If testing can be developed which might yield an early indication of malignant transformation.
- If "designer" neoplastic agents might be produced which could block malignant protein interactions at different levels of the cell cycle.
- If "designer" neoplastic agents might be produced which could block malignant interactions between malignant cells.
- If biomarkers could be found which would aid in the early or definitive diagnosis of many different non-neoplastic diseases.

WILL PROTEOMICS LEAD TO A CURE?

Science is constant. Human striving is also constant. With constant inspection of our genomic DNA and its protein products, researchers may be on the verge of unlocking the heretofore opaque functioning of our cells and our cellular machinery. Designer proteins might be able to stop or reverse the malignant process. Perhaps, incisionless cures will follow soon.