Epigenetics and Cancer: Fighting the Disease

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“I have neither given nor received unauthorized aid on this assignment.”
Introduction:

Cancer is the second greatest cause of death in the United States, accounting for 23.1% of all deaths in 2004 (American Cancer Society). One of every two men and one of every three women will develop some form of cancer during their lifetimes (National Cancer Institute). Unfortunately, cancer is not just one disease, but an umbrella term for a highly varied collection of diseases. There are over a hundred different kinds of cancer. Even if you narrow your view to a specific type of cancer, the variety in cause and pathology can be mind-boggling. Most of the research we have done on cancer has involved changes in the actual DNA or the testing of chemical compounds on tumor shrinkage. However, there is another angle that we’ve only just recently delved into: Epigenetics. Epigenetics is defined as heritable changes in gene expression that are not accompanied by changes in DNA sequence (Jones & Baylin, 2007). This newer field could open up many possibilities for future cancer treatment.

Part A:

Our body is home to millions of cells, each containing a multitude of strictly-controlled biochemical processes. This means that there are many points where that control can falter and lead to cancer. For decades scientists have been intently studying the origins of human cancer and debated the relative roles of genetic versus epigenetic abnormalities. It is known that distinct gene expression programs are switched on or off during growth, development, and differentiation, but it has only recently become evident that epigenetics play an important role in these processes (Lohrum, Stunnenburg & Logie, 2007). A large flow of data has indicated the importance of epigenetic processes, especially those that result in silencing key regulatory genes (Jones & Baylin, 2007). This advance in knowledge has lead to the proposal that almost all cancer types show genetic as well as epigenetic abnormalities (Lohrum, Stunnenburg & Logie, 2007). Some
recent advances include the understanding of gene silencing as part of global epigenomic alterations in cancer as well as the understanding that pathways relevant to stem cell growth and differentiation become altered (Jones & Baylin, 2007).

With every case of a cancer, the key feature is the unmanaged cell proliferation that apoptosis (a form of programmed cell death) would normally stop. Our epigenome controls which stretches of DNA are active. “Our genome wraps around cellular capstans, histones [the chief protein component of chromatin], which are tagged by enzymes with molecules such as acetyl and methyl” (Goff, 2006). How our genome is tagged and wrapped determines which genes are turned on and off. When genes that control things like apoptosis and how frequent cell proliferate are turned off, it leaves room for cancer to occur. Gene silencing is an important process that stops a gene from continuing to express itself or ‘silences’ it. This process is necessary for eukaryotic organisms to live and is especially important to the execution of key biological processes such as differentiation, imprinting and silencing of large chromosomal domains such as the X chromosome over the female life span (Jones & Baylin, 2007). However, like most biological processes, gene silencing can malfunction and result in disease (e.g., cancer).

Gene silencing involves multiple processes such as “noncoding RNAs, covalent modifications of chromatin, physical alterations in nucleosomal positioning, and DNA methylation” (Jones & Baylin, 2007). The most characterized epigenetic mechanism is DNA methylation. DNA methylation is the addition of a methyl group to a piece of DNA which can silence the gene resulting in loss of gene function. In many species silencing can be initiated and maintained exclusively by processes involving the covalent modifications of histones and other chromatin components (Jones & Baylin, 2007). However, vertebrates have developed a system
that uses the heritability of DNA methylation patterns to add another layer of control to the process of modifying histones (Jones & Baylin 2007).

Potentially ‘methylable’ CpG dinucleotides (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) are not evenly distributed in the human genome, but occur together in regions known as CpG islands and are usually unmethylated in normal cells (Esteller, 2007). “In cancer cells, the transcriptional silencing of tumor-suppressor genes by CpG-island-promoter hypermethylation is key to the tumorigenic process”, contributing towards all of the typical signs of a cancer cell that result from tumor-suppressor inactivation (Esteller, 2007). Hundreds of genes could potentially be inactivated in a lone cancer by promoter methylation (Jones & Baylin, 2007).

Cancers cells are profoundly distorted, especially so from an epigenetic view. Esteller points out that “Human tumors undergo a massive overall loss of DNA methylation, but also acquire specific patterns of hypermethylation, [an increase of methylation activity that results in heritable transcriptional silencing], at certain promoters. In addition, these DNA-methylation changes are linked with the presence of an aberrant pattern of histone modification” (2007). Histone modifications act in various biological processes such as gene regulation, DNA repair and chromosome condensation (necessary for mitosis). This means that cancer cells within a tumor will have extreme difficulty regulating genes and repairing themselves along highly increased proliferation.

Both HATs and HDACs have been found mutated or deregulated in various cancers (Lund & Lohuizen, 2004). “Changes in the behavior of two epigenetic enzymes, Histone Acetyl Transferase (HAT) and Histone Deacetylase (HDAC) seem to play a role in many cancers by switching on the wrong set of genes” (Goff, 2006). The result of the use of HDACs is a global
non-specific reduction in gene expression. Both normal and cancerous cells use HDACs, but luckily cancer cells are more likely to be killed by their inhibitors (Histone Deacetylase Inhibitors - HDACI) than normal cells (Goff, 2006). Some cancers respond better to HDACIs so the drugs have been targeted at certain tumor types.

**Part B:**

The impact of cancer on our society is obvious. It is a leading killer of human beings, second only to heart disease. More Americans will die of cancer in the next 14 months than have perished in every war the United States has ever fought combined (Leaf, 2007). Even as our efforts at research and treatment have greatly intensified over the past decades and cancer funding has soared, the annual death toll has risen 73%--over one and a half times as fast as the growth of the U.S. population (Leaf, 2007). We have been fighting a ‘war’ of sorts for decades to find some sort of cure or preventative measure for this deadly illness. The result? Even with age and population adjustments, the same percentage of people are dying of cancer today that were in the fifties, sixties, seventies, etc. As Leaf says, “Hope and optimism, so essential to this fight, have masked some very real systemic problems that have made this complex, elusive, relentless foe even harder to defeat” (2007). We have approached cancer research in much the same repetitive way until recently.

The hope now is that epigenetics will lead the way for a new set of drugs that will deal with cancer cells in a completely different way. Goff shows her belief in this when she says “Understanding the epigenome will yield new and exciting ways to reveal cancers and help our immune system to fight back” (2006). So far, scientists have identified at least 60 presumably beneficial genes that are abnormally silenced in one or another cancer that allow tumors to take hold (Begley, 2004). It was recently found that the silence/unsilence pattern of one gene
strongly predicts whether breast cancer is likely to recur. Of the women in whom this gene was operating normally, 90% were metastasis-free 10 years after treatment, compared with 65% in whom the gene was silenced (Begley, 2004). It is thought the gene is involved in blocking metastasis, so silencing it is bound to be trouble (Begley, 2004). These two discoveries greatly help to define how epigenetics and cancer are connected, but do not suggest a way to use the information provided as a treatment.

A different example of the progress we’re making is Dr. Sara Sukumar’s Hopkins test for breast cancer that looks for unusually high amounts of chemical tags embedded by the process of methylation within critical gene regions (Johns Hopkins Kimmel Cancer Center, 2006). This test can be used for any cancer where fluid can be obtained relatively easily, such as lung, head and neck cancers, and pancreatic and cervical cancers (Johns Hopkins Kimmel Cancer Center, 2006). The Hopkins test determines the methylation percentage present in each of five to ten cancer genes (Johns Hopkins Kimmel Cancer Center, 2006). The percentages add together for a total score that is compared to a threshold to determine potential presence of cancer cells (Johns Hopkins Kimmel Cancer Center, 2006).

“Now that we know the screening tool is effective in finding cancer cells within breast duct fluid, we need to improve the accuracy of obtaining the fluid,” says Sukumar, who is worried that the gene screen may miss cancers if they overlook any hidden breast ducts (Johns Hopkins Kimmel Cancer Center, 2006). Misdiagnosis is a large, life-threatening situation for cancer patients. Goff stresses that it is such a serious problem, a group of American lawyers have created a law firm specializing in cancer misdiagnosis (2006). Hopkins’ new test outdid the old test by correctly detecting 71% of known cancer samples as compared to 33% and ruled out
83% of known negative samples (Johns Hopkins Kimmel Cancer Center, 2006). It is important to develop tests that can accurately determine the type of cancer correctly.

The Hopkins’ test is very beneficial because it not only can better determine if the patient has cancer, but has the potential to properly diagnose what they do and do not have in terms of cancer. For example, if fluid is drawn from all the aforementioned places and none of the samples test positive for cancer, you can be pretty sure that you do not have breast, lung, head and neck, or pancreatic and cervical cancer.

On the other end of the epigenetics and cancer spectrum from the cancer identifying tests are the cancer treatments. Readjusting the HDAC:HAT balance has proved to be a useful strategy for fighting cancer and has led to a family of drugs using HDAC inhibitors (HDACI) which are currently leading the race to be offered to patients (Goff, 2006). HDACIs can shrink blood cancers such as lymphoma and many solid tumors such as kidney and prostate (Goff, 2006). SAHA, an HDACI has already reached a phase III clinical trial stage which means it is being tested on humans but will need more time before becoming a standard treatment (Goff, 2006). HDACIs have also been shown to switch on immunity genes which help the body recognize foreign or unwanted cells (Goff, 2006).

From here, hopefully we will be able to close in on a group of cancers and types cancer patients that will respond best to HDACI treatment. Since many cancer fighting drugs are used in combination with other medicines for optimum results, it could be that HDACIs will be the greatest help in tandem with another drug. “In any case,” Goff says, “the arsenal of anti-cancer therapies continues to grow” (2006).
Welcome news for their clients then, that epigenetics carries a new beacon of hope for cancer diagnostics. "Epigenetic changes are more clearly associated with the progression of tumors than mutations are," says Begley, "Epigenetics may be as important in certain conditions as the DNA sequence is in other cases” (2004). If we can study more of how tumors form, maybe we could do more, on an epigenetic level to stop tumors from getting out of hand and spreading.

It is often stressed that cancer needs to be caught early to be fully treatable. The sooner you catch it, the better your chances of survival. As Leaf says, “the trick is to intervene earlier in [the cancer formation] process--especially at key points when lesions occur (precancerous cell phases). To do that, the medical community has to break away from the notion that people in an early stage of carcinogenesis are ‘healthy’ and therefore shouldn't be treated” (2007). People are not healthy if they're heading towards having cancer.

Therefore, the surest way to decrease the number of cancer deaths is to take advantage of epigenetic and other tests like the Hopkins’ test and get them done regularly and treat people showing even small signs of carcinogenesis. This should be done especially if we are able to identify cancer mutation genes in individuals. Tests could also be something as simple as looking at the amount of methylation or HDAC in the body once it is furthered defined what cancers those things are associated with. If it becomes financially possible for everyone in the nation to get tested for common cancers maybe once every several years or so and treated any probably cancer cases immediately, we would probably see a huge decline in deaths due to cancer.
We've prevented millions of heart attacks and strokes by using the very same strategy of prevention (Leaf, 2007). A perfect example is the Pap smear, which detects premalignant changes in the cells of the cervix. “That simple procedure, followed by the surgical removal of any lesions, has dropped the incidence and death rates from cervical cancer by 78% and 79%, respectively, since the practice began in the 1950s” (Leaf, 2007). In countries where Pap smears aren't done, cervical cancer is a leading killer of women (Leaf, 2007).

Epigenetics has come a long way in helping us to understand cancer in the short time that we have been researching it. The field has a great potential to not only help people who have cancer, but perhaps detect pre-cancerous patients.
Works Cited

Part A


Part B


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