A PROPOSED INFORMATION–BASED MODALITY FOR THE TREATMENT OF CANCER

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Abstract. Treatment modalities for cancer involve physical manipulations, such as surgery, radiation or chemotherapy. This is a proposal for an information–based modality: sending information to the cancer to cause it to go into apoptosis. It is based on a theory of Structure Encoding in DNA where information about body part structure controls the epigenetic state of cells in the process of going from pluripotent cells to fully differentiated cells. This implies a model of cancer where cells stuck in an epigenetic state during the process of differentiation lead to malignancy, called the Epigenetic Differentiation Model. Under this model, cancer can be caused by genetic errors or by errors in epigenesis, such as methylation errors. A major feature of the Structure Encoding Theory is that the characteristics of the differentiated cell are affected by information and signal passing in the tissue microenvironment, which specifies the exact location of a cell in a body part structure. This is done by exosomes that carry fragments of long non–coding RNA and transposons that convey structure information. In the normal process of epigenetic differentiation, the information passed may lead to apoptosis due to the constraints of a particular body part structure. The proposed treatment involves determining what structure information is being passed in a particular tumor, then adding artificial exosomes that overwhelm the current information with commands for the cells to go into apoptosis.

1. Introduction

Treatments for cancer take a variety of forms [1] [2]. These include:

- Manipulation of the physical cancer cell, such as surgery and radiation therapy.
- Manipulation of the processes in the cancer cell, such as antimetabolites, hormone therapy and antitumor antibiotics.
- Manipulation of the mitosis of the cancer cell, such as alkylating agents, topoisomerase inhibitors and mitotic inhibitors.
- Manipulation of the tumor support systems, such as angiogenesis therapy.
- Manipulation of the immune system — immunotherapy.

The treatment modality I am proposing is based on the manipulation of information. The idea is to pass to the cancer cells information that will cause them to stop growing or force them into apoptosis. The advantage of using information is that it could be specific for the cancer cells only — that is, the information would not be read by most normal cells, and therefore not affect them.

It is based on a theory for Structure Encoding in DNA [3]. If this theory is correct, then many cancers are caused by cells getting stuck in the epigenetic process of going from pluripotent stem cells to fully differentiated cells. This results in multiple copies of a single cell at a particular developmental stage that just repeats that stage. The theory states that cells in the process of differentiation need to receive information from neighboring cells that helps the cell determine its ultimate fate in the context of the body part structure it is to be a part of.

Given this cancer model, the proposed treatment is to overwhelm the structure information being passed into a cancer cell from its neighbors with information that tells the cell that it should be in the state of apoptosis. Note that instead of disrupting the processes in the cancerous cells or its environment, the proposed

treatment disrupts the information passed to the cancerous cell. It is tricking the cancer cell to self–destruct by feeding it the "wrong" information.

It is important to identify the distinction between signals and information. A signal is a simple unit of quantitative data. Morphogens and hormones are examples of signals. The degree of response to a signal is in proportion to the quantity of a signal. In contrast, the term information is used here in the more complex sense of an encoded sequence. Information means something as a whole and is less dependent on quantity or concentration. The DNA code for proteins is an example of information. In the fields of electrical engineering and computer science, a signal is considered analog, and information is digital.

This paper is a proposal — it will not specify a treatment in detail. Experimentation will be needed to determine which information sequences are relevant for which cancers, based on the information being passed in the tumor. Then more experimentation will be needed to determine what information will be accepted by the tumor and what information leads to apoptosis.

Section 2 will describe the Structure Encoding Theory. Section 3 will present the Epigenetic Differentiation Model of cancer based on this theory. Section 4 contrasts this model with other models. Section 5 will provide evidence for this model. Section 6 will present the hypothesis of an information–based modality for the treatment for cancer in light of this evidence.

2. Structure Encoding in DNA

The theory for Structure Encoding in DNA [3] claims that the bulk of the DNA in multicellular organisms encodes for body part structure, not for proteins. This

differs from the central dogma of molecular biology that focusses on the translation from DNA to RNA to protein.

It begins with the observation that differentiation in metazoans and plants starts with the morphogenetic processes controlled by chemical signals like morphogens. But as Kerszberg and Wolpert [4] point out: "morphogens may represent a rather crude positional information system, which is then more finely tuned by cell–cell interactions. Clearly, the morphogen gradient does not act alone and is itself specified by a variety of complex cellular mechanisms." That is to say, simple quantitative signals are not sufficient for the precise determination of structure in multicellular organisms. More detailed information passing is also required.

According to this theory, DNA contains structure information in its own encoding in the intergenic regions. This structure data consists of repeated patterns in "non–coding" RNA (in the sense that it does not code for proteins), representing different cell types in different locations. This data is manipulated by transposons to determine the fate of each individual cell.

The structure information is organized in a hierarchy. Genes such as the Hox genes control the gross structure, but also control which fine structure details are applicable by selecting the transposons and long non–coding RNAs ($lncRNAs$). Disabling extraneous structures is accomplished through deactivation by methylation. This process is important in embryogenesis [5]. The overall structure of a body part can be specified at one level, but substructures can be specified once and reused multiple times, like a computer subroutine.

One of the primary purposes of epigenetics is to control the process of going from pluripotent stem cells to fully differentiated cells. This process turns on certain

families of genes and turns off others, adjusting the Genetic Regulatory Network to activate the interlocking biochemical processes required for a specialized cell in a complex body part. This requires information to be presented to the cell about its location in the body part structure in the context of the other nearby cells.

Transposons and lncRNA manipulate the DNA [6] [7] [8] [9] [10]. They have been found to be active in stem cells in the process of epigenetic differentiation [11]. Their purpose is to fold the DNA in relation to the 3–dimensional structure of the body part the cell is in. To make this possible, it is necessary for structure information to be passed to the cell from its neighbors. Extracellular Vesicles (EVs) such as exosomes [12] pass the information to the cell to determine the structure [13] [14]. Studies have shown that lncRNA expression differs depending on the tissue [15] [16]. This information is in the form of incomplete fragments of lncRNAs and transposons. The fragment specifies where the particular body part information is encoded in the lncRNA or transposon sequence, in relation to its neighbors. The fragment tells the cell where exactly it is located in the structure – at the point the fragment ends.

This process occurs in the heterochromatin. LncRNAs have been known to affect chromatin modification [17] [18]. Epigenetic modifications determine the selection of the specific cell type (or apoptosis) at a specific location through transposon splicing and histone modification [19]. This, in turn, configures the genetic regulatory network in the cell.

I shall refer to this theory as the *Structure Encoding Theory (SET)*. I will also use the term *Epigenetic Differentiation* to refer to the process by which pluripotent stem cells, through multiple generations of cell division, result in fully differentiated

cells. This process is driven by epigenetic changes in the cells at different stages, as they react to the signals and information in the microenvironment.

3. Cancer Arises From Errors in Epigenetic Differentiation

The theory described in the previous section suggests the cause of many cancers: in the process of epigenetic differentiation, an error either in the genetic information or in the epigenetic state leads to a neoplasm that can become cancerous. The important point is that, regardless of the cause, the cancer cell is stuck in a particular epigenetic state.

Cancer manifests itself in different ways depending on the body part and the stage of epigenetic differentiation where the error arose. What these cancers have in common is that they are stuck in the state where things went wrong. Epigenetic differentiation is a fundamental process in embryogenesis, but it is also part of the normal processes of a living organism as it grows, repairs damage, and replaces older cells with new ones. So cancer can arise at any stage of life.

The degree and quality of cancer differ depending on the epigenetic state when it arose. Early in the process, the cell is a stem cell, leading to a cancerous stem cell. Later in the process, the neoplasm manifests itself as an abnormal growth of a particular kind of cell, a situation that is less dangerous than if the error had occurred earlier on in the process. The types of genetic and epigenetic errors that would lead to cancer in the process of epigenetic differentiation may be benign in a fully differentiated cell. These errors would affect that cell and that cell only, but would not lead to an abnormal cancerous growth.

DNA damage appears to be a common cause of cancer. Cancer can be caused by alterations in oncogenes, tumor–suppressor genes, and micro-RNA ($miRNA$) [20].

But errors in the processes of epigenetic differentiation, such as methylation errors [5], errors in chromatin, or errors in the regulation of the genetic regulatory network can also cause cancer [21]. Although cancer is an error of epigenetic differentiation, the root cause can be errors in DNA transcription or errors in the processes of epigenesis.

Some cancers have multiple genetic errors because the correction mechanism is turned off [22]. The theory of Structure Encoding, especially the idea that transposons manipulate the DNA for the purposes of structure determination can explain why DNA repair genes get deactivated. Repair genes could be turned off in cell differentiation if they interfere with the operation of transposons and lncRNA [23]. This would then lead to a sharp increase in the number of genetic errors.

Some cancers have a purely epigenetic origin. Although this means that these cancer cells would have little or no mutations of any consequence, epigenetic errors result in the abnormal expression of certain genes. An example of this are cancers that are mostly due to incorrect methylation [5].

As mentioned in the previous section, methylation is important in the process of structure determination. There are two generally recognized problems with methylation in cancer: transcriptional silencing of tumor suppressor genes by CpG island promoter hypermethylation and global genomic hypomethylation [5] [24] [25]. Hypermethylation often results in disabling genes that repair DNA or trigger apoptosis. Sometimes the effects of methylation silencing and gene mutations have the same effect. Hypomethylation is an error in epigenetic differentiation where the cell has failed to proceed down the path of differentiation to its final state. Instead, the

genetic regulatory network for multiple cell types remains active all at the same time, which could lead to cancer [19].

As the process of differentiation continues, intercellular communications establish the microenvironment that is associated with the cells of a particular body part at that stage of development [26]. Errors in communication play a part in cancer, since they are errors in differentiation. Early on, epigenetic differentiation is controlled by morphogen signals. Hox antisense intergenic RNA (HOTAIR) is one of the most frequently reported lncRNAs involved in cancer development [27].

Exosomes are important components and regulators of the cell microenvironment [28] [29]. They have long been recognized as having a part to play in cancer [30] [31] [32] [33] [34] [35] [36] [37]. Radiation treatment and cancer have been shown to change the expression of exosomes [38] [39]. Exosomes are carriers for a variety of things, such as proteins, RNA and DNA [40]. According to SET, some of these exosomes are carrying detailed structural information, in the form of non–coding sequences that are part of transposons and lncRNA [41]. Exosomes also carry signals that establish the tissue microenvironment, such as exosomes containing miRNA [42] and morphogens such as Wnt and Hedgehog [43].

The miRNAs that appear in exosomes are used for signaling, which helps to determine the microenvironment [44] [45]. For example, exosomes containing miRNA from mesenchymal stem cells have been shown to suppress angiogenesis in breast cancer cells [46]. They are also known to control apoptosis [47] [48] [49].

It has been known that lncRNAs control the expression of miRNAs [50] [51] and that the expression of miRNAs is controlled by methylation [52]. There is a strong correlation between the location in the genome of specific miRNAs and HOX genes,

indicating their involvement in epigenetic differentiation [53]. The miRNA controls the regulatory network by turning off proteins [54] [55]. On the other hand, the p53 repair protein is known to turn on miRNAs [56] [57]. Note that miRNAs are specific for different families of cells since they are involved in differentiation [58].

It could be argued that, since miRNA are small, non–coding RNA sequences, they can be considered information. For example, they are known to bind to messenger RNA (*mRNA*) at a site that has been termed a "zipcode" [59]. But there is usually no relationship between different miRNAs. Therefore, for the purposes of this paper, they will be considered as individual signals.

Exosomes also carry long non–coding RNA and transposons [60] [61]. Some transposons carried by exosomes include certain Long Interspersed Nuclear Elements (*LINE–1*) [62] [63] and Human Endogenous Retroviruses (*HERV*) [64]. These contain information sequences in non–coding segments. According to SET, they encode information about where in a body part the cell is located. This is especially true if the sequence is incomplete — this indicates the location in the structure.

Note that in this model, the lncRNA and transposons that are passed by exosomes are often specific to that particular cancer, depending on which body part the cancer cell came from. The exception is a case where some common information encoding appears as a subroutine in multiple body parts.

So, given the theory of Structure Encoding in DNA, cancer arises from an error in epigenetic differentiation, caused either by errors in the DNA or by errors in the process of epigenesis. The cancer, though, is dependent on intercellular communications, either through morphogens or through material contained in exosomes.

In summary, the main points are:

- Cancer begins at any step of the process of epigenetic differentiation. The characteristics of the cancer are dependent on the stage of epigenesis.
- Cancer can be caused by genetic errors or by epigenetic errors such as incorrect methylation or intercellular communication.
- Some cancers exhibit a large number of genetic errors because genetic error correction was turned off at the stage where the cancer started.
- Epigenetic differentiation is controlled by signals and information passed in the microenvironment of the cell. Signal passing is done through morphogens and exosomes containing miRNA. Information passing is through exosomes containing lncRNA and transposons. This information also controls the progress of a cancer.

I will refer to this as the *Epigenetic Differentiation Model (EDM)*. In the next section, I will compare this model to other models.

4. Epigenetic Differentiation Model of Cancer Compared To Other Models

According to EDM, the Cancer Stem Cell (*CSC*) model [65] [66] [67] [68] [69] represents cancers that started in an early stage of differentiation. If a cell becomes cancerous early, then it most likely is or acts like a stem cell. Their ability to form new tissues makes them more likely to lead to the uncontrolled growth of cancer [70] and to metastasize [71].

Although the cancer cells are stuck in a particular stage of epigenetic differentiation, some processes in epigenesis could be continuing. This results in creating a variety of cells derived from the CSC [72]. This is especially true in the case

of cancer stem cells giving rise to cells that are further differentiated, leading to tumor heterogeneity. The epigenetic process will also alter the microenvironment, also affecting other cells [73] [74]. Note that this process may not necessarily be one way. Epigenetic processes can sometimes lead to stem cells derived from more differentiated cells [75].

The reason a tumor is not made of just the same stem cell is that the epigenetic process establishes a microenvironment. This can either affect local, non–cancerous cells or turn cancerous cells into non–stem cells. This leads to abnormal structures composed of populations of cells [76].

The CSC model has been contrasted to the older Clonal model, where cancer is the result of multiple clones of a cell with genetic errors [66] [77] [78]. The two models are not mutually exclusive [79]. It has been suggested that the stem cell model is actually explained by the process of mutation of cancer cells in a clonal model [80]. That cancer can manifest itself in these different ways is explained in EDM as a difference in the stage at which the cancer cell got stuck. A cell that becomes cancerous in the early stages of epigenetic differentiation manifest as a cancer stem cell. The clonal model applies later in epigenetic differentiation, going from multipotent to fully defined calls. EDM predicts that cancers can differ because of the cause of the cancer, genetic or epigenetic errors, manifests in different ways depending on the epigenetic stage.

This progress from stem cell to fully differentiated cells has been pointed out by Hanahan and Weinberg: “The origins of CSCs within a solid tumor have not been clarified and indeed may well vary from one tumor type to another. In some tumors, normal tissue stem cells may serve as the cells–of–origin that undergo oncogenic

transformation to yield CSCs; in others, partially differentiated transit–amplifying cells, also termed progenitor cells, may suffer the initial oncogenic transformation thereafter assuming more stem–like character." [81]

Vogelstein et al. [82] divide mutations into "driver gene" mutations and 'passenger mutation". They classify genetic errors in cancer into three core cellular processes: cell fate, cell survival and genome maintenance. In EDM, passenger mutations are the result of the correction mechanism being turned off.

EDM has features in common with Tissue Organization Field Theory ($TOFT$) [83] [84]. In summary, TOFT is based on the ideas that carcinogens disrupt the interactions that establish the local microenvironment and that proliferation is the default state of all cells. The disruptions of the microenvironment cause the proliferation to disrupt the normal organizational pattern. Both TOFT and EDM place an emphasis on intercellular communications and epigenetics. The main difference is that TOFT focuses on morphogenic fields, but EDM, since it is based on SET, also considers the detailed structure information passed between cells.

As the tumor grows, it requires the materials to help it grow. This involves angiogenesis. Facilitated Variation is a theory that explains angiogenesis [85]. Since the cancer cells are stuck in an intermediate state of epigenetic differentiation, they are predisposed to promoting angiogenesis since the development of the related nutrient–supplying components of the tissue must be active while a body part is being formed. This is done by the expression of signals in the microenvironment using lncRNAs [86] [87]. These signals may be different from the information defining cellular structure.

Metastasis is often associated with the ability of the cancer to make the epithelial–to–mesenchymal transition (*EMT*) [88] [89] [90]. Since EMT is associated with early embryogenesis [26], EDM predicts that CSC tumors are more likely to metastasize due to processes like EMT. On the other hand, cancers that start from cells late in the development process, since they are almost fully differentiated, are less likely to metastasize.

How does this model of cancer explain the hallmarks of cancer [91] [81]? If EDM is correct, most of the hallmarks of cancer are actually properties of epigenetic differentiation that are carried over from the epigenetic state where the cancer arose and do not necessarily require any extra mutations or other modification of the cell beyond this. For example, Schmidt and Chang point out that each of the hallmarks of cancer is modulated by the activity of multiple lncRNAs [92].

Let's address the acquired capability hallmarks one–by–one.

- Self–Sufficiency in Growth Signals: this is due to the cancer starting in a cell that is in the process of epigenetic differentiation, which is occurring during the natural process of growth.
- Insensitivity to Antigrowth Signals: this is also due to the cell being stuck in a state of growth.
- Evading Apoptosis: in EDM, the ability to evade apoptosis varies depending on the state that the cell was in when the cancer condition arose.
- Limitless Replicative Potential: this is a restatement of the essential point of EDM — the cancer cell is stuck in the process of transition from a pluripotent cell to a fully defined cell. This is part of the growth and

development of a body part. Since the process is not turned off, there is limitless replication.

- Sustained Angiogenesis: angiogenesis is part of the normal process of growth, and is automatically established by the cancer cell.
- Tissue Invasion and Metastasis: in EDM, this, like evasion of apoptosis, varies from tumor to tumor. For example, metastasis is more likely to happen if the cancer cell is capable of EMT. This model predicts that, in general, CSC cancers are more likely to metastasize.
- Reprogramming Energy Metabolism: according to EDM, this is done through the release of signals, such as miRNA, during the process of epigenetic differentiation.
- Evading Immune Destruction: at present, EDM does not address the ability to evade the immune system.

The Hallmarks of Cancer include two enabling characteristics: Genome Instability and Mutation and Tumor–Promoting Inflammation:

- Genome Instability and Mutation: according to EDM, only certain cancers have genome instability, depending on whether or not genome correction was turned off at that stage of differentiation. If it was, the degree of mutation is much higher. But there can be cancers where this does not happen.
- Tumor–Promoting Inflammation: as with the ability to evade immune destruction, the epigenetic model does not address this.

Therefore EDM explains the hallmarks of cancer, except for the immune responses.

5. Evidence for the Epigenetic Differentiation Model

Before discussing the hypothesized treatment, I need to show evidence for the Epigenetic Differentiation Model. This will help determine if a treatment based on this model is feasible.

I claim that cancer is an error in epigenetic differentiation. Some studies have looked into this, for example, showing that the normal repair of a DNA break can occasionally cause heritable silencing of a CpG island—containing promoter by recruitment of proteins involved in silencing, possibly leading to cancer [93]. EDM claims that, although cancer is a problem related to epigenesis, it can occur either with errors in the expression of proteins or with errors in non–coding information that lead to epigenetic errors. Some studies have even shown that mutations in coding regions are lower than in non–coding transcribed regions [94].

EDM claims that DNA repair genes are suppressed at times during epigenetics. The tumor suppressor gene p53 is an example of this. At times during the epigenetic differentiation of stem cells, p53 is turned off [95] [96]. Besides genetic errors in p53 that lead to cancer, the p53 genes can be controlled by epigenetic processes involving miRNA [57], transposons [97] and lncRNA [98]. For example, knockdown of lncRNA-ST8SIA3 leads to upregulation of genes involved in the p53 response [99]. The lncRNA TP73-AS1 is upregulated in cancer – its knockdown inhibits the proliferation of cancer cells [100]. Also, field defects can arise due to the supression of repair processes [101].

Exosomes are important in determining the microenvironment and in structure determination. Multiple studies have shown that exosomes are abnormally expressed in cancer [32] [102] [41] [34] [103] [38] [104].

According to EDM, the closer to the stem cell where the process of epigenesis gets stuck, the more dangerous the cancer. According to SET, this is at the time when the morphogen gradients are being established and morphogenetic genes like the Hox genes are active. These processes are also associated with non–coding RNA, such as HOTAIR, which are expressed near the start of the process of epigenetic differentiation. Consequently, lncRNAs such as HOTAIR are found to be associated with a number of cancers, such as in laryngeal squamous cell carcinoma [41] since they are at the beginning of the process [23] [105].

It has been noted that miRNAs are passed in exosomes and that they influence cell proliferation and apoptosis, both positively and negatively [106] [107] [102]. For example, restoration of miR–137 expression resulted in a significant decrease in the proliferation of colorectal cancer [108].

Transposons and lncRNAs appear in the exosomes [109] [110] [111]. They are known to affect the tumor microenvironment [112]. LINE–1 appears in exosomes [113], also HERV retrotransposons [64]. These lncRNAs are implicated in cancer [114] [115] [103]. For example, lncRNA–ROR was shown to be increased in malignant hepatocytes [116], and LINE–1 methylation is associated with more aggressive colorectal cancer [117]. Some lncRNAs have been observed to regulate apoptosis [118] such as LNC01234 [119], PVT1 [120], GAS5 [118] and URHC [121].

Each tumor cell is different in the expression of lncRNA and transposons in exosomes [122] [102] [123] [103]. Because of this, exosomes are being considered as biomarkers for cancer [124] [41] [61].

It is known that lncRNAs affect the progress of cancer [125] [92] [126]. For example, knockdown of lncRNA-ST8SIA3 led to upregulation of genes involved in

the p53 response [99]. Other lncRNAs are known to control apoptosis [105] [127], such as C17orf76–AS1 (LRRC75 antisense RNA1) [111], MINCR [128], LINC00460 [129], LINC00152 [130], SNHG7 [131] and SNHG1 [132]. Lnc–ROR is known to trigger EMT [133] and affects p53 [98].

Studies have shown that methylation errors are as important as genetic errors [24] [25]. Methylation patterns have been shown to differ in different cancers [134]. Methylation errors can go in either direction. Hypermethylation turns off tumor suppressor genes, causing the tumor to grow uncontrollably [135]. Hypomethylation leaves on transposons, such as LINE–1, which is consistent with SET and EDM [136] [117]. According to SET, transposons play a part in epigenetic differentiation by determining the location of the cell in a structure. But turning on transposons inappropriately correlates with pathology in certain cancers [137].

EDM and SET predict that structure determination involves the transfer of fragments of lncRNA and transposons, as some studies have shown [124]. But lncRNA fragments may not be identified because of the sampling method. Some methods may autocomplete the fragment or flag a fragment as the whole unit [138] [102].

6. Hypothesis: An Information–Based Modality for Cancer Treatment

The Structure Encoding Theory and the Epigenetic Differentiation Model for cancer suggests a possible modality for cancer treatment.

Presuming that cancer happens when a cell gets stuck in an epigenetic state, then it would be likely that the cells are passing location information using extracellular vesicles such as exosomes between cells to control the epigenetic state. According

to SET, this would be non–coding RNA and transposons which transfer position information. Also, according to SET, this information will be an initial segment that marks the position. This information will vary from tumor to tumor, depending on the position information related to the cancer cell and its microenvironment.

SET predicts that certain position information passed to a cell could force the cell into apoptosis during normal differentiation. Cells are forced into apoptosis to define a structure, for example, in the creation of voids in tissues, or to eliminate cells that are at the edge of a body part. Note that this is different from apoptosis that happens because of DNA transcription errors, for example.

This leads to the statement of the hypothesis:

Hypothesis: An Information–Based Modality for Cancer Treatment

Given Structure Encoding Theory and the Epigenetic Differentiation Model for cancer, many or most cancers pass structure information between the tumor cells in the form of fragments of transposons and lncRNAs. The hypothesis is a treatment for cancer that incorporates into the tumor microenvironment information passed via exosomes to instruct the local cells to go into apoptosis. This will overwhelm the current microenvironment and force the tumor cells to self–destruct.

Using exosomes containing transposons and lncRNA can be done in a variety of ways. For example, HERV affects the immune system, leading to apoptosis [139]. The expression of lncRNA INXS is associated with the expression of BCL-X protein-coding mRNA, leading to apoptosis [140]. This is in contrast to cancer treatments that suppress exosomes [141].

Considerable analysis will be required to determine what information is passed in a cancer tumor and also what information is passed during the normal stages of

epigenetic differentiation that lead to apoptosis. But once this is determined, flooding the tumor with the desired information may cause it to shrink. Exosomes have been used in various treatments [142]. Research is ongoing to manufacture artificial exosomes [143]. Another method is to have cells naturally generate exosomes then isolate them for use [144] [145].

Of course, this treatment won't work if apoptosis is turned off, which happens, for example, when p53 is disabled. There are two major reasons for apoptosis: the destruction of cells that can't be repaired, and the destruction of cells not required in structure determination. At least one of these methods of apoptosis must be turned on for the treatment to work.

This treatment also presumes that the change can be made by flooding the existing information. For example, increases in exosomes with lncRNA GAS5 has been shown to be associated with apoptosis [146]. Apoptosis is known to start by suppressing lncRNAs [105]. It could be possible to remove information, but this would be harder to do.

The correct treatment in each case could be determined experimentally by trying different lncRNA fragments and seeing what happens. For example, exosomes with different lncRNA sequence lengths are associated with different miRNA expressions [51]. It is likely that lncRNA begins with some sort of header information. Presenting the tumor cells with some sequence changes past this header might force it into an apoptosis state. These changes could be substitutions, truncations or extensions.

This leads to the following test of the hypothesis:

Experimental Test Sequence

(1) Determine which exosomes containing transposon and lncRNA fragments cause apoptosis during the normal process of cellular differentiation. Create a library of such sequences.

(2) Determine which exosomes containing transposon and lncRNA fragments are associated with which cancer tumors.

(3) Match the transposon and lncRNA fragments in the tumor to the closest fragments that cause apoptosis.

(4) Create artificial exosomes containing the fragments that cause apoptosis.

(5) Flood the tumor with these artificial exosomes and check that this initiates apoptosis.

The first two steps will require the creation of a comprehensive catalog of fragments of transposons and lncRNA and their effects during the process of epigenetic differentiation and cancer. Multiple studies have begun the work of determining how transposons and lncRNA control apoptosis, both in the normal process of development [105] [133] [127] [98] and during cancer [114] [118] [115] [121] [116] [111] [131] [130] [129] [120] [103] [128] [117].

The catalogs will be built from studies that correlate transposons and lncRNA with their associated body part and what fragments lead to what outcome both during normal development and different cancer tumors. It may eventually be possible to develop algorithms that provide general rules for these matches. Finally, some experimentation may be necessary to determine how to deliver the appropriate sequences to the tumor, based on the current sample, and incorporate them into the tumor microenvironment, so that this information overwhelms the current information.

Information–based treatments are not just limited to inducing apoptosis. The injection of information can also change the epigenetic state, which can ameliorate the effects of cancer. Berdasco and Esteller mention the possibility of reversing the damage to the epigenetic state [21], but their approach is to manipulate the process of epigenetics itself, instead of manipulating the information presented to the cell and letting the cell do it.

A possible advantage of information–based therapy is that it may be less likely for the cancer cells to become resistant to this approach compared to treatments that target signaling pathways. Signaling pathways react to changes in their environment. It is much harder for the cell to epigenetically reprogram itself to react to a change of information.

There is a second modality using morphogens and miRNA signals instead of lncRNA information. This modality is already being considered for treatments. As mentioned before, certain miRNAs act as signals to control apoptosis. Treatments involving miRNA could be very effective [48] [147]. They could be actively manipulated to force the cancer into apoptosis either directly [148] [149] or by removing the methylation of the tumor suppression genes [24]. Also, for cancer cells early in the stages of epigenetic differentiation, the concentration of signals associated with morphogenesis can be manipulated.

Since miRNAs often work to suppress gene expression, treatment must be tailored with this in mind. Some treatments work by sponging excess miRNAs [150] [151] [148]. Some treatments involve adding miRNA exosomes [152]. Since miRNA is a marker for different cancers because they are specific to different cancers [153], that makes them a good target for a signal–based treatment.

The drawback of using signaling instead of information is that signals themselves are often not specific to the tumor, and could affect non–cancer tissues. Treatment based on information sequences is specific to the tumor and can be identified based on the information already occurring in the exosomes in the tumor microenvironment. Also, signaling is more sensitive to quantity. In contrast, for an information–based treatment, it is only necessary to overwhelm the current information.

7. Conclusions

I have suggested a modality for cancer treatment based on controlling the cancer by overwhelming the tumor with information that might cause it to self–destruct. Because information–based treatment does not involve physical manipulation, such as surgery, radiation or chemotherapy, it has advantages. The information can be specially tailored to the tumor, in contrast to a physical manipulation that can possibly have effects beyond the tumor.

There are significant sexual differences in epigenetic differentiation [154] [155] [156] [157]. This may explain the differences in cancer between the sexes and why so many cancers are in the reproductive organs.

Information–based treatment modalities can be used for other diseases that are related to epigenetic differentiation, for example, schizophrenia, which may be due to structural problems [158]. If started early, an information–based treatment could slow or ameliorate the disease.

Information–based treatments could also promote angiogenesis for situations such as heart attacks.

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