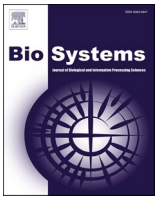
BioSystems 211 (2022) 104587

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems



A proposed Information–Based modality for the treatment of cancer

Antony Van der Mude

ARTICLE INFO

Keywords:
Cancer
Transposons
Long non-coding RNA
Apoptosis
Epigenetics

ABSTRACT

Treatment modalities for cancer involve physical manipulations such as surgery, immunology, radiation, chemotherapy or gene editing. This is a proposal for an information–based modality. This modality does not change the internal state of the cancer cell directly — instead, the cancer cell is manipulated by giving it information to instruct the cell to perform an action. This modality 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 development from pluripotent cells to fully differentiated cells. It has been noted that cancer is often due to errors in morphogenetic differentiation accompanied by associated epigenetic processes. This implies a model of cancer called the Epigenetic Differentiation Model. A major feature of the Structure Encoding Theory is that the characteristics of the differentiated cell are affected by inter–cellular information passed 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, which 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 (National Cancer Institute, 2020) (American Cancer Society, 2020). 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 genes of the cancer cells — gene therapy.
- Manipulation of the immune system — immunotherapy.

The treatment modality I am proposing is based on the manipulation of information passed to the cell, not the manipulation of the cell directly. 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.

The terms information, signal, message and data are often used interchangeably. I am going to use the terms signal and information to differentiate between analog and digital modes of data transfer. A *signal* is a unit of quantitative, analog data. Morphogens and hormones are examples of intercellular signals. The degree of response to a signal is in proportion to the quantity of a signal. In contrast, *information* refers to some sort of encoded sequence. Information means something as a whole — it is a digital message — and is less dependent on quantity or concentration. The DNA code, Morse code, computer data files and written books are examples of information.

Information theory was pioneered by Claude Shannon in his papers entitled “A Mathematical Theory of Communication” (Shannon, 1948). This was where the term “bit” was first coined. Information is capable of being reduced to a bit string and is transmitted through some sort of carrier medium. What Shannon was considering was the transmission of messages over the medium of copper telephone lines. On the other hand, a signal is not usually differentiated from the medium that carries it. In Electrical Engineering and Computer Science, there is a distinction between analog and digital computers. Analog computers are controlled by signals such as voltages, whereas digital computers store and process information. There are also computers known as Digital Signal Processors that have inputs called Analog–to–Digital Converters (ADC). The function of an ADC is to convert an analog signal into information which

E-mail address: vandermude@acm.org.

https://doi.org/10.1016/j.biosystems.2021.104587
Received 13 June 2021; Received in revised form 20 November 2021; Accepted 1 December 2021
Available online 13 December 2021

is a bit string representing an integer that corresponds to the signal quantity.

The modality presented here is a manipulation of information instead of signals. In biology, morphogens and hormones are examples of signals in the sense that they are chemical compounds where what matters is the amount of the compound at a certain time and place. This can provide two problems. The first problem is that the amount is an approximate value — it is hard to exactly convert a signal into a precise value. The ADC, for example, can have conversion errors for a number of reasons, including problems with the reference voltages. The second problem is that it is hard to specify a particular cell to be the recipient of the signal. Any other nearby receptor for the chemical that embodies the signal could be the receiver.

On the other hand, information is more exact and specific. In the cell, information is often encoded in DNA or RNA, which is naturally interpreted as a sequence of bits of information. There is also a distinction between the information and its medium. In this paper, the medium of transmission is presumed to be exosomes, extracellular vesicles that carry the DNA or RNA that contain the information. For information transfer, the quantity is not usually important as long as the information is transferred. What is important is the simple fact that the information was received. Also, the intended recipient can be specified more precisely than for a signal. This often happens in cellular processes where only certain proteins or DNA/RNA sequences are capable of responding to the DNA/RNA information being passed. This means that a treatment modality based on information passing can possibly be more precisely targeted.

Information transfer has its own problems. In contrast to the approximate nature of signals, bit errors in information transfer can sometimes make a big difference. Also, the number of possible information sequences grows exponentially by the length of the sequence. This makes it difficult to figure out what is the appropriate information sequence to send. Third, the receiver of an information sequence is typically much more complicated than the receptor of a signal. This receiver may also have to be pre–configured to accept a certain possible set of information sequences. A modality based on information transfer will have to address these problems.

An information–based modality might seem to be similar to gene therapy (Dunbar et al., 2018) (Goswami et al., 2019) (Shahryari et al., 2019) since they both involve genetic information, but there are major differences. In this proposed modality, the information being passed is in the form of non–coding RNA or transposons. In contrast, gene therapy for cancer typically involves the delivery of genes using vectors such as viruses to incorporate these genes into the target cell. In this fashion, gene therapy alters the cellular mechanisms of the target cells. The result of gene therapy is a cell with an altered or augmented genome, resulting in different functioning of the cell.

A therapy based on information passing does not change the genetic mechanisms of the cell. Instead, it provides information that instructs a change in the epigenetic behavior, leading to a different phenotype — that is to say, a different behavior of the cell, such as changes to the state of the genetic regulatory network. But the DNA of the cell is not altered. An information–based modality does not have to specifically target cancer cells in the way that gene therapy does. Instead, the information can be tailored in such a way that it is ignored by almost all other cells except the cancer cells and their progenitor.

Since the cells are not being altered through drugs or gene therapy, there is less likelihood that non–cancer cells will be affected. It is expected that intercellular information exchange would only affect cells in a particular epigenetic state since that state primes the cell to recognize and process the individualized information. Most other cells would ignore the information because it is not targeted to them. This modality, using information rather than signaling, is also more specific than therapies that are based on intercellular signal passing. For example, signals such as cytotoxic proteins are also known to affect cells other than the intended target (Jia et al., 2012).

An information–based modality is based on a theory for Structure Encoding in DNA (Van der Mude, 2020). If this theory is correct, then many cancers are caused by errors in the epigenetic process of going from pluripotent stem cells to fully differentiated cells. The theory states that cells in the process of differentiation will receive information from neighboring cells that identifies where in the body part structure that cell is located. This information begins with a rough indicator in the form of morphogen gradients and proceeds to more detailed information in the form of exosomes carrying transposons and long non–coding RNA.

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, which is done with chemotherapy or gene therapy, the proposed treatment disrupts the information passed between cancerous cells. It is tricking the cancer cell to self–destruct by feeding it the "wrong" information.

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 of cancer in light of this evidence.

2. Structure Encoding in DNA

The theory for Structure Encoding in DNA (Van der Mude, 2020) 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 focuses 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 (2007) 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 (Herman and Baylin, 2003). 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 (Cabili et al., 2011) (Nagano and Fraser, 2011) (Babaian and Mager, 2016) (Sun et al., 2018a) (Faulkner and Billon, 2018). They have been found to be active in stem cells in the process of epigenetic differentiation (Schumann et al., 2019). 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 (Hessvik and Llorente, 2018) pass the information to the cell to determine the structure (Valadi et al., 2007) (Miranda et al., 2014). Studies have shown that lncRNA expression differs depending on the tissue (Sun and Kraus, 2013) (Liu et al., 2016). 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 (Mercer et al., 2009) (Spizzo et al., 2012). Epigenetic modifications determine the selection of the specific cell type (or apoptosis) at a specific location through transposon splicing and histone modification (Daniel et al., 2011). 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 etiology, cancer often happens due to problems with the process of epigenetic differentiation.

Cancer is commonly defined as abnormal cell growth (Wikipedia contributors and h, 2021). Normal cell growth is usually mediated either by the process of morphogenesis or repair. So cancer must be understood in terms of the development of structures. Robert Weinberg, in "The Biology of Cancer" expresses it as follows (Weinberg, 2013):

> … mutated genes may divert cells into acquiring novel, often highly abnormal phenotypes. Such changes may be incompatible with the normally assigned roles of these cells in organismic structure and physiology. Among these inappropriate changes may be alterations in cellular proliferation programs, and these in turn can lead to cells that no longer obey the rules governing normal tissue construction and maintenance.
>
> When portrayed in this way, the renegade cells that form a tumor are the result of normal development gone awry. In spite of extraordinary safeguards taken by the organism to prevent their appearance, cancer cells somehow learn to thrive. Normal cells are carefully programmed to collaborate with one another in constructing the diverse tissues that make possible organismic survival. Cancer cells have a quite different and more focused agenda. They appear to be motivated by only one consideration: making more copies of themselves.
>
> Cancer manifests itself in different ways depending on the body part and the stage of epigenetic differentiation where the error arose. Epigenetic differentiation is a fundamental process in embryogenesis, and 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 processes of development and repair involve the differentiation of individual cells in the context of the other cells in the organism. To do this correctly, there needs to be information about the body part structure. As described in the previous section, this process is mediated by epigenetics. It is known that epigenetic changes are present in most cancers (Baylin and Jones, 2016). These changes can, for example, lead to alterations in the pathways relevant to stem cell growth and differentiation (Jones and Baylin, 2007).

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 is a common cause of cancer. Cancer can be caused by alterations in oncogenes, tumor–suppressor genes, and micro–RNA (*miRNA*) (Croce, 2008). But errors in the processes of epigenetic differentiation, such as methylation errors (Herman and Baylin, 2003), errors in chromatin, or errors in the regulation of the genetic regulatory network, can also cause cancer (Berdasco and Esteller, 2010). 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 (Schmitt et al., 2012). 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 (Rossi and Antonangeli, 2014). 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 is cancers that are mostly due to incorrect methylation (Herman and Baylin, 2003).

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 (Herman and Baylin, 2003) (Esteller, 2005) (Agarwal et al., 2012). 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 (Daniel et al., 2011).

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 (Cabrera et al., 2015). Exosomes are important components and regulators of the cell microenvironment (Wendler et al., 2013) (Colombo et al., 2014). They have long been recognized as having a part to play in cancer (Silva and A Melo, 2015) (Yu et al., 2015) (Kalluri, 2016) (Rajagopal and Harikumar, 2018) (Tai et al., 2018) (Osaki and Okada, 2019) (Tian et al., 2019)

(Turchinovich et al., 2019). Radiation treatment and cancer have been shown to change the expression of exosomes (Luo et al., 2019) (Ni et al., 2019). Exosomes are carriers for a variety of things, such as proteins, RNA and DNA (Thakur et al., 2014). 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 (Dragomir et al., 2018). Exosomes also carry signals that establish the tissue microenvironment, such as exosomes containing miRNA (Grange et al., 2011) and morphogens such as Wnt and Hedgehog (Becker et al., 2016).

The miRNAs that appear in exosomes are used for signaling, which helps to determine the microenvironment (Figueroa et al., 2017) (Kogure et al., 2019). For example, exosomes containing miRNA from mesenchymal stem cells have been shown to suppress angiogenesis in breast cancer cells (Lee et al., 2013). They are also known to control apoptosis (Jovanovic and Hengartner, 2006) (Othman and Nagoor, 2014) (Slattery et al., 2018).

It has been known that lncRNAs control the expression of miRNAs (Salmena et al., 2011) (Ahadi et al., 2016) and that the expression of miRNAs is controlled by methylation (Weber et al., 2007). There is a strong correlation between the location in the genome of specific miRNAs and HOX genes, indicating their involvement in epigenetic differentiation (Calin et al., 2004). The miRNA controls the regulatory network by turning off proteins (Lim et al., 2005) (Esquela-Kerscher and Slack, 2006). On the other hand, the p53 repair protein is known to turn on miRNAs (Wan et al., 2011) (Hu and Gatti, 2011). Note that miRNAs are specific for different families of cells since they are involved in differentiation (Negrini et al., 2007).

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" (Bolukbasi et al., 2012). 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 (Yang and Li, 2018) (Hinger et al., 2018). Some transposons carried by exosomes include certain Long Interspersed Nuclear Elements (*LINE–1*) (Spadafora, 2015) (Ardeljan et al., 2017) and Human Endogenous Retroviruses (*HERV*) (Balaj et al., 2011). 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 can begin 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 (Visvader and Lindeman, 2008) (Shackleton et al., 2009) (Gupta et al., 2009) (López-Lázaro, 2015a) (Manzo, 2019) 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 (Tomasetti and Vogelstein, 2015) and to metastasize (López-Lázaro, 2015b).

Cancer cells can start in a particular stage of epigenetic differentiation, but some processes in epigenesis could be continuing and changing. This results in creating a variety of cells derived from the CSC (Sundar et al., 2014). 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 (Hanahan and Coussens, 2012) (Kreso and Dick, 2014). Note that this process may not necessarily be one way. Epigenetic processes can sometimes lead to stem cells derived from more differentiated cells (Marjanovic et al., 2013).

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 (Dalerba et al., 2007).

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 (Shackleton et al., 2009) (Wang et al., 2014) (Greaves and Maley, 2012). The two models are not mutually exclusive (Rich, 2016). It has been suggested that the stem cell model is actually explained by the process of mutation of cancer cells in a clonal model (van Niekerk et al., 2017). That cancer can manifest itself in these different ways is explained in EDM as a difference in the epigenetic state of the cancer cells. 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 states that cancers can differ because of the cause of the cancer — genetic or epigenetic errors — and can manifest in different ways depending on the epigenetic stage.

This progress from stem cells 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." (Hanahan and Weinberg, 2011).

Vogelstein et al. (2013) 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.

It has been well known that driver mutations are often associated with particular types of cancers (Wood et al., 2007) (Vandin et al., 2012) (Roy et al., 2014) (Iranzo et al., 2018). The specificity of driver mutations associated with certain tumors is due to the epigenetic differentiation of the cells, which is implied by EDM. If EDM is correct, the same mutation in a cell of a different type would not lead to cancer, or that

some genes are oncogenes in some cell types and tumor suppressors in others (Colaprico et al., 2020). Note that this specificity applies only to driver mutations associated with particular types of cells. There also exist oncogenes that are involved in many types of cancers. According to EDM, these genes control the process of epigenetics generally regardless of type.

EDM has features in common with Tissue Organization Field Theory (*TOFT*) (Soto and Sonnenschein, 2004) (Baker, 2015). 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. *Facilitated Variation* is a theory that explains the development of ancillary components such as angiogenesis (Gerhart and Kirschner, 2007). Cancer cells that are in an intermediate state of epigenetic differentiation are predisposed to promoting these features as the tumor grows. This is done by the expression of signals and information in the microenvironment. An example is the promotion of angiogenesis using lncRNAs (Lang et al., 2017a) (Lang et al., 2017b). Cancer Associated Fibroblasts (*CAF*) and Tumor Associated Macrophages (*TAM*) are examples of cells that perform these supporting functions. CAFs establish the network of intercellular communication that supports the tumor structure and helps it grow (Huang et al., 2019). TAMs, besides establishing intercellular communications in the tumor microenvironment, are also involved in the immune system (Jinushi et al., 2011).

Metastasis is often associated with the ability of the cancer to make the epithelial–to–mesenchymal transition (*EMT*) (Thiery et al., 2009) (Kong et al., 2011) (Jolly et al., 2015). Since EMT is associated with early embryogenesis (Cabrera et al., 2015), EDM predicts that tumors that have a lot of stem cells 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 (Hanahan and Weinberg, 2000) (Hanahan and Weinberg, 2011)? 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 (Schmitt and Chang, 2016).

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

- Self–Sufficiency in Growth Signals: this can be due to the cancer occurring in a cell that is in the process of epigenetic differentiation, due to an error during the natural process of morphogenesis.
- Insensitivity to Antigrowth Signals: this can also be due to errors in morphogenesis.
- 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 arises during the process of transition from pluripotent cells to fully defined cells. 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 can often be 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 (O'Hagan et al., 2008). 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 (Tuna and Amos, 2013).

EDM claims that DNA repair genes are suppressed during some stages of epigenetics. The tumor suppressor gene p53 is an example of this. At times during the epigenetic differentiation of stem cells, p53 is turned off (Soto-Reyes and Recillas-Targa, 2010) (Aloni-Grinstein et al., 2014). Besides genetic errors in p53 that lead to cancer, the p53 genes can be controlled by epigenetic processes involving miRNA (Hu and Gatti, 2011), transposons (Rebollo et al., 2012) and lncRNA (Toraih et al., 2019). For example, knockdown of lncRNA–ST8SIA3 leads to upregulation of genes involved in the p53 response (Loewer et al., 2010). The lncRNA TP73–AS1 is upregulated in cancer — its knockdown inhibits the proliferation of cancer cells (Li et al., 2018). Also, field defects can arise due to the supression of repair processes (Facista et al., 2012).

Exosomes are important in determining the microenvironment and in structure determination. Multiple studies have shown that exosomes are abnormally expressed in cancer (Kalluri, 2016) (Wei et al., 2017) (Dragomir et al., 2018) (Tai et al., 2018) (Zhao et al., 2019) (Luo et al., 2019) (Lucien and Leong, 2019).

According to EDM, the closer to the stem cell where the process of epigenesis goes awry, 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 (Shen et al., 2015). Consequently, lncRNAs such as HOTAIR are found to be associated with a number of cancers, such as in laryngeal squamous cell carcinoma (Dragomir et al., 2018) since they are at the beginning of the process (Rossi and Antonangeli, 2014) (Zhao et al., 2015).

It has been noted that miRNAs are passed in exosomes and that they

influence cell proliferation and apoptosis, both positively and negatively (Godlewski et al., 2008) (Yeung et al., 2016) (Wei et al., 2017). For example, restoration of miR–137 expression resulted in a significant decrease in the proliferation of colorectal cancer (Balaguer et al., 2010).

Transposons and lncRNAs appear in the exosomes (Gezer et al., 2014) (Kahlert et al., 2014) (Chen et al., 2016). They are known to affect the tumor microenvironment (Wang et al., 2016). LINE–1 appears in exosomes (Nolte-'t Hoen et al., 2012), also HERV retrotransposons (Balaj et al., 2011). These lncRNAs are implicated in cancer (Gibb et al., 2011) (Carreira et al., 2014) (Zhao et al., 2019). For example, lncRNA–ROR was shown to be increased in malignant hepatocytes (Takahashi et al., 2014), and LINE–1 methylation is associated with more aggressive colorectal cancer (Voichitoiu et al., 2019). Some lncRNAs have been observed to regulate apoptosis (Pickard et al., 2013) such as LNC01234 (Ghaffar et al., 2018), PVT1 (Salehi and Sharifi, 2018), GAS5 (Pickard et al., 2013) and URHC (Xu et al., 2014).

Each tumor cell is different in the expression of lncRNA and transposons in exosomes (Li et al., 2013) (Wei et al., 2017) (Yan et al., 2015) (Zhao et al., 2019). Because of this, exosomes are being considered as biomarkers for cancer (Ke et al., 2017) (Dragomir et al., 2018) (Hinger et al., 2018).

It is known that lncRNAs affect the progress of cancer (Hewson et al., 2016) (Schmitt and Chang, 2016) (Sun et al., 2018b). For example, knockdown of lncRNA–ST8SIA3 leads to upregulation of genes involved in the p53 response (Loewer et al., 2010). Other lncRNAs are known to control apoptosis (Zhao et al., 2015) (Han et al., 2019), such as C17orf76–AS1 (LRRC75 antisense RNA1) (Chen et al., 2016), MINCR (Chen et al., 2019), LINC00460 (Lian et al., 2018), LINC00152 (Bian et al., 2017), SNHG7 (Wang et al., 2017) and SNHG1 (Zhang et al., 2018a). Lnc–ROR is known to trigger EMT (Lou et al., 2017) and affects p53 (Toraih et al., 2019).

Studies have shown that methylation errors are as important as genetic errors (Esteller, 2005) (Agarwal et al., 2012). Methylation patterns have been shown to differ in different cancers (Fernandez et al., 2012). Methylation errors can go in either direction. Hypermethylation turns off tumor suppressor genes, causing the tumor to grow uncontrollably (Miao et al., 2019). Hypomethylation leaves on transposons, such as LINE–1, which is consistent with SET and EDM (Hur et al., 2014) (Voichitoiu et al., 2019). 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 (Sunami et al., 2011).

EDM and SET predict that structure determination involves the transfer of fragments of lncRNA and transposons, as some studies have shown (Ke et al., 2017). 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 (Huang et al., 2013) (Wei et al., 2017).

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

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

Presuming that a cancer arises in the process of epigenetic differentiation, it would be likely that the cancer 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:

Using exosomes containing transposons and lncRNA can be done in a variety of ways. For example, HERV affects the immune system, leading to apoptosis (Bannert et al., 2018). The expression of lncRNA INXS is associated with the expression of BCL–X protein–coding mRNA, leading to apoptosis (DeOcesano-Pereira et al., 2014). This is in contrast to cancer treatments that suppress exosomes (Marleau et al., 2012).

Another example is the case where the loss of the MPP8 gene in the Human Silencing Hub (HUSH) complex reactivated LINE–1, which led to tumor suppression in acute myeloid leukemia (AML) (Gu et al., 2021). Under the EDM model, what is happening is that the HUSH complex is turning off the process of epigenetic differentiation. This turns off the activity of the LINE–1 transposons. Normally, in the process of development of the bone marrow, there are a certain number of hematopoietic stem cells (HSC) that need to be created. This is part of the structure of the marrow and according to SET it is under the control of intercellular information such as the LINE–1 transposons. Once the structure is completed, any further attempt to create more HSCs will be controlled by the action of the LINE–1 in the heterochromatin, resulting in the activation of p21 and p53 mediated apoptosis. Under the EDM model, AML can be due to errors in cancer stem cells, including the upregulation of the HUSH complex. If this happens, this cascades down to a problem in the suppression of the LINE–1 regulation of the bone marrow structure. An information–based modality for the treatment of this cancer would work as follows: instead of attempting to restore the proper functioning of the regulatory network in the cell, either through chemotherapy or gene editing, what is done instead is to flood the site of the leukemia with exosomes containing the particular configuration of the LINE–1 transposon that stops the growth of HSCs in a healthy marrow. It is expected that this would halt the growth of the cancer.

Considerable analysis will be required to determine in general 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 (Lener et al., 2015). Research is ongoing to manufacture artificial exosomes (García-Manrique et al., 2018). Another method is to have cells naturally generate exosomes then isolate them for use (Ohno et al., 2013) (Zhang et al., 2018b).

Note that studies of transposons and apoptosis in the cell may not help in finding which exosome–containing transposons work best, because apoptosis in those studies is often due to errors in epigenetic development. Therefore, it is important for an information–based modality to determine that the apoptosis is caused by the transfer of information between cells, and not because of errors in the cells themselves that lead to apoptosis.

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 (Koldemir et al., 2017). Apoptosis is known to start by suppressing lncRNAs (Zhao et al., 2015). 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 (Ahadi et al., 2016). It is likely that lncRNA begins with some sort of header information.

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.

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:

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 (Zhao et al., 2015) (Lou et al., 2017) (Han et al., 2019) (Toraih et al., 2019) and during cancer (Gibb et al., 2011) (Pickard et al., 2013) (Carreira et al., 2014) (Xu et al., 2014) (Takahashi et al., 2014) (Chen et al., 2016) (Wang et al., 2017) (Bian et al., 2017) (Lian et al., 2018) (Salehi and Sharifi, 2018) (Zhao et al., 2019) (Chen et al., 2019) (Voichitoiu et al., 2019).

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.

The challenge of this approach is that it is based on transposons and lncRNAs that are unique to each particular cancer. Research up to now is typically focused on transposons and lncRNAs that show up with many cancers, and the ones that are unique to each tumor is ignored. If this information–based modality is to be specific to the tumor, then the unique information being passed between the cells in the tumor will need to be identified.

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 (Berdasco and Esteller, 2010), 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 (Othman and Nagoor, 2014) (Rothschild, 2014). They could be actively manipulated to force the cancer into apoptosis either directly (Pileczki et al., 2016) (Mansoori et al., 2016) or by removing the methylation of the tumor suppression genes (Esteller, 2005). 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 (Ebert et al., 2007) (Ebert and Sharp, 2010) (Pileczki et al., 2016). Some treatments involve adding miRNA exosomes (Bader et al., 2010). Since miRNA is a marker for different cancers because they are specific to different cancers (Hayes et al., 2014), 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 (McDonald et al., 2005) (Pask et al., 2009) (Ferguson-Smith, 2011) (Autuoro et al., 2014). 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,

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.

schizophrenia, which may be due to structural problems (Gejman et al., 2010). 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.

Conflicts of interest

None.

8 Acknowledgements

I should like to thank Andrew Moore for helpful suggestions that improved the overall presentation and for his encouragement. I also would like to acknowledge the anonymous reviewer for comments that helped to clarify the presentation.

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