

Forces, Chromosomal Configurations, and Carcinogenesis: Towards Another Therapeutic Approach

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Abstract

Previous studies of *in vitro* and *in vivo* morphogenesis may suggest a more inclusive principle governing biological processes. In this regard, methylglyoxal (MG) in very low, non-toxic concentrations and ascorbic acid have been shown to promote *in vitro* morphogenesis in various types of plants. Forces of cohesion and adhesion might be involved in such development. These are conveyed through the electronic desaturation of protein by means of MG and ascorbic acid. In low concentration, MG with ascorbic acid or ascorbate might induce adhesion within the histone proteins making up a part of the chromosomes in mammals. As proposed, this may induce specific regions of gene inactivation, through heterochromatinization, and specific chromosomal re-configurations, that would be needed for the completion of stable development, by means of chromosome stabilization via differential adhesion, and the consequent prevention of carcinogenesis. Such re-configurations may reflect accommodation to cohesive and adhesive stress. Forces, including those of adhesion and cohesion, may reflect the deep guidance of the universal constants of physics, which would occur through a constant, regenerative-defining component of those constants. The component would be to define or geometrically guide the regeneration of stability, coherence, and constancy in nature at various scales, through dynamic accommodation, which would be most manifest in biological processes. Awareness and elaboration of such may open up new therapeutic vistas, especially with regard to the treatment of cancer.

Keywords: Accommodation; Adhesion; Ascorbic acid; Biology; Callus; Carcinogenesis; Chromosome; Cohesion; Completion; Concentration; Configurations; Correspondence; Development; Dimensional/dimensionless Constants; Evolutionary; Force; Heterochromatin; Methylglyoxal; Morphogenesis; Physics; Principle; Stability; Stress; Therapeutic; Unifying; Universal

Albert Szent-Gyorgyi's Investigations; Their Connections to Plant Development *In vitro*: Implications for a Unifying Theory

Various types of forces, such as cohesive and adhesive forces, are involved in physical and biological processes. Many of these processes appear to have developmental features through different scales of nature, and such processes may reflect a universal dynamic of accommodation involving the universal dimensional constants. A particular avenue of plant tissue culture research, utilizing the process of electronic desaturation, might very well point to such a subsuming, universal process. Through the process of electronic desaturation of proteins in living cells, cohesive and adhesive forces are generated and regenerated between cellular proteins and between structured water and the proteins throughout

and between mammalian cells. Those forces stabilize cells and tissues and prevent carcinogenesis [1,2]. In electronic desaturation, methylglyoxal-ascorbic acid complexes attach to particular protein regions, which enable or promote the conduction or movement of outer electrons of the proteins via methylglyoxal-ascorbic acid to oxygen. When such cohesive forces cease to exist in cells due to the conversion of methylglyoxal (MG) to D-lactic acid by glyoxalase, carcinogenesis ensues. Glyoxalase is an enzyme that can actively exist in cells. As noted by Szent-Gyorgyi [1,2], the presence of oxygen, MG, and ascorbic acid enabled the evolution of organisms with high levels of development and a general capability of preventing dedifferentiation that could lead to carcinogenesis.

Earlier articles, most recently in 2019 [3,4], described investigations, based on Szent-Gyorgyi's research on mammalian cells, detailing the effects that MG and

ascorbic acid have on morphogenesis *in vitro* from plant callus or neoplasm, where MG and ascorbic acid (AsA) were necessarily involved in such development. The theoretical implications of these *in vitro* investigations of plant development are conjectured as being subsumed under a broad theory or unifying and trans-scalar perspective that could include biology and physics. This theoretical perspective was alluded to in that earlier review [4], and will be illustrated further in this article. Moreover, this article will illustrate in more detail the avenues whereby methylglyoxal and ascorbic acid or ascorbate, in critical concentrations, could have a therapeutic role with respect to carcinogenesis.

MG in Biological Development. Its Beneficial Effects in Low Concentrations

As pointed out by the author in an earlier review [4], high concentrations of MG are toxic to developing, normal tissues. One could conclude, thereby, that MG would not be suitable for cancer treatment. This would thus present an argument against its use in cancer research. However, Szent-Gyorgyi's research indicated that MG was not toxic to normal, mammalian tissue, only to tumorous tissue. From his research, he concluded that critical, though low concentrations of MG with ascorbic acid prevent carcinogenesis in normal tissues. Out of many low concentrations of MG, an investigator could discover the most effective low concentration of MG with regard to reversing carcinogenic processes. And with MG in that regard, one could discover the most effective, synergistic concentration of ascorbic acid or ascorbate. As described in this article, the investigations with plant tissue culture and with mammalian cells provide important information on this matter. A comprehensive understanding would be the future objective of *in vitro* research and clinical trials. Such *in vitro* research could also include further studies involving plant tissue culture, MG, and ascorbic acid.

In this regard, the author's earlier research in plant tissue culture in fact showed that MG, at very low, non-toxic concentrations, and AsA promoted organogenesis and embryogenesis from the calli or neoplasms of various types of plants, while greatly inhibiting the growth of such calli. The research also showed that these chemicals were implicated in the stabilization of such development. However, high concentrations of MG were inhibitory to biological development and ensued in necrosis of normal developed tissues. Subsequent research by others over many years also demonstrated this situation, where MG was present in very low, non-toxic concentrations, allowing for effective *in vitro* morphogenesis [4]. This might suggest that certain, low concentrations of MG could reverse the carcinogenic processes in humans, and thereby be effective in a medical protocol. Various investigations

also demonstrated that MG and AsA are very beneficial for plant physiology, especially when under abiotic stress [4].

Most recently, it was observed that "methylglyoxal triggers the heat tolerance in maize seedlings by driving the AsA-GSH [ascorbic acid-glutathione] cycle" [5]. Szent-Gyorgyi showed that glutathione, a co-enzyme of glyoxalase, is involved along with MG in the control of mitosis [2].

According to Szent-Gyorgyi's investigations, glutathione, as a co-enzyme, activates the glyoxalase system. MG prevents the activation of glyoxalase through its molecules binding also with its co-enzyme. Through this process, involving biochemical feedback loops, a critical concentration of MG is maintained in the cells for electronic desaturation, and thereby, a critical degree of adhesion and cohesion is enabled through and between cells, and their structures. Such a critical degree of adhesion or cohesion seems to help to maintain or to allow a globally controlled or guided mitosis during development. Without MG in the cells, following from the uncontrolled activation of the glyoxalase system, mitosis would have become uncontrolled due to the loss of cohesion or adhesion. This would have occurred through the prevention of electronic desaturation due to the absence of MG in the cells [2]. It could be concluded or predicted that removal of methylglyoxal in critical, non-toxic concentrations from the plant system would be harmful and might ensue in the generation of plant tumors or plant mortality under abiotic stress.

As noted, various studies have shown that MG is cytotoxic in particular situations. However, as research has also shown, MG is not cytotoxic at very low concentrations. In such concentrations, MG greatly enables completed morphogenesis. This is especially the situation with ascorbate [3,4]. As past research has shown, MG must be used in very low concentrations for it to be effective, and thus beneficial. Otherwise, it would inhibit morphogenesis and be cytotoxic [3]. It was suggested that a high degree of adhesion was inhibitory to developing plant tissue due to an increased concentration of MG in the tissue. In this context, without specifying the concentrations and conditions of its use, it is incorrect to state that MG is generally or categorically toxic for biological processes and for medical treatment. As one important experimental condition, an investigator should also consider whether or not ascorbate is present. It is also important to ask the question: If MG is generally so toxic, why has it been shown to be beneficial over many years and regions for plant development? On a very basic level, MG is shown to be a promoter of chlorophyll synthesis in plants [6], and thereby, again demonstrating its importance in plant physiology and development. Based on earlier observations on *in vitro* morphogenesis, this author had predicted such a role [7].

In general, it would appear that MG must be present in very low concentration *in vivo* with ascorbate for the occurrence of coherent, non-diseased biological processes, involving necessarily, adhesive and cohesive forces of specific, low degrees. This is very relevant to cancer research and treatment. It is predicted that future investigations will further demonstrate the physiologically, beneficial effects of MG in very low concentrations. This would especially be the situation in connection with the presence of ascorbic acid or ascorbate. These investigations may provide further insight into ways to reverse carcinogenic processes.

Regarding the consequences of MG's non-presence, as noted earlier through the research of Szent-Gyorgyi, the removal of methylglyoxal from living cells, due to its conversion by the enzyme glyoxalase to D-lactic acid in the cells, results in the carcinogenic state or situation. In this regard, methylglyoxal exists in the cells of healthy Douglas fir needles, which are developed tissues. Active glyoxalase was not present in the needle cells. However, in non-differentiated callus, obtained via fir needles present on the culture medium containing auxin, it was found that active glyoxalase was present in significant concentration in callus cells. MG was not present in the callus [8].

One can conclude from this that there is a non-toxic, beneficial involvement of MG in plant development. Its lack in callus is very likely associated with the inability of morphogenesis to occur from such callus. It is also suggested that the lack of MG in plant tissue ensues in uncontrolled mitosis. And this gives further credibility to the view that critical degrees of cohesion and adhesion, arising through MG-ascorbic acid-mediated electronic desaturation of proteins, could be necessary for such development, and the negation of the cancerous state in plants and animals. Biological development is conjectured as being the ongoing accommodation to cohesive and adhesive stress generated within organisms. It is through accommodating to such stress that carcinogenic processes can be prevented or reversed.

Forces, Heterochromatin, and Chromosomal Re-configurations: A Broader View of Development and Carcinogenesis

Various proteins in the cell, such as the histone proteins of the chromosomes of higher vertebrates, could undergo electronic desaturation via MG and ascorbic acid or ascorbate, with critical degrees of adhesive and cohesive forces being generated as a consequence. Within the proteins of mammalian chromosomes, a differential adhesion via MG and ascorbate might occur in different regions of the chromosomes where the proteins are present. This adhesion could mediate in an intense

chromosome coiling within those regions, stabilizing the chromosomes for a stable end to development. This would be represented on the cytogenetic level as heterochromatic regions occurring in the genome, and thereby, differential, normal gene inactivation within heterochromatic regions at the closing or final stages of development. It is generally well known, through classical genetic studies over many years, that genes in plants and animals are inactive within heterochromatin. Such heterochromatin would stabilize the genome against uncontrolled gene activity at the closing stages or at the end of biological development, in which such uncontrolled gene activity could otherwise lead to carcinogenesis.

Most relevantly, leukemic lymphocytes in humans do not have heterochromatin in their nuclei when examined under an electron microscope. Mature, non-leukemic, normal lymphocytes do, in contrast, exhibit profusely such heterochromatic regions within their nuclei when also examined under an electron microscope. (See [9], especially the electron micrographs of the two types of cells on pages 714 and 715.) This might suggest that a differential adhesion, inducing a differential chromosome coiling could be an underlying process in controlling and stabilizing differentiation and development at its closing, final stages, and thereby prevent carcinogenesis. "The studies with MG and ascorbic acid as applied to plant callus or plant neoplasm has enabled, through the revealing of an implicit theory, this type of constructive and testable conjecture" [4].

Within vertebrate chromosomes, the chromatin is composed of nucleosomes. Each nucleosome is composed of histones and DNA wrapped around the histones. Each nucleosome is organized at a higher level as a condensed solenoid or a highly ordered coil in which DNA is highly coiled around the histone core. Such chromatin is attached to a central, non-histone protein scaffold. Genes within such coiled regions of the solenoid-shaped nucleosomes are inactive [10]. Methylation of the histone proteins, via enzymes, in the nucleosomes ensure the permanent coiled state of the nucleosomes and thereby permanent gene inactivation or silencing. Hence, the stabilization of gene inactivation during development, especially at its close, is associated with chromatin condensation or coiling. This would also occur in the production of heterochromatin, where histones are involved. However, this does not rule out the necessary involvement of cohesive and adhesive forces in these condensation or coiling processes and the permanent existence of the solenoid state. In fact, the formation of each nucleosome involves the strong attraction of the histone cores (due to electric forces) to the DNA, whereby the "histone cores act as 'magnetic forms' that promote and guide the DNA" around histone cores in the formation of the structure of the nucleosome [10].

And any enzymes involved could be the specific guides of such forces. Coiling of the nucleosomes themselves produces the higher-ordered solenoid morphology within the chromatin of the chromosome [10]. Such higher-ordered coiling might very well involve directed adhesive forces and be a projected feature from a trans-scalar, encompassing process.

What is important is not the particular chemical mediator of adhesion, but the necessary generation and presence of adhesive forces for the coherent function of an organism, and thereby the maintainer of its adaptive integrity, its constancy, especially at the close of development. However, controlled acetylation of the histones within the nucleosomes, via enzymes that bind to histones, ensues in its uncoiling. This enables the controlled transcription of the DNA, and thereby gene activation [10]. This suggests, nevertheless, the controlled generation of repulsive forces enabling uncoiling through enzyme activity, involving transient adhesion of enzymes to histones. This would be within the context of global stabilization. Though important for biological function, and as pointed out earlier [3,4], MG with ascorbic acid would be one of many mediators of cohesive or adhesive forces necessary for biological development and its stabilization. This would be a stabilization through higher-ordered coiling and the production of a higher-ordered helix.

As to the specifics of this conjecture or hypothesis with regard to the importance of MG and ascorbate in development, does MG-ascorbate induced, fine-tuned adhesion within regions of chromosomes of cancerous cells make the chromosomes and genome stable and interconnected, by changing chromosomal architecture, after the application of MG and ascorbate? Does such a change in chromosomal architecture ensue in the cessation of carcinogenesis? If this hypothesis or view pertaining to MG-ascorbate-induced, fine-tuned adhesion within chromosomal regions is supported by experiment, this may open up a fine-tuned cancer therapy, whereby specific application of adhesive force on the chromosomal level ensues in the negation of carcinogenesis.

Towards such negation of carcinogenesis, the effective degree of such applied force would be based on the critical concentrations of MG and ascorbate within the cells. It would be through such critical, low concentrations, experimentally determined, that would enable MG with ascorbate to become very beneficial agents in cancer therapy. Further parallel studies with plant tissue culture systems, involving effective concentrations of MG and ascorbate, might also provide further, complementary insights with regard to effective cancer treatments. These investigations may reveal in what manner plant chromosomes in callus interact with MG and ascorbate,

so as to enable organogenesis within and from callus. Those investigations could also elucidate the cohesive and adhesive forces involved. Such could point to new insights, and thus, treatments.

Methylglyoxal, Its Beneficial Concentrations, and Chromosomal Configurations

MG does in fact interact with mammalian chromosomes. MG interacts with certain histone proteins of chromosomes in human cell lines in culture causing changes in chromosomal configuration affecting gene expression. "Indeed, MG was found to significantly alter the gene expression in numerous embryonic kidney cells *in vitro*" [11]. In other *in vitro* studies, treatment of nucleosomes with MG ensued in the increased stability of the nucleosomes due to additional intra-nucleosome bonding involving the generation of histone-DNA links through MG mediated glycation [12]. In those studies, MG in low concentration was further associated with a low degree of higher-ordered coiling or compaction of the arrays of solenoid-shaped nucleosomes making up the chromatin, possibly, it could be conjectured, due to a lower degree of adhesive force within the array level of the nucleosomes, whereas a very high concentration of MG ensued in a hyper-compaction or intense coiling of the nucleosome array, possibly, it can also be conjectured, due to too much adhesive force [12]. The overall effects of such hyper-coiling were changes in chromatin architecture [12]. And such changes in chromatin architecture, indirectly due to accumulated MG, were found in breast tumor cells [12]. This would appear not to support the hypothesis.

However, MG, also mediating increased adhesion through more and more adhesive bonds or cross-links in specific chromosomal regions might, in too high a concentration, globally bring about chromosomal distortions in other chromosomal regions, leading to uncoiling in those regions, whereby uncontrolled gene activity would occur, resulting in carcinogenesis. The investigations by Zhang and his associates [12] would seem to suggest this possibility. Their investigations also suggest that too much cohesion or adhesion in particular or certain chromosomal regions can bring about chromosomal instability, and thereby, cause carcinogenesis or aberrant development. With regard to development, they point out that DNA transcription, involved in normal gene activation, could be prevented due to changes in chromosomal architecture following aberrant coiling. In this context, the hypothesis is still feasible, and not contradicted, when one takes into account the different effects of different concentrations of MG application in developmental situations. It is the particular concentration of MG applied to or involved in a developmental situation that determines whether MG is deleterious to that situation. This would be either

in regard to causing chromosomal aberrations through aberrant coiling, or, with regard to being efficacious for promoting complete development. This issue could be further investigated.

Using MG in Beneficial Concentrations with Ascorbate: Therapeutic Investigations

In that regard, what is very important and interesting here is that MG is shown to affect or modify directly genome or chromosomal behavior, with developmental consequences, which does give global support to the hypothesis. The real test would be the effect MG has, in very low concentration with ascorbate, on chromosomal configurations, the forces involved, and whether carcinogenesis can cease as a consequence. *In vivo* and *in vitro*, does MG in low concentrations with ascorbate, as opposed to high concentrations, modify the histone proteins of the chromosome by enabling adhesion in critical degrees and patterns within particular regions of such proteins? Does such a pattern of adhesion ensue in a chromosomal architecture that would prevent uncontrolled gene activity? This would be in place of a chromosomal architecture that would promote such gene activity, and thereby carcinogenesis. Through experiments *in vitro* and through clinical investigations, the exact degree of low MG concentration, which would be medically effective, would have to be determined. As noted, further parallel studies of plant tissue culture systems, interacting with critical concentrations of MG and ascorbate, may also provide insights, especially with regard to the control of chromosome configurations and mitosis in developing tissue.

It would be the particular chromosome configuration, stabilized by cohesive or adhesive forces in a particular pattern and degree, that would be critical in preventing or reversing carcinogenesis. Does this particular pattern and degree of adhesion, occurring through electron mobility and MG-mediated cross-linkages, which would also enable such mobility, induce a particular chromosomal architecture? Is this an architecture that enables the formation of specifically patterned regions of heterochromatin that, at the close of development, would stabilize such development?

If so, this may suggest, nevertheless, an effective cancer treatment, through which, MG with ascorbate could be directed to induce that architecture. This would be by chemically engaging particular regions of the chromosomal proteins of carcinogenic cells. Yet, due to various factors, such as accumulating in high concentrations, MG without ascorbate may enable, through creating force-induced distortions, the generation of chromosomal configurations that promotes carcinogenesis. Depending on conditions,

such as MG concentrations and the presence of ascorbate, MG can either be an inhibitor of carcinogenesis or its source. Further experimentation should better define those non-deleterious, beneficial conditions.

With respect to the generation of functional and dysfunctional chromosomal configurations, and their respective force arrangements, the concentration of MG with and without ascorbate in cells may thus also have a bearing on which chromosomal configuration arises. If ascorbate were added to the breast tumor cells in culture, would this result in further chromosomal configurational changes in those cells, leading to such cells becoming non-carcinogenic? This would be worth investigating. More inclusively, the question is what can repeatedly occur in an *in vivo* context as opposed to an *in vitro* situation regarding the effects of MG in certain non-toxic concentrations with and without ascorbate. Relevantly, genotype does play a role in MG effectiveness [3,4]. This issue of genotype should also be considered in evaluating MG's usefulness, especially in determining which concentrations of MG are not toxic. Nevertheless, the adhesive and cohesive forces, arising through MG-ascorbate mediated electron movements in proteins, and between proteins, and the related involvement of MG in establishing adhesive cross-linkages or bonds, would appear to be, in critical degrees, a significant dynamic in stabilizing and completing an organism in a non-distorting manner, with relevance to preventing carcinogenesis. As illustrated through the investigations in plant tissue culture, specific, low concentrations of MG with ascorbate would appear to be an important avenue towards the reversal of various types of carcinogenic processes. In various organisms, the range of those specific, beneficial concentrations, including that of ascorbate, could be determined exactly through *in vitro* experiments and *in vivo* trials.

Conclusion: Cancer Treatment is Viewed from a Higher, Heuristic Perspective

For many years, MG was considered to be too toxic to use in cancer therapy. However, as we have seen, MG, when used in very low concentrations with ascorbate, promotes morphogenesis from plant neoplasms or callus. It does so by reversing the carcinogenic state within such neoplasms. As described, MG has an effect or influence on mammalian chromosomal configurations. Specific configurations of which, probably involving heterochromatin, are likely related to the prevention of carcinogenesis or its cessation. Very low concentrations of MG with ascorbate could be very beneficial in promoting such specific configurations.

Through further experimentation and clinical trials, those exact, beneficial concentrations, and the best manner of

their application, will most likely be further elucidated. In view of the studies with plant tissue culture, MG in a low, critical concentration with ascorbate may reverse the emergence of carcinogenic processes in mammalian tissue through stabilizing a developmental state or promoting a new one. Thereby, it is important to determine the conditions of its use during further *in vitro* experiments and in future clinical trials. In so doing, MG, it is predicted, will be shown in general to be beneficial and medically effective.

The use of MG appears to reflect underlying, universal dynamical processes. In this context, our understanding of biological processes could be improved, and thereby, point us to more effective cancer treatments. In this regard, effective cancer treatment, with general relevance to natural phenomena, would be a derivative of the application of a proposed universal and unifying principle involving a generative drive via forces. Though imperfect, such a drive would be towards constancy and stability in nature via dynamic completion. Conjectured as being universal in nature, this drive, involving forces of low stress, would nevertheless appear to be most manifest in biological processes. Even though biological, these processes, encompassing various physical forces, such as adhesive and cohesive forces, might very well involve the operation of the universal dimensional physical constants of physics.

These constants, especially their dimensionless components, might very well reflect a unifying principle operating in the universe, which enables increasing stability and completion within the universe. The non-aberrant, chromosome coiling of heterochromatization, and of the nucleosome solenoid, in the stabilization of a completed development, might very well be a reflection of a universal, generative, dynamical pattern and principle involving vortical processes in nature.

Adhesive and cohesive forces, operating in plant and mammalian development and beneficially generated through critical, cellular concentrations of methylglyoxal and ascorbate, would beneficially affect chromosomal configuration and organismic integrity. Thereby, carcinogenic processes or states, if they arise, could be negated or reversed. In this situation, the process of negation could be investigated, as well as the forces involved. Such a beneficial generation of forces in development would also reflect, it is conjectured, a general process of forces operating through all phenomena.

This would be an accommodating process via forces, in critical degrees, enabling the generation of stability and coherency in nature at various scales, including the chromosomal. The dimensional universal constants of

physics are seen as reflecting and representing such a universal drive towards increasing stabilization through increasing dynamical completion. These constants not only represent the sustenance of constancy in nature through forces, these constants represent the guidance of the forces towards the state of increasing stability and completion in nature in accommodation to stress. In so doing, this would give natural processes features of morphogenesis and evolution. An important geometrically defining component of and uniting many if not all the universal, dimensional constants is a dimensionless biological constant, which is equal to 1.618 or to its reciprocal [See 13]. This constant becomes evident in many biological phenomena. Such a constant represents or geometrically reflects a rate of vortical generation or regeneration. This vortical or spiral regeneration could occur through all levels of an accommodating, evolving organization in nature. This becomes evident at one level through chromosomal coiling, which gives such regeneration coherence. And such vortical regeneration would enable various features or phenomena of nature, biological and physical, to have universal correspondence with one another in terms of dynamic morphology [See 13]. This might suggest a type of universal entanglement, which is known to occur at the sub-atomic level [14,15].

The author appreciates that the view presented here is very theoretical, if not almost philosophical. Why should it even be included in an article about cancer treatment, one might ask? As an answer, medicine could effectively be approached from such a perspective. Earlier research suggests the feasibility of this type of approach. This perspective, which integrates paradigms, could be constructive and heuristic in the long term. Such flexibility is needed in our age. Continued investigation and elaboration of such a proposed trans-scalar, dynamic pattern in accommodation to stress, at various levels of an organization, physical and biological, may open up new therapeutic vistas in medicine.

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