The Many Models of Carcinogenesis: En Route to a Unified Theory

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ABSTRACT

There are currently at least ten 'theories' of carcinogenesis, with levels of explanatory power ranging from almost none to moderate. More appropriately referred to as models or hypotheses, these ten theories are: the Egg Cell Genetic Program Hypothesis, the Atavistic Hypothesis, the Quantum Field Stem Cell Differentiation Hypothesis, the Tissue Organization Field Hypothesis, the Cancer Stem Cell Hypothesis, the Bad Luck Hypothesis, the Ground State Hypothesis, the Epigenetic Hypothesis, the Clonal Expansion Hypothesis, and the Somatic Mutation Hypothesis. Experimental support for these models varies from very few to thousands of published studies. Central to all of the models, including those that invoke resurrection of ancestral cell division phenotypes, is alteration of normal genetic programing (gene expression profiles). A large body of experimental work has shown that this altered gene expression during carcinogenesis happens in three primary ways: mutation, epigenetic modification, and metabolic disruption. Collectively, various combinations of these transformation drivers lead to disruption of cell cycle control, DNA damage/apoptosis, electrochemical and water balance, body location constraints, and elimination of anti-tumor immune responses. If one views mutation, gene expression, and epigenetics as aspects of cancer genetics, the existing models can by in large be viewed as mutualistic rather than as adversarial, each contributing to a framework that supports an authentic, though still inchoate, unified theory of carcinogenesis.

1.1 The 'Theories' of Carcinogenesis

With global life time cancer rates of up to 38% in countries with very high human development levels, at least a third of us in the so-called developed world will develop a cancer at some point in our lives (Zheng et al 2023). The investment of time and money by the Chinese, American, and European scientific establishments has been extraordinary, leading to a number of promising treatments, some of which (for example imatinib mesylate and monoclonal antibodies like ipilimumab) have significantly extended long-term survival rates and appear to elicit complete cures of some cancers in at least some individuals. But despite the impressive advances, we still have no comprehensive clinical approaches, chemotherapeutic or otherwise, that broadly treat and cure cancer. The recent discovery that dormant cancer cells can be reactivated by certain chemotherapeutic agents (He et al 2025) reveals just how little we understand about tumors, circulating tumor cells, metastasis, and the drug paradigms that are in common use. The reasons for this are many, but in the final reckoning, all relate to our incomplete understanding of the transformation processes. The intensive effort to understand the many types of cancer has generated mountains of data that has poured into thousands of scientific reports describing the subtleties of hundreds of different types of cancer, and still we seem to have only scratched the surface. Varied experimental and sometimes philosophical approaches have led to a large number of competing 'theories' such that at the present there are at least ten competing models that are presented as self-proclaimed scientific theories (note that these 'theories' were identified in the technical literature through prior knowledge, combined with Google Scholar, Google AI, and PubMed searches). As scientific theories, these models would be expected to provide extensive explanatory power in accounting for the origins of cancer in the human body as well as to provide a theoretical

framework that offers rational design of effective cures. None of these theories do this to any appreciable extent. We all know that this level of understanding has been elusive - most of our chemotherapeutic agents are still aimed at controlling cell division or poorly understood aspects of the anti-cancer immune response. Because all of the published cancer 'theories' lack robust explanatory power that has led to rational cures, I refer to them herein as models or hypotheses. As shown in Figure 1, there are currently at least ten such models: the Egg Cell Genetic Program Hypothesis, the Atavistic Hypothesis, the Quantum Field Stem Cell Differentiation Hypothesis, the Tissue Organization Field Hypothesis, the Cancer Stem Cell Hypothesis, the Bad Luck Hypothesis, the Ground State Hypothesis, the Epigenetic Hypothesis, the Clonal Expansion Hypothesis, and the Somatic Mutation Hypothesis. Each puts forth intriguing speculations and contains at least some tenets that are supported by experimental evidence. All of them invoke changes in cellular metabolism that can be traced back to malfunctioning proteins or gene expression profiles, hence back to altered genes and/or genetic programs. These existing hypotheses, which should be viewed as working models, have varying degrees of explanatory power. Below, I provide brief explanations of each, outlining the empirical basis, some shortcomings, their relationships with each other, and the prospects for a true unified theory of carcinogenesis.

Quantum Field Stem Cell Differentiation Hypothesis and Egg Cell Genetic Program Hypothesis: These two models have very little empirical evidence but are conceptually interesting. The Quantum Field Stem Cell Hypothesis has been tested by modeling stem cell differentiation processes in tumors with quantum field theory applied to cellular systems (Biava et al 2019). The authors model biointerfacial water and extrapolate the behavior of water to that of cellular systems. While intriguing in its way, it is not clear how quantum field theory and symmetry-breaking transformation approaches used in condensed matter physics (at the level of atomic and sub-atomic interactions) can reasonably be applied to the atomic complexities of even a single pathway in a cell let alone to an entire cell. The Egg Cell Genetic Program Hypothesis as put forth by Majerus (2022) discusses several of the 'theories' of cancer listed above, which he rightly terms models, and attempts to unify them under his Egg Cell Genetic Program model by speculating that during transformation the genetic program of the egg cell is reinitiated. As a corollary, he proposes the possibility that cancer cells have reverted to embryonic forms of energy metabolism, basing his notions largely on results from studies by Leese and others (Leese 1991; Leese 2003; Leese et al 2007; Bradley and Swann 2019) which suggested that the mitochondrion is less active in the early embryo (discussed in Dumollard et al 2009; Bradley and Swan 2019; Majerus 2022). While appealing in its simplicity, this hypothesis suffers from the fact that cancer cells vary greatly in their energy metabolism and mitochondrial function (for examples see Martinez-Outshoom et al 2011; Wallace 2012; Lin et al 2018), and are known to switch between glycolytic and oxidative modes (Yu et al 2017; Panieri et al 2022; Milella et al 2025). In addition, to my knowledge, direct experimental evidence showing reactivation of egg-specific gene expression paradigms does not exist.

The Atavistic Hypothesis: The Egg Cell Genetic Program Hypothesis briefly described above is reminiscent of an older idea that is embodied in the Atavistic Hypothesis of carcinogenesis. Originally proposed by Snow in the late 1800's (Snow 1893) and more recently resurrected by Israel in 1996, the Atavistic Hypothesis suggests that cancer may be occur through reactivation of genetic programs that encode traits of ancestral single-celled eukaryotes (hence an atavistic origin of cancer). This idea has been formulated into the 'Atavistic Theory of Carcinogenesis' (again, more aptly referred to as a hypothesis) by Davies and Lineweaver (2011) and Vincent (2016). These initial publications were

speculative in nature, relying heavily on an analogy with computers and a dismissal of classical 'Darwinian' genetics, but recent development of sophisticated multiple-alignment techniques and phylostratigraphy has made it possible to trace genes and promoters through evolutionary time and make reasonable inferences about ancestral gene expression profiles in extant multi-cellular and single-celled organisms. Trigos and colleagues (Trigos et al 2017; Trigos et al 2018) have used this approach to test the Atavistic Hypothesis by comparing gene expression profiles of cancer cells and normal cells with predicted gene expression in unicellular organisms, finding that cancer cells express a high number of more primitive, unicellular genes. Work by Zhou et al (2018) has also provided evidence suggesting that cancer cells suppress post-metazoan genes and inappropriately express pre-metazoan genes. These authors frame their interpretations in the historically popular 19th century idea that ontogeny recapitulates phylogeny, concluding that cancer cells reverse recapitulate phylogeny. It is important to note that Zhou et al (2018) repeatedly dismiss the 'gene-centric' models of carcinogenesis and actively downplay the importance of somatic mutations paradigm while at the same time invoking altered gene expression profiles as explanations, making it clear that they do not they do not appear to consider gene expression to be part of 'the gene-centric' mainstream understanding of cancer. This raises and important question, how can one invoke genetic processes as an explanation while at the same time rejecting a genetic paradigm? This question will be discussed at length in sections 1.4 and 1.5. Vinogradov and Anatskaya (2025) have devised an experimental system that appears to discriminate between ontogenic dedifferentiation to a state of stemness and evolutionary reversal to unicellular state, concluding that with a number of different tumor types (but not all) the unicellularity signature is higher than the ontogenic signature. This suggests that in many cancers an evolutionary reversal to single celled genetic programs occurs. These results also suggest that dedifferentiation into a state of 'stemness' may in some cases be a reversion to unicellularity. Lineweaver et al (2021) extend this idea and argue, from a theoretical standpoint, for a serial atavistic model based upon the recent phylostratigraphic data sets. Nicolescu (2025) discusses at length the question of stemness vs unicellularity, and importantly points out that tumor cells, whether or not they have a high degree of unicellularity, must retain what he terms 'stemgermline' properties that allow continual regeneration of a high potency stem cell while also continuously producing committed tumor cells. Finally, Carvalho (2025) also briefly discusses the implications of this work for therapeutic approaches.

Tissue Organization Field Hypothesis: This model has been presented as a revolutionary alternative to the Somatic Mutation/Clonal Expansion hypotheses (Soto and Sonnenschein 2011; Baker 2015; Huang et al 2025). This hypothesis posits that it is the cellular environment rather than the mutation profile of the cell that dictates the transformation process, and that cancer reflects a reversion to an ancestral state of proliferation and migration (note that this model incorporates elements of the Atavistic Hypothesis). Experimental work aimed at addressing the roles of tumor microenvironment in carcinogenesis has progressed, and we now know that in at least some cases altered tissue environments can be the driving force behind transformation (reviewed in Yuan et al 2024). Since it is also well-established that the tumors regularly modify their own microenvironment (Hinshaw and Shevde 2019; Arneth 2019; Desai et al 2025), we can only conclude that transformation can happen both ways. Because this hypothesis has been controversial for its outright rejection of the genetic basis of cancer, it is worth examining the core arguments of the most recent formulation by Haung, Soto, and Sonnenschein (2025). With the title "The End of the Genetic Paradigm of Cancer", the authors argue that the mutations are not the cause of cancer and that a pluralistic view involving tissue environment and genetic alteration is necessary. They also invoke epigenetics and altered gene expression profiles as a universal driving force in

carcinogenesis. They for some reason do not discuss the fact that epigenetics is a sub-field of genetics, and that genes are required for gene expression. In their work they present a speculative hypothesis to describe carcinogenesis based upon mathematical models presented by Huang in 2012 and Saez et al. in 2022. Those models themselves are based upon a landscape analogy proposed by Conrad Waddington in 1957 (newest edition Waddington 2014) to explain cell fate pathways during animal development. Specifically, in their work they offer as an alternative to the 'genetic paradigm' a 'gene expression paradigm' that they attempt to describe with an abstract mathematical model in which the epigenetic and gene expression profile is likened to a physical landscape whose branching valleys represent cell fate decisions. Low probability branch points are considered to be 'cancer attractors' which they speculate are latent metazoan programs whose atavistic reactivation leads to transformation into cancer cells (note that this part of their model is a variation of the Atavistic hypothesis described above in this section). In their framework, the unicellularity programs are being reactivated through disruption of gene regulation programs; thus, genes and gene expression, but not mutations, are central to their arguments. They also argue at length that evolutionary processes (such as basic inheritance of genes) do not operate in cancer cells, citing as evidence the fact that mutations seem to be randomly distributed in at least some tumors, but leaving out description of the clear evidence (discussed below in this section) showing clonal selection by chemotherapeutic agents and the immune system.

Their notion of a cancer attractor is interesting and worth discussing. Attractors are mathematical models that have been borrowed from chaos theory, where normal (linear) and strange (non-linear) attractors describe the occurrence of predictable events in chaotic systems that in turn lead to emergent patterns that can sometimes be depicted as fractals. In their discussions, the authors liken carcinogenic events (specifically, disruption of gene expression programs) to simple point attractors, the simplest of the attractors. While intriguing, the reasons for choosing simple point attractors rather than the complex strange attractors more appropriate to complex systems are not made clear by the authors, and there are a number of conceptual problems associated with applying attractor math to cellular systems which are not discussed. Pogun (2001) discusses the issues at length, and aptly ends his critical analysis of attractors in biological systems with a quote from physicist turned biologist, Francis Crick: 'Biology is thus (because evolution results in a complexity that is hard to unscramble) very different from physics…. The basic laws of physics can usually be expressed in exact mathematical form, and they are probably the same throughout the universe. The 'laws' of biology, by contrast, are often only broad generalizations, since they describe rather elaborate chemical mechanisms that natural selection has evolved over billions of years…. Elegance and a deep simplicity often expressed in a very abstract mathematical form, are useful guides in physics, but in biology such intellectual tools can be misleading….'. While Pogun is clearly making an appeal to authority by quoting Crick, a variety of practical considerations leads me to concur. Foremost among these is the fact that it is impossible to apply the deterministic differential equations of Lorenz and others to cellular systems because of sweeping assumptions (including reduction in complexity) that must be made about the thousands of interacting gene expression programs in order to assign values to Lorenz's σ, ρ, and β coefficients (Lorenz 1963). There are similar problems with assigning analogous variables in other strange attractor equations/systems. Finally, to date there is no experimental evidence for their attractor hypothesis because there is no way to actually experimentally induce, control, or measure these 'cancer attractor' states in a cell, hence no way to test this interesting hypothetical model. Because it awaits experimental validation, it should not be viewed currently as an alternative theory of carcinogenesis with attendant explanatory power.

Cancer Stem Cell Hypothesis: The Cancer Stem Cell Hypothesis is also a modern formulation of an old idea (Durante 1874; Cohnheim 1867; Lapidot et al 1994; Wicha et al 2006; Zhu and Fan 2018; Batlle and Clevers 2017; Gupta et al 2019). It is widely accepted now that at least some (and perhaps most) tumors have populations of transformed cells that exhibit a high degree of stemness, that is, they have the ability to regenerate themselves and to give rise to determined offspring. These cancer stem cells are relatively resistant to many of the chemotherapeutic agents, and can give rise to drug resistance mutants that lead to recurrence and metastasis. Because of this, therapeutic approaches targeting cancer stem cells are under investigation (for examples see Yang et al 2020; Shibata and Hoque 2019). There is compelling evidence for the existence of cancer stem cells, although the roles of these cells in the transformation process are still incompletely understood and vigorously debated (Rahman et al 2011; Hernández-Camarero et al 2018; Osman et al 2020). The stem cell model has been somewhat controversial because it only incompletely explains the breadth of experimental evidence (see Rahman et al 2011). One of the central questions is whether observed stemness arises from the original condition of the cell in the body or a reversal from a more differentiated state. On this front, Hernandez-Camarero (2022) point out that it has been shown that stemness can be a relatively late development in the life of a tumor, which muddies the waters of the original formulations of the Cancer Stem Cell hypothesis that initially suggested that all of the cells in a tumor arise from a single transformed stem cell. There are a number of variations of the Sem Cell Hypothesis (not discussed herein) that all derive from the observation that stemness of the original or later cells is an important condition in the formation of a tumor. In sum, the Cancer Stem Cell models are in general well-supported experimentally, and have led to efforts to target stem cells in treatment regimens (Yang et al 2020) but still lack comprehensive explanatory power.

The Epigenetics Hypothesis: Epigenetics has historically been a subfield of genetics. Epigenetic alterations in DNA methylation, histone modification, and chromatin remodeling can lead to altered gene expression patterns, and, not unexpectedly, cancer (Shen and Laird 2013). This was first reported by Versteege et al in 1998, who observed mutations in the hSNF5/INI1 gene from malignant rhabdoid tumors of children (this gene product is an important member of the SWI/SNF chromatin remodeling complex). Recillas-Targa (2022) and Huo et al 2021 review the literature on the epigenetic influences in cancer, and Wu et al (2023) relate epigenetic modifications to metabolic outcomes for a number of different diseases, outlining potential therapeutic targets. The connection between epigenetic gene silencing and disrupted DNA repair in cancer cells has been empirically established in many systems (reviewed in Rembialkowska 2025), and in general the link between disruption of other gene expression pathways associated with cancer is also clearly established for many cancers. Epigenetic changes are thought to occur in all human cancers (Baylin and Jones 2016), and many authors publishing in this field point out that gene mutation and epigenetic modification can not be disentangled from each other when attempting to understand carcinogenesis. As with the other models of carcinogenesis, this model does not explain everything about transformation.

Somatic Mutation Hypothesis and Clonal Expansion Hypothesis: Perhaps the best-supported models are the Somatic Mutation Hypothesis and the closely related Clonal Expansion Hypotheses, both of which place DNA mutation in a rogue cell followed by continuous uncontrolled cell division at the heart of carcinogenesis (for recent examples see Zhu et al 2019; Zhu et al 2022; Bunz 2022; Laplane and Maley 2024; Tiwari and Kujan 2025). Both models are supported by extensive experimental evidence showing

that tumors can arise from a single mutated cell that, due to loss of DNA damage control and repair pathways, accumulates mutations during repeated mitotic divisions (clonal expansion) that give rise to the cells which populate the growing tumor mass. Hand in hand, these models provide a framework for understanding the varied mutational profiles that are observed in cells within a tumor, the development of large tumors in our animal models from a single cell, and the inevitable resistance to chemotherapy that develops. In its simplest formulation, mutations occur first, and metabolic perturbations of the cancer cell and its environment occur second. This hypothesis is unequivocally supported by thousands of studies demonstrating that mutagenic chemicals and radiation transform cells and cause cancers in animal models. It has existed in its modern guise for over a hundred years and is well-supported by many whole genome studies including a recent analysis of over 2000 human cancers genomes (Pan Cancer whole Genomes Consortium 2020 with over one hundred contributing authors). Other work with cancer tissue fields and DNA adducts has also provided a large body of evidence supporting a causative role for genetic disruption, clonal expansion, and evolution of cell populations during carcinogenesis (Iwashita et al 2021). Related work has developed the concept of driver genes, and to date disruptions in at least 568 cancer-associated genes have been identified (Martinez-Jiminez et al 2020; Dietlein et al 2020). While the combined tenets of these two models have significant explanatory power, they do not explain all observations, and a number of authors in the past and recently have pointed out these short-comings (for examples see Soto and Sonnenschein 2011; Brucher and Jamall 2016; Majerus 2022; Monti et al 2022; Jassim et al 2023). In a measured analysis, Jassim and colleagues (2023) call into question the generally held view that cancer is strictly a 'disease of the genome'. They cite studies showing high levels of mutation, including numerous cancer driver genes, in non-cancerous tissues (among others, Yizhak 2019, Martincorena et al 2015, and Martincorena et al 2018). This is an important observation which seems to suggest that there are normal metabolic programs that can override at least some pathways of carcinogenesis, and that it is disruption of those blockade pathways, through epigenetic and/or mutagenic processes, that finally activate the already existing mutated cancer pathways. Another example illustrating the limitations of the Somatic Mutation/Clonal Expansion models comes from studies showing that in some cases certain types of cancer cells can be 're-normalized' by transferring them into different environments (Illmensee and Mintz 1976; Maffini et al 2005), including, surprisingly, exposure to axolotl oocyte extracts (Saad et al 2018). This in turn suggests that despite the mutational load at least some cancer phenotypes can be reversed. In cases of naturally developing human cancer *in vivo*, however, the question still remains, what is it that releases the cancer blockade, is it mutations in genes that control those blockade pathways, or is it a release mediated by environmental conditions (perhaps inflammation or non-mutagenic carcinogens) that either free up gene expression programs or allow mutations to occur? Or some combination of the two? These questions will be discussed at length in the upcoming sections.

Bad Luck Hypothesis and Ground State Hypothesis: The Bad Luck Hypothesis (Tomasetti and Vogelstein 2015; Albini et al 2015; Tomasetti et al 2017) and the complementary Ground State Hypothesis (Jassim et al 2023) present comprehensive interpretations of recent data gathered using powerful, modern big data approaches. The Bad Luck Hypothesis suggests that tissues with high cellular turn over (hence high rates of stem cell division) accumulate mutations because of the background mutation rate inherent in DNA replication, with the random mis-incorporations leading to transformation of a low but constant percentage of those cells into cancer cells. This hypothesis is supported by the observation that highly replicating tissues generate tumors at much higher rates than slowly replicating tissues. Despite having intuitive appeal, the original model received critical commentary aimed at the assumptions about stem

cell replication rates (Rozhok et al 2015) and the fact that it ignored a large body of work providing evidence for the role extrinsic factors, not just bad luck due to intrinsic mutations (Goldstein and Patel 2019). Minteer et al (2023) also point out that age-related modifications in the epigenome also contribute to cancer development, suggesting that it is not just bad luck mutations but also bad luck epigenetic changes that lead to cancer. The related Ground State Hypothesis (Jassim et al 2023) uses lineage tracing of genetically modified stem cells in mouse models along with elements of the Bad Luck and the Tissue Field Organization hypotheses to explain the behavior of cancer cells in their experiments, emphasizing the complex interactions between mutation profiles and the tumor microenvironment. This hypothesis describes the convergence of intrinsic and extrinsic factors to account for many empirical observations, including the fact that stem cells from juveniles are much less likely to transform than their aged counterparts and that tumor cells are known to corrupt their microenvironments. Both of these models extend the experimental underpinnings of the Somatic Mutation model to include experimentally supported elements of the Tissue Organization Field model (discussed above in this section and in section 1.3), and are important contributions to a unified theory of carcinogenesis.

1.2 Where Fact Meets Fiction: the Warburg Effect

In considering use of the phrase 'disease of the genome' used by Jassim et al in their critique of the Somatic Mutation model, the question arises: what is a disease of the genome? The genome is not the metabolic driver in a cell, it is only the repository of the genes, which themselves are instructions for protein synthesis. It is the mutated proteins or their dysregulated expression (epigenetic or otherwise) which are the actual players in the metabolic dysfunctions seen not only in cancer but every other metabolic disease or condition. One wonders why it is common to refer to cancer as a disease the genome instead of a metabolic disorder? For example, no one would refer to X-linked severe combined immunodeficiency or hemophilia as diseases of the genome, despite the fact that they are clearly caused by genetic lesions in crucial genes. Even conditions such as Type I Diabetes cannot be disentangled from genes and altered gene expression – the deleted β-islet cells are the sole purveyors of insulin because the two insulin subunit genes despite being present in all cells in the body are inexpressible in any other cell type. Since continuous gene expression is responsible for the continual modulation of proteins that regulate the entirety of cellular and overall organismal metabolism, altered genes, altered gene expression, or direct disruption of proteins (from toxins or other disruptors) determines the nature of a metabolic disturbance and the alterations in gene expression that occur in response. Furthermore, even if one refuses to view cancer as a 'disease of the genome', reading genome to synthesize proteins and functional RNA (gene expression), cannot be parsed out into some other category in order to downplay the importance of the genes themselves. Because mutated genes and disrupted gene expression both result in disrupted metabolism (and sometimes vice versa), it is clear that cancer is a metabolic disorder whose cellular dysfunction and deregulation is related to disrupted genes and/or gene expression. The hallmarks of transformation (unregulated cell division, loss of apoptosis/DNA damage sensors, altered ion and water balance, loss of controls over position in the

body, immune suppression) are all mediated by disruptions of cellular metabolism that can always be traced back to genetic lesions or altered gene expression paradigms. To say that cancer is NOT a disease of the genome but IS a disease of gene expression does not improve the explanatory power of the models that have set themselves to overturning the genetic paradigm

Related to the above points is the fact that the 'Warburg Effect' (Warburg 1956) is often cited as evidence that cancer is a 'metabolic' disease' and not a 'genetic disease' (among others, see Otto 2016; DeBerardinis and Chandel 2020). The Warburg effect, also termed aerobic glycolysis, is described as a situation in which high levels of glycolysis are observed despite the presence of Oxygen, and was claimed by Warburg and supporters to be not a hallmark but THE ONLY disturbance in a cancer cell. As discussed at length below in this section, we now know that this is not the case. It is a surprising revelation to learn that in his 1956 paper Warburg, by that time a Nobel laureate, appears to have rejected the notion that genes and mutation had anything to do with the function of the metabolic enzymes and respiratory transport proteins that he was studying and whose disruption he declared to be the cause of ALL cancers. In considering Warburg's views in the 1940's and 1950's and on into the late 1960's, it is worth reviewing some of the early observations and ideas about carcinogenesis. Whitman in 1919 wrote a paper titled 'Somatic Mutations as a Factor in the Production of Cancer'. As seen by the title of the paper, the term 'genetic mutations' was already in use by that time; thus, before Avery, Hershey, Chase, and others proved that DNA hosted the genes, it was known that changes could occur in the genetic material, whatever it was. During this same period, chromosomes were shown by Morgan and colleagues to house the genetic material (genes), and by the time Hershey and Chase reported their experiments with bacteriophage in 1952, the world had already known for 8 years that DNA was the principle of heredity in bacterial transformation events (Avery et al 1944). By that time, Whitman and other cell biologists had also already established a link, originally recognized by von Hansemann (1891), between chromosomal aberrations, mitotic disruption, and cancer. In 1956, when Warburg wrote his famous paper, DNA was known to be the vehicle of heredity, the double helical nature of the DNA helix had already determined by Watson and Crick, and the mystery of DNA replication and the three-letter genetic code had been deduced by Francis Crick. The involvement of an intermediary RNA molecule in the synthesis of proteins had also been predicted by Crick and colleagues by 1961 (Crick et al 1961). In addition, Beadle, Tatum, and others (Beadle and Tatum 1941; Horowitz et al 1945) had by that time gathered evidence in strong support of the one gene one protein hypothesis that had been proposed a decade earlier, and by 1962 the three-nucleotide coding scheme of the gene proposed by Crick had been confirmed by Nirenberg and Matthaei (Matthaei and Nirenberg 1961; Matthaei et al 1962). In his 1967 paper Warburg states that there is only one cause of cancer, that being replacement of oxygen-based respiration with sugar fermentation to meet energy needs. In this paper Warburg dismisses the evidence that viruses can cause cancers in animals, and though he later mentions the Rous Sarcoma Virus and in his 1969 paper (Warburg 1969), he states that no human tumors are caused by viruses (here he employs a classical logical fallacy, the appeal to ignorance, as if somehow the lack of evidence at the time precluded the possibility of tumor promoting viruses in humans - we now have accumulated evidence showing that at least 10-15% of human cancers have a viral etiology). In this 1969 paper, he still makes no mention of genes and DNA and their connection to the enzymes that he discusses in relation to aerobic glycolysis and as potential cures for cancer. The consequence of this has had lasting negative impact on the field - his apparent refusal to consider the relationship between genes and the biochemical pathways he was studying has reached out through the decades to the present, creating misunderstanding amongst scientists in the field of cancer biology and much confusion

in the lay populace. This has a direct bearing when thinking about the various models of carcinogenesis, especially when considering those that attempt to reject or marginalize the importance of genetic alterations in favor of metabolic causes - authors in this category almost invariably invoke the Warburg Effect as evidence that the metabolic disturbances are causing cancer, even though it is now known that the energy metabolism of a cancer cell is in general flexible and that any modified glucose metabolism is is always associated with genetic alterations in glycolytic and related genes.

Today it is clear that anaerobic glycolysis is not a hallmark of all cancers. As far back as 1956 Wein House noted that a variety of tumors generate carbon dioxide at rates in the same range as that in various normal tissues (Wein House et al 1956), suggesting that aerobic metabolism is functioning normally in most tumors. Importantly, Wein House refers to Warburg's 'Effect' as a hypothesis, appropriately treating it as a speculation rather than a fundamental physical reality. Note that first Warburg and then Burke & Schade vigorously contest Wein House's objections (see Wein House et al 1956 for the jointly published debate), arguing that the shift to cancer phenotypes is due simply and solely to a shift to aerobic glycolytic metabolism. Since then the role of the mitochondrion in cellular metabolism has been intensely studied (reviewed in Grasso et al 2020; Ziegler 2021), leading to a clearer picture of mitochondrial function as it relates to oxidative phosphorylation, glycolysis, and metabolic flexibility in cancer cells. In 2004, Zu and Guppy critically reviewed the literature pertinent to Warburg Effect, stating that there is no strong evidence that cancer cells are necessarily glycolytic – most are readily able to utilize lipid and amino acid catabolism as well as glucose to generate ATP, and can switch from glycolytic to oxidative pathways for ATP synthesis. They also review meta data, concluding that the glycolytic contribution to total ATP synthesis in cancer cells is not distinguishable from that of normal cells. In the same vein, Potter and colleagues in 2016 noted that preferential aerobic glycolysis (the Warburg Effect) is not a hallmark of all cancers, and that mitochondrial oxidative function remains fully intact in many cancers. These authors also note that observed anaerobic glycolysis in cell culture, where most experimental work has been conducted, is an artifact of high glucose concentrations in tissue culture media. In terms of the connection between genes and the Warburg Effect, we now know that the connection between mutated genes and the disrupted glycolytic pathways has been clearly established in many studies. For example, Zhang et al (2013) demonstrated the connection between mutated genes and anaerobic glycolysis by showing that certain p53 mutations induce increased glucose metabolism (the Warburg Effect) in cultured cells and knock-in mice by promoting translocation of GLUT1 glucose transporters to the plasma membrane. Pascale et al (2020) review the genetic lesions that cause or influence the Warburg Effect, and their discussion suggests that while altered glucose metabolism seems to be a characteristic of many (but not all) cancers, the Warburg Effect is an 'epiphenomenon' (a byproduct) of the transformation process. Thus, it now seems indisputable that Warburg's experiments, while impeccably executed and relevant in 1929, did not have sufficient scope to provide even a moderate degree of explanatory power in the cancer story. Today they can be interpreted as a conditional example within the range of metabolic profiles exhibited by tumor cells, and should not be viewed as foundational evidence supporting anti-genetics models of carcinogenesis.

1.3 Genes, Gene Expression, and the Genetic Paradigm

There exists an effort to overturn the 'genetic paradigm' of cancer. Diffuse rumblings have appeared in many publications, but perhaps show up most poignantly in a recent review by Huang, Soto, and

Sonnenschein, who in their title hail the 'end of the genetic paradigm of cancer' (Huang et al 2025). In that work, the authors state that the genetic paradigm (embodied in the Somatic mutation and Clonal Expansion models) claims to represent the truth about carcinogenesis and that it is a paradigm that needs replacing. The authors argue that there is not a causal relationship between mutant genes and cancer, and that their gene expression/epigenetics paradigm, in which epigenetic and metabolic disturbances alter gene expression programs, is significantly different than the 'genetic paradigm'. Importantly, the authors draw a distinction between disrupted genes and disrupted gene expression, which in the strict sense may be valid because of course genes are stretches of DNA and gene expression is the decoding of that DNA to produce proteins or functional RNA's. But again the question arises, how can gene expression be left out of what they are referring to as the 'genetic paradigm'? Gene expression can be altered for many reasons: mutation of promoters, mutation of micro-RNA's, mutation of transcription factors, chronic inflammatory processes, non-mutagenic tumor promoting chemicals, viral infections, epigenetic modifiers, and a myriad of chemicals that influence the feedback loops inherent in the transcriptional control mechanisms of a cell. The gene expression profile/epigenetic paradigm that is invoked as an alternative to the genetics-based models is in fact integral to the modern conceptual framework of genetics and is routinely discussed by cancer biologists as a fundamental aspect of carcinogenesis. Thus, said another way, the altered gene expression patterns invoked by Huang et al (2025) are an integral part of the 'genetic paradigm' they are attempting to replace. Furthermore, the replacement paradigm they propose is not incommensurable in the Kuhnian sense because it uses the language and conceptual framework of genetics; thus, it does not constitute a true paradigm shift (a revolution) in the Kuhn tradition. Could it be that the entire controversy is really a prosaic argument about semantics rather than one about the basis and explanatory power of any of the models? Maybe. Regardless of whether or not it is a new paradigm, testing of the Tissue Field Organization hypothesis has improved our understanding of the tumor microenvironment and the way that it both controls and is controlled by tumor cells (Maffini et al 2005; Zunder et al 2020). For example, although there is ample evidence showing that cancer cells modify and maintain their microenvironment due to mutated genes, murine studies suggest that observed tissue remodeling (PTEN-ETS2 mediated) observed in the murine breast cancer models occurs prior to tumorigenesis and is due to mutations in genes in neighboring cells that control tissue architecture (Trimboli et al 2009; Jones et al 2019). While that work demonstrates a role for mutated genes in disrupting microenvironments prior to tumorigenesis, it is important to keep in mind that extrinsic factors such as chronic inflammation might also be expected to modify the tissue environment in ways that select for the mutagenic profiles that we observe in at least some tumors, or that possibly even promote mutagenesis by impeding DNA repair mechanisms. Thus, in the end, the Tissue Organization Field model does not seem to be the harbinger of death for the genetic paradigm and instead provides evidence for a unified theory underpinned by the laws that govern genes, gene expression, and inheritance.

1.4 A Holistic Genetic Paradigm: Genes, Epigenetics, and Gene Expression

In the life of a cell, the proteins can never be disentangled from the genes that encode them, and the proteins cannot be disentangled from the metabolic processes of the cell or organism. Expression of any given gene is modulated by its own product and products of other genes, as well as vast arrays of microRNA and siRNA, and all of these influenced by complex environmental signals originating in the cytoplasm and outside of the cell. The complexities of interlacing genetic programs and their metabolic output are staggering. In some cases, the theories of carcinogenesis attempt to disentangle the

metabolic and genetic aspects of the transformation process, and as discussed above in section 1.3, there are many authors who appear to view genes, gene expression programs, and disturbed metabolic states as distinct, unrelated processes (Brucher and Jamall 2016; Capp 2017; Adriji 2017; Huang et al 2025). However, if the 'genetic paradigm' is viewed holistically to include gene mutations (in promoters, open reading frames, splice junctions, tRNA's, rRNA's, and microRNA's), chromosomal aberrations, epigenetic dysfunction, and altered gene expression, all of the 'theories' of carcinogenesis coalesce rather than diverge. Viewed in this manner, they are all related to each other, each filling gaps that are missing in the others. This is a critical point, especially in light of active dismissal of mutagenic processes in carcinogenesis. Disruptions in many hundreds of unique driver genes have been observed in thousands of human tumors (Bailey et al 2018; Martinez-Jiminez et al 2020; Dietlein et al 2020), suggesting that disruption of relatively few of the many thousands of pathways can lead to cancer. There are some disruptions that are central to the transformation process, for example mutation or dysregulation of genes involved with the p53 pathway are observed in nearly all cancers, and chromosome instability is also observed in nearly all solid tumors (Cimini 2008; Adriji 2017). This combined with the fact that our animal models as well as inheritable predispositions to cancer clearly show that cancer can be induced by mutational processes, which makes the link between genetic mutation and cancer difficult to ignore. Yet, it is now becoming apparent that mutations are not the entire story of cancer in humans.

There are a number of gaps in the mutation-based mainstream views of the field, one of which is that the transformation processes operating in short-lived rodents are not precisely the same as those that lead to tumors in long-lived humans. But what about cancer in other long-lived animals? Large data sets do not exist for any other long-lived animal. Investigations of cancer in our vertebrate relatives are limited in scope, but with the limited data available we observe a descending trend of cancer in mammals, reptiles, and amphibians. Boddy (2020) has summarized necropsy data from San Diego Zoo and generated a testable model for large mammal cancer incidence. On this line of inquiry, there have been studies suggesting that elephants develop cancer at much lower rates than humans (Callaway 2015; Gaughran et al 2016; Nunney 2022), potentially due to p53 gene amplifications in the pachyderm lineage. The elephant data sets are relatively small, and while the idea was initially intriguing, it turns out that the replicated p53 genes in the elephants all had stop codons that eliminated the DNA binding site of the p53 protein, making those duplicated genes unlikely to function as a transcription factor in the canonical p53 fashion (Nunney 2022). Another gap in our understanding is that despite the well-established links with mutations, the field has also had to attend to the fact that there are a number of carcinogens that are not mutagens yet still act as potent agents of cellular transformation (Riva et al 2020). The existence of non-mutagenic tumor promoting agents has been long known (Sugimura 1982; Balmain 2020; Guerra et al 2023) and there are many examples of non-mutagenic metabolic disruptions involving altered DNA methylation patterns (epigenetic) that lead to transformation.

Another gap has become apparent, that there are clearly situations where changes in gene expression (at transcriptional, translational, and post-translational levels) occur because of changes in tissue architecture/environment, in turn contributing to carcinogenesis. Capp (2017) discusses this point and notes that there is ample experimental evidence for renormalization of cancer cells when cultured with certain normal cells. He also discusses the body of evidence showing that tissue architecture disruption can lead to transformation through altered gene expression profiles. He is careful to point out that mutation is still a pre-requisite for transformation, but still places tissue disruption before mutation in

the hierarchy of events. Although he does not discuss the well-established direct link between mutagens and transformation in many experimental systems or the fact that the distinct transcriptional profiles of the primary glioblastoma cultures he describes are almost certainly the result of mutations in promoter regions, his commentary is valuable because it emphasizes one of the central questions that has emerged in the field, whether or not tissue disruption occurs before or after transformation. It is also worth reiterating that Capp and others wanting to overturn the 'genetic paradigm' exclude altered gene expression from the genetic paradigm. As I suggest above in this section, in section 1.3, and in section 1.5 below, when gene expression and epigenetics are also viewed as aspects of a holistic genetic paradigm, the controversy melts away and instead these opposing models become mutualistic. In the final analysis, all known human cancers exhibit significant mutation profiles (including chromosomal rearrangements) that include five or six driver genes and always include lesions in the p53 pathway and/or DNA repair pathways (the ependymomas were thought to be an exception to this rule because early studies showed virtually no mutation load and high epigenetic modification, but work by Pajtler et al (2015) has shown that these tumors, like all other tumors, have many chromosomal rearrangements that lead to a variety of gene fusions including those involving RELA and others involving YAP1). While the mutational triggers in carcinogenesis have been clearly demonstrated in animal models, the human data sets, despite being immense, have not been able to directly address the question of which comes first, the mutation or the metabolic disturbance, for the simple reason that we cannot directly experiment with humans in the straightforward ways needed to answer that question. Thus, this important question remains unanswered in natural cancers that we see in humans.

From another angle on this general front, many non-genotoxic aspects of our modern environment are under investigation. For example, there are long-standing questions about tumor promoting capacity of induced electric fields, induced magnetic fields, and radiofrequency radiation (collectively referred to as EMF's), and a significant number of studies have linked a variety of cancers to chronic non-mutagenic EMF exposure. Potential links between chronic disruption of circadian cycles caused by modern lighting, night work, and computers are also under serious investigation (Pariollaud and Lamia 2020; Kisamore et al 2024). In terms of causation, none of these potential disruptors can be teased apart from the unhealthy modern diet of highly processed food and the pervasive lack of vigorous exercise that are prevalent in our modern environment – establishing causation is always the vexing problem. Collectively, the various bodies of work show us that cancer can result from a variety of metabolic disruptions either leading to or arising from genetic (or epigenetic) lesions causing gene mis-expression or protein malfunction, and that the mutated genes or dysregulated expression patterns can be passed on to progeny tumor cells, perpetuating the dysregulated metabolism of the cancer cell. It is also soberingly clear that the cellular system of coincident, intersecting biochemical pathways is complex to the point of impenetrability. Because of these complexities, the existing hypotheses have varying degrees of explanatory power, and even when considered holistically still have fairly low explanatory power. A robust unified theory will require more information about the roles of tumor promoting agents, the combinatorial activity of driver mutation gene products, the process of renormalization, the myriad disruption in genetic programs, the roles of cancer stem cells, and the importance of unicellular gene programs; we are still on the path toward developing a unified theory with sufficient structure to fully explain carcinogenesis.

1.5 A Unified Theory of Carcinogenesis: How close are we?

Accounting for the various competing models seems at first glance an impossible task. But the underlying body of collective experimental work supports at least a partial unified theory of carcinogenesis, especially if we can agree that the 'genetic paradigm' includes gene expression and epigenetic phenomena. Once that point has been agreed upon, all of the models support, at least to some degree, an overarching theory of carcinogenesis. As depicted in Figure 2, there are two fundamental pathways leading to alteration of gene expression patterns: mutational events and metabolic disruption. The characteristic cellular manifestations, or hallmarks, of the disrupted system are aberrant cell division, changes in stemness, blocked apoptosis, loss of DNA damage control (including DNA repair pathways), occupation of inappropriate tissues, aberrant electrochemical balance, and suppression of the anti-tumor immune response. Most of these hallmarks were noted by Hanahan and Weinberg (2000) who at that time presented a clear explanation of the hallmarks of cancer, presaging two and a half decades of experimental work and importantly pointing out that tumors should be viewed as complex, vascularized tissues that develop from a variety of genetic alterations. Hanahan (2026), writing 25 years later, notes that their original framework has held up well. While not strictly attempting to unite the various 'theories' of cancer, their work has provided a holistic framework for understanding the disruptions that lead to cancer. Other features of the transformation process have been suggested in recent years, including disrupted hydration states (for reviews see Haussinger 1996; McIntyre 2006) and disrupted cellular electrophysiology (Sheth and Esfandiari 2022; Zamay et al 2025). It is probable that chemicals or other insults which modify aquaporin function and ionic balance create situations that influence gene expression, and it may be that in many cases it is this signaling that shifts the gene expression programs into transformation programs. Related to this is the possibility that disrupted hydration shells around cell membranes and proteins (termed biointerfacial water) might be contribute to or in some cases be the primary conveyor of the signals that shift gene expression into the transformation pathways that shut down cell cycle control, DNA repair, and apoptotic pathways, allowing mutations to accumulate in inappropriately dividing cells.

Jassim and colleagues (2023) have taken long steps towards unifying a theory of carcinogenesis with their Ground State model which is formulated to account for the observation that animals who have lived longer are much more likely to develop organ-specific cancers regardless of the mutation load. Earlier, Rosenfeld (2013) attempted to bridge the Somatic Mutation and Tissue Organization Field models, arguing persuasively for a unified theory of carcinogenesis. His logic, while somewhat abstract in the sense that he invokes the concept of 'self-organized criticality' with its attendant mathematical descriptions, arrives at the concrete conclusion that the Tissue Field Organization model and the Somatic Mutation models are simply two aspects of the same phenomenon. He concludes that the theoretical framework supporting each cannot be disentangled from that of the other. I am of the same opinion. In addition, there are empirical elements of the other hypotheses that also contribute to our unified knowledge base. Hernandez-Camarero et al (2022) discuss a merging of some of the theories (what the authors refer to as the stochastic, hierarchical, and dynamic models of carcinogenesis, which are all essentially variations of the Somatic Mutation and Cancer Stem Cell models), pointing out that inflammation and elevated deaminase activity also have a role in the transformation process. Those authors also invoke elements of the Tissue Organization Field hypothesis when they point out that that disrupted tissue environments can promote the transformation process. Thus, their work also takes some significant steps toward a unified theory of carcinogenesis. Similarly, the Atavistic model,

formulated to explain evidence suggesting that inactivation of genetic programs responsible for multicellular life and coincident activation of primitive gene expression programs used in a unicellular lifestyle, also contributes significantly to a unified theory with perturbed gene expression at its heart.

As noted above (section 1.4), one of the most important overarching questions still remaining is whether or not mutated genes, which clearly occur in cancer cells, are always a cause or whether they can be the consequence of transformation processes in long-lived humans. Three decades ago, Prehn (1994) raised the issue of who begets who, mutations or metabolic disturbances. This is an important question because, although we find point mutations, amplifications, translocations, inversions, and deletions in open reading frames, promoters, splice junctions, and untranslated regions of genes that control or modulate the cell cycle, DNA damage, apoptosis, body location (ability to invade), and immune suppression in all cancers, the question of whether or not those mutations are present at time zero or whether they accumulate during the process of transformation in human cancers is still a largely unanswered question. Modern sequencing technology has shown us that significant numbers of cancer promoting mutations occur in non-cancerous tissues (Rhozok and DeGregori 2015; Zhu et al 2019; ; Zhu et al 2022; Priestly et al 2019; Pan Cancer Whole Genome Consortium 2020; Rahal et al 2024), suggesting the possibility that many cancers could arise from cells that are metabolically normal but genetically primed to transform if metabolic conditions (including epigenetic status) stray from normal. Clearly our studies in animal models with bona fide mutagens demonstrate that increasing doses of mutagen result in increased number and extent of tumors (i.e. increased tumorigenesis), showing that DNA damage alone can be one cause of metabolic disruption that leads to cancer. Certainly, at least some human cancers develop in this relatively straightforward manner. But the contributions of chronic metabolic disruption to the transformation process is likely to be significant. There is ample evidence now showing that metabolic and epigenomic alterations of gene expression profiles can create conditions that either allow mutations to accumulate or activate the already genetically disrupted pathways (Dando et al 2015; Nanda et al 2020; Wang et al 2020; Shorthouse 2022; Xu et al 2023). Whole genome sequencing of normal and cancerous tissues suggests that often times cells with preexisting genetic lesions are selected for by tumor promoting conditions such as inflammation, non-genotoxic carcinogens, and obesity (discussed in Jassim et al 2023). Nanda and colleagues (2020) state that metabolic imbalance such as hypoxia or inflammation can precede genetic lesions in animal models, but this has not actually been established in humans. In considering this last data set, we must remember the fact that a required metabolic disruption preceding a genetic disruption does not mean that the genetic lesion is not required for the transformation process. One last consideration at this juncture is the near universality of disruption in the p53 pathway, which strongly suggests that accumulation of genetic lesions in genes involved with the DNA damage detection/apoptosis system is a prerequisite to transformation into the malignant state (Morris et al 2019; Marei et al 2021).

The fundamental aspects of the framework proposed herein are supported by four conceptual foundations: 1)Mutated driver genes are always present – I use the term driver gene in a broad sense to including mutations in proteins, promoters, enhancers, mRNA splice junctions, or microRNA's that control translation. Mutation profiles that allow cancers to form can either antecede or follow the metabolic disturbances that initially alter gene expression. 2)Disturbed gene expression profiles are always observed, either through mutation of important genes, disturbed epigenetics (methylation patterns, chromatin remodeling), or other environmental disturbances that influence transcription factors or microRNA's, hence gene expression (transcription and translation). 3)Metabolic disturbances

of the cancer cell and its tissue environment always occur, either before or after transformation. 4) Cancers can form from either terminally differentiated cells whose differentiation state has been reversed (either to a state of stemness or unicellularity) or directly from stem cells in the tissue of origin. In the end, perhaps decades from now, instead of multiple 'theories' of carcinogenesis we will have just one theory of carcinogenesis that with wide reaching explanatory power that allows us to prevent and cure cancer. Even employing the gene expression paradigm, this unified theory is currently only partially formed because many of the foundational supports are incompletely understood and the hypotheses attendant to each are the subjects of active research. Thus, it still lacks the explanatory power of a robust theory that allows effective treatment and prevention of cancer.

Finally, in considering a unified theory of carcinogenesis founded on altered gene expression, the Popperian notion of falsifiability naturally arises, presenting two attendant questions: 1)Are there any experimental works that falsify the holistic genetic paradigm as described in 1 and 2 above, and 2)Is there an experimental result that would falsify the unified theory, or at the least force us to substantially reformulate it? The answer to one is no, to my knowledge no one has described a situation in which altered gene expression is not detected in the cancer or pre-cancer cell. In fact, it would be truly revolutionary if it were discovered that altered metabolism occurred without some alteration in expression of one or more genes. This result would upend everything we know about gene expression and the cellular response to chemical or other changes in its environment. This leads to an answer for question 2, which is that one could set up the following experiment: First, obtain a normal human cell from a human body and characterize its gene expression profile without killing it (at this juncture, we don't have the tools to do this). Then sequentially expose it to a known carcinogenic insult, monitoring initial changes in gene expression and then following the course of development into a cancer cell. Repeat this with a single cell from every tissue for every known or suspected carcinogen. The holistic genetic theory would predict a change in gene expression that always accompanies the early stages of carcinogenesis. If ever it was found that one of these cells developed into a cancer cell with no detectable changes in gene expression, the unified holistic genetic theory of carcinogenesis would then have to be modified to account for that observation, or perhaps completely abandoned if there was some other underlying principle discovered.

1.6 Conclusion

In conclusion, it seems clear that the supporting bodies of scientific work which underpin the various 'theories' of carcinogenesis are all pertinent to a unified theory of carcinogenesis with gene expression as its unifying thread. So how do we integrate the various bodies of work into a useful theory of carcinogenesis with attendant predictive powers? Obviously, filling in the persistent gaps in our knowledge base will move us closer to a robust formulation of a unified theory. At this juncture, one of the largest voids in our knowledge is the absence of informative studies that track carcinogenesis in humans. Since many of us will develop a cancer at some point in our lives, this void could be filled by well-planned longitudinal studies that track metabolic profiles (microbiome, metabolome, diet, exercise, exposure to genotoxins, exposure to tumor promoters, exposure to artificial light, etc.) of a large number of individuals from birth to diagnosis. Yet another gap is the question of whether the apparent stemness of many cancer cells is due to dedifferentiation processes or malignant transformation of actual stem cells – it seems likely that both pathways to malignancy exist, as well as a pathway leading

to a unicellular-like state. The related question of unicellularity vs stemness is also an important one to answer. On another front, the growing awareness that cancer forms in many ways through disruption of many metabolic pathways has led to the realization that genetic lesions, while required, are not necessarily the initiating causes of the transformation process in every case - improved understand of the contributions of tissue milieu will also provide support for a unified framework. Finally, development of methods to better understand the conditions that disallow transformation in the presence of pre-existing driver gene mutations will be crucial in future cancer prevention strategies. Related to all aspects of cancer research is the need for continued development of algorithms to process the enormous amounts of data generated by our modern analytical methods as we enter the age of individualized medicine. It will be the combined power of the human intellect and processing power of supercomputers that brings us to a robust practical understanding of cancer causes and cures.

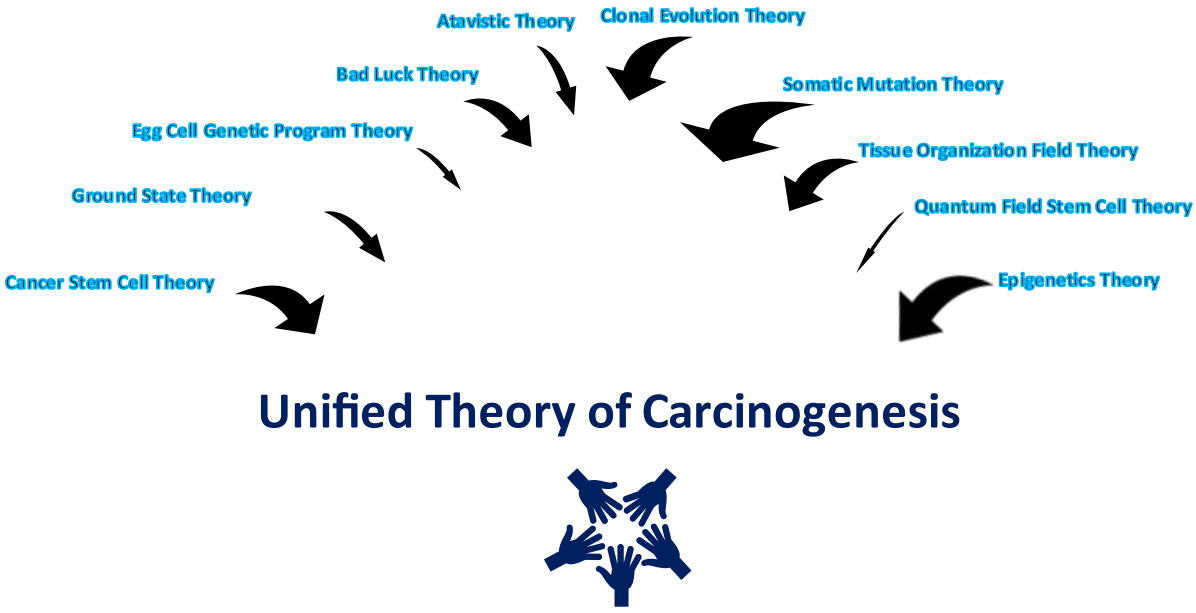


Figure 1 - The ten 'theories' (models) of carcinogenesis are depicted above. The arrow weight corresponds to the size of the body of literature supporting each of the models in a semi-quantitative manner. This weighting was estimated using Google AI with following search terms: 1) How many review articles have been published on the stem cell theory of cancer? Greater than 3,100. 2) How many review articles have been published on the ground state theory of cancer? Fewer than 5. 3) How many review articles have been published on the egg cell genetic program theory of cancer? Fewer than 5. 4) How many review articles have been published on the bad luck theory of cancer? 10-15. 5) How many review articles have been published on the atavistic theory of cancer? 20-30. 6) How many review articles have been published on the clonal evolution theory of cancer? Over 6,000. 7) How many review articles have been published on the somatic mutation theory of cancer? Over 25,000. 8) How many review articles have been published on the tissue organization field theory of cancer? 40-50. 9) How many review articles have been published on the quantum field theory of cancer? Fewer than 5. 10) How many review articles have been published on the epigenetics theory of cancer? 5,000-7000.

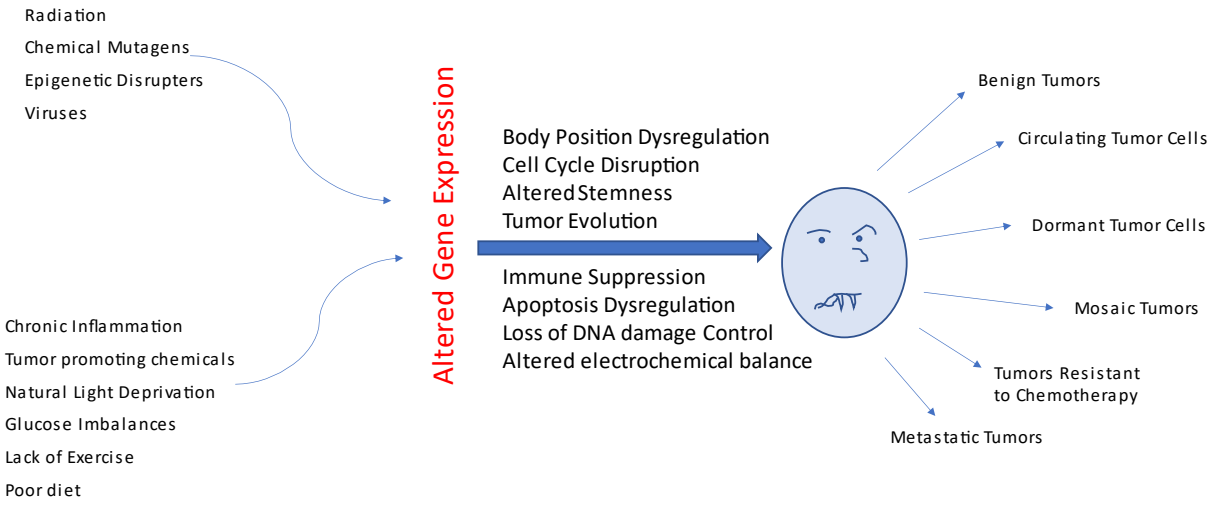


Figure 2 – The interplay between various metabolic and genetic (including gene expression) factors involved with the transformation process. Varying degrees of stemness, mutation background, epigenetic determinants, and metabolic disruption conspire in the transformation process. In terms of the transformation of any given cell, there are countless permutations of the processes.

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