Biochemistry – not oncogenes – may demystify and defeat cancer

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Abstract

The presence of mutated genes strongly correlates with the incidence of cancer. Decades of research, however, has not yielded any specific causative gene or set of genes for the vast majority of cancers. The Cancer Genome Atlas program was supposed to provide clarity but it only gave much more data without any accompanying insight into how the disease begins and progresses. It may be time to notice that epidemiological studies consistently show that the environment, not genes, has the principal role in causing cancer. Since carcinogenic chemicals in our food, drink, air and water are the primary culprits, we need to look at the biochemistry of cancer, with a focus on enzymes which invariably facilitate transformations in a cell. In particular, attention should be paid to the rate-limiting enzyme in DNA synthesis, ribonucleotide reductase (RnR) whose activity is tightly linked to tumor growth. Besides circumstantial evidence that cancer is induced at this enzyme's vulnerable free-radical-containing active-site by various carcinogens, its role in initiating retinoblastoma and HPV-related cervical cancers is well documented. Blocking the activity of malignant RnR is a certain way to arrest cancer.

Keywords: carcinogenesis; cancer treatment; cervical cancer; DNA synthesis; free-radical; retinoblastoma; ribonucleotide reductase; somatic mutation theory (SMT)

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In 2005, at the onset of The Cancer Genome Atlas (TCGA) program, Dr. Eric C. Lander, director of Broad Institute of MIT and Harvard, declared in New York Times, "Knowing the defects of the cancer cell points you to the Achilles' heel of tumors" [1].

At Cancer World 2013, Nobel laureate James Watson opined, "We can carry on and sequence every piece of DNA that ever existed, but I don't think we will find any Achilles heels [of cancer]" [2].

1. Introduction - cancer war not won

The current year 2021 marks the 50th anniversary of the declaration of 'war on cancer' by U.S. President Nixon. He was inspired by President Kennedy's declared goal in 1961 to land a man on the Moon by the end of the decade – which had come true, to international acclaim. However, progress in the field of cancer has been quite limited despite plentiful funding over the last five decades.

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The overall survival rates have improved, to varying degrees, for all cancers, primarily due to early detection and intervention. Preventative measures like the reduced use of tobacco products have also lowered the incidences of lung cancers [3]. However, effective treatment remains out of reach for most cancers.

Common reasons given for this slow progress is that cancer is a very complex disease -- and that it may not be one but many diseases. However, there is another possibility, raised as early as 1994 by Scientific American magazine: "Have the researchers and clinicians been barking up the wrong trees…?" [4]. Then as well as now, the 'wrong trees' referenced in this statement, would all be gene-related, since the vast majority of cancer research projects, during the last five decades, have focused on the genetic aspect of the disease. Could this approach, this emphasis on genes, be wrong to understand and tackle cancer?

There is growing evidence that this in fact may be the case [5-7]. The close correlation between mutagenesis and cancer may not be causative in nature. Mutated genes may simply be a consequence of carcinogenesis, initiated elsewhere upstream. If so, then the genes-centered rationale may be hampering researchers in their fight against cancer.

This possibility is explored here. The article also discusses an alternative mechanism for the induction of cancer where a free-radical-based enzyme plays a central role; it may explain many hitherto mystifying aspects of the disease. Finally, a way to control cancer by biophysical means is cited.

2. Essence of the gene-centric view of cancer

Per the prevailing genetic model, cancer is caused by mutation of genes, that are either inherited or acquired.

- An 'inherited gene mutation' is present in the egg or sperm cell of the parents. In rare instances, post-zygotic *de novo* mutation can occur during early embryonic development. Such germline mutation is in every cell and so may be passed on to the next generation.

- An 'acquired (somatic) mutation' is not present at birth, but is acquired sometime later. Acquired mutations are much more common and most cancers are caused by them. This somatic mutation theory (SMT) has become the dominant paradigm in cancer research [8].

Per the SMT, a multistep process – initiation, promotion and progression – of random mutations in some key genes leads to cancer. These key genes are either oncogenes or tumor suppressor genes.

An oncogene results from mutation of proto-oncogenes. The latter are healthy normal genes that help cells grow. Oncogenes can become permanently activated causing cells to grow out of control. Too many copies of a proto-oncogene are also called 'oncogene'.

Tumor-suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (apoptosis). When these genes are mutated or defective, cells can grow out of control, leading to cancer [8].

Sustained proliferative signaling leads to nuclear genomic instability, which underlies various hallmarks of cancer.

(Further elaborations of this model – epigenetic alterations and the classification of mutations as drivers or passengers – are discussed elsewhere in the article.)

2.1. Core deficiencies of the genetic theory of cancer

2.1.1. Carcinogens relegated to the side

Only 5 to 10% of all cancers are attributable to genetic defects. The remaining 90–95% have their roots in the environment and lifestyle [9].

In other words, most cancers are caused by chemical carcinogens, be they in tobacco products, food additives, pesticides, or environmental pollutants. But the genetic theory of cancer minimizes their significance. Cancer risk is typically discussed in terms of the importance of genes: high-penetrance, moderate-penetrance and low-penetrance [10]. In the least important last group are two kinds of genes: DNA-repair and xenobiotic metabolizing genes [11, 12]. The word 'xenobiotic' means 'foreign to the body' – and only under this category carcinogens are mentioned, almost as an afterthought.

Chemical carcinogens are, of course, foreign to the body but they must be put front-and-center when we are trying to understand cancer.

2.1.2. No mechanism for selective mutations

In our body, exogenous chemicals go through one or more metabolic pathways – the majority mediated by the versatile cytochrome P450 enzymes – which may result in excretable compounds, or produce metabolites that are reactive and toxic [13]. In the case of asbestos particles as well as UV light and ionizing radiation, reactive oxygen species (ROS) are produced [14-16]. How can these myriad reactive molecules *selectively* attack only those genes which are involved in cell duplication (chromosome segregation, mitosis, cytokinesis), DNA repair or cell death (apoptosis)? Such genes are a small minority – less than 10% – of the protein-coding genome [17-20], and from the perspective of these relatively tiny chemical compounds, the DNA strand of one gene is no different than that of any other gene. (Carcinogens are usually not known to cause other kinds of genetic damage to the cell, which would indicate genome-wide assault.) No mechanism is known by which carcinogens, or their metabolic products – or old age – might impair *only* those genes – a superset of proto-oncogenes and tumor suppressor genes – which are involved in cell division, DNA repair and apoptosis.

2.1.3. The immediate cause of unrestrained cell growth unknown

Even if we ascribe carcinogens-or-their-transformed-products some mysterious power to locate the relevant proto-oncogenes to damage them – or attribute such damage to age-related "bad luck" random deteriorations – how would these point mutations trigger uncontrolled cell growth?

Normally, a defect in an entity results in its functioning at a reduced level or not functioning at all. (That is what happens when 'tumor suppressor genes' are mutated.) Despite decades of intensive hunt, no cancer-causing genes (oncogenes) have been identified that are necessary-and-sufficient to cause cancer.

Over the last two decades, modifications in epigenetic regulators like CpG island methylation, histone acetylation and miRNA-associated silencing have been introduced as possible pathways in tumorigenesis [21]. The mechanisms of such alterations do seemingly account for the role of xenobiotics in our environment [22]. However, the immediate cause of uncontrolled cell proliferation remains as elusive as ever.

In brief, the gene-based theory of cancer fails to answer certain basic questions about the process of carcinogenesis. The raison d'être for the concept of 'oncogenes' is *correlation* or the presence of mutated genes at the site of cancerous growth. Could these mutated genes be end-products of malignant growth, similar to dead and wounded soldiers at the end of a war? Even healthy soldiers do not cause war since they are simply following orders from higher-ups. Could genes be no different, merely responding to biochemical signals or cues?

The next two sections evaluate in detail the evidence for the role of genes in causing inherited and non-inherited cancers.

2.2. In hereditary and familial cancers, few oncogenes identified

Having certain inherited genetic mutations may increase a person's risk of developing cancer, but it does not necessarily mean that person will get cancer. Such medical conditions are usually called "syndromes". The most common hereditary cancer susceptibility syndromes are Lynch syndrome, Li-Fraumeni syndrome, Von Hippel-Lindau syndrome, Familial Adenomatous Polyposis (FAP) and Cowden syndrome. The cancer risk can be passed from generation to generation in a family, though some *de novo* mutations are also seen without a family history. They all follow an autosomal dominant inheritance pattern, wherein a single copy of the specific mutation is enough to predispose a person to the disease [23, 24]

In all these syndromes, tumor suppressor genes in germline mutations are the culprit [25].

The tumor suppressor genes (*BRCA1* and *BRCA2*) are also implicated in familial breast and ovarian cancers. They increase susceptibility to these cancers and are passed down through a family in an autosomal dominant manner. Only 5-10% of breast cancers fall in this "hereditary" category; most such cancers occur sporadically in people with no family history [25].

A tumor suppressor gene is also involved in retinoblastoma, which is a historic case. The mutation or deletion in its *RB1* gene was the earliest one identified, in 1971, and gave a boost to the gene-based view of cancer [26]. This childhood disease is unique and not called a syndrome since the non-functional *RB1* gene does not simply predispose but directly causes cancer of the retina when both alleles are defective or missing. Approximately one out of three cases are due to germline mutation, usually acquired during early development in the womb, and rarely inherited from a parent. The majority of retinoblastomas are non-congenital and develop in only one eye [24, 25].

On the other hand, mutations in the proto-oncogenes have been identified in only two types of such cancers: *RET* and *MYCN/ALK* genes in Multiple Endocrine Neoplasia type 2 (MEN2) and neuroblastoma, respectively. MEN2 occurs via a germline mutation, linked to a high lifetime risk of developing medullary thyroid cancer, but some sporadic mutations are needed for the onset of the disease [25, 27]. Neuroblastoma is a cancer of nerve cells and occurs mainly in children, but a family history of the disease is found in only 1% to 2% of cases [25].

Thus, in cancers with hereditary components, time and again, the genes associated are tumor suppressor genes. Only rarely do we find proto-oncogenes, and when we do, some external non-inherited factors are involved in turning them into bad cancer-causing oncogenes. (In the next section, oncogenes are discussed in detail.)

2.3. In somatic cancers, many oncogenes, but no clear causative role

Despite extensive search, over the last many decades, for proliferation-inducing 'oncogenes' and mutated 'tumor suppressor genes', no meaningful pattern has emerged for any type of non-inherited (somatic) cancer.

The findings of various studies show several inconsistencies [28]. For example:
- The same tumor may contain many distinct foci, with different subpopulation of mutations in each [29].
- Mutations may vary dramatically from one stage of tumor progression to another [30].
- Metastasized tumors often have different mutations than the primary tumor [31].
- For the same type of cancer, mutated genes are often different and random, in different individuals [30].
- The presence of mutations differs from country to country. In non-small cell lung cancer tumors, mutations found in 15 out of 58 Japanese patients were there in only 1 out of 61 U.S. patients with the same cancer [32].

Thus, mutated genes in a tumor are varied and random at all levels, making any functional and causal interpretation very difficult. As if every cancer cell is a unique experiment in nature, having its own mutational signature, reflective of its distinct lineage history within the evolving neoplasm [33].

Unsurprisingly, the majority of representative "high-quality" cancer research papers are unreproducible. Scientists at Amgen could replicate findings in only 6 (11%) of 53 such published papers [34].

2.4. Epidemiological evidence against the genetic basis of cancer

The genetic theory of cancer explains the increase in human cancers in post-industrial societies by pointing to the significant lengthening of our lifespan. It posits that age-related molecular and physiological deteriorations may act in concert to promote cancer. The combined pathogenetic effects of accumulated "bad luck" mutations, increased epigenetic dysregulation, telomere dysfunction, reduced DNA repair capacity and altered stromal milieu – all take their toll on cells [35, 36]. In short, according to the gene-based view, cancer is largely a disease of old age.

But epidemiological studies often undermine this assertion. An editorial in the New England Journal of Medicine stated: "Geographic differences, trends over time in the risk of cancer, and detailed studies of migrant populations overwhelmingly implicate environmental exposures as major causal factors and often identify the responsible carcinogens (e.g., tobacco, alcohol, radiation, occupational toxins, infections, diet, drugs). From this work has come the widely accepted estimate that 80 to 90 percent of human cancer is due to environmental factors" [37].

Data analysis of childhood cancers from 19 European countries showed an annual increase of 2% in infant cancer from 1978 to 1997. Incidence rates of many, but not all, cancers in children and adolescents were rising [38].

Similarly, an epidemiological study, funded by the National Cancer Institute (NCI), alarmingly found that the incidence of cancer in the '15 to 29 years' age group increased steadily between 1975-2000 [39].

A recent study has estimated the cancer burden attributable to 13 occupational carcinogens across 195 countries in the years 1990-2017. It found that, except in the most advanced countries (top 1/5th), cancer deaths were higher in the '50 to 69 years' age group compared to the 'older than 70 years' group; people aged '15 to 49 years' also died from cancer [40].

Such findings cannot be reconciled with the view that cancer is essentially a disease of old age.

2.4.1. Epidemiology gold standard – the study of twins

Studies of monozygotic (identical) and dizygotic twins are unsurpassed in distinguishing genetic from environmental traits.

A study published in Lancet reported that if one member of a pair of identical twins develops acute leukemia in childhood, the chances of leukemia developing in the other twin are no higher than 20%. The concordance decreases with increasing age of onset of leukemia, being highest during the first year of life and low after 7 years of age [41].

Among 432 sets of twins, when at least one was affected by Hodgkin's disease, none of the 187 pairs of dizygotic twins became concordant for Hodgkin's disease, and only 10 of the 179 pairs of monozygotic twins did [42].

In a 2000 study, the data on 44,788 pairs of twins in Sweden, Denmark and Finland showed that inherited genetic factors make a minor contribution to susceptibility to most types of cancers. The environment had the principal role in causing sporadic cancer [43]. This study was updated and expanded in 2016 to include Norway and many more cancer types [44]. The data showed an excess cancer risk in twins whose co-twin was diagnosed with cancer: an absolute 5% and 14% higher in same-sex-dizygotic and monozygotic pairs, respectively, by the age of 100 years. Notably, more than two-thirds of these twins were diagnosed with a different malignancy, which can only partially be explained by pleiotropy. Furthermore, the median time between cancer diagnoses in concordant pairs of twins was fairly long: 4 - 15 years. These results suggest the majority role for non-genetic factors such as environment and lifestyle.

Such studies contradict the view that genes play a preeminent role in incidences of cancer.

2.5. The Cancer Genome Atlas (TCGA) program – more data, no clarity

In 2006, a landmark cancer genomics program, The Cancer Genome Atlas (TCGA), was launched by the NCI, sequencing over 20,000 primary cancers spanning 33 cancer types [45].

The goal of the program was to generate sufficient data so that some knowledge gaps are filled and the landscape of cancer genetics becomes comprehensible. However, these aims were not achieved. No recognizable patterns emerged. No synergistic accounts could be provided. Observed genetic mutations remain heterogeneous or diverse as well as random and complex [46, 47]. We do have an ever increasing collection of genetic changes associated with cancer, that need cataloging [30].

The enormous amount of data has not yielded any specific gene mutation – or any combination of mutations – that is necessary, let alone adequate, to initiate the transition from one stage of malignant neoplastic progression to the next. A considerable disconnect is seen between nominal 'oncogenic mutations' and cancer phenotypes [48].

There is a sense that accumulated data may be overwhelming the researchers' abilities of interpretation [33]. However, a small effort is made by putting all the mutations in two groups: drivers and passengers. Driver mutations are causal, whereas passenger mutations occur by chance. Such ad hoc elaborations have been seen, by some critics, as akin to the use of epicycles in pre-Copernican astronomy [49]. The futility of such attempts becomes obvious when driver mutations are found in benign and premalignant conditions, occasionally at higher frequencies than in their malignant counterparts [50]. The concept of the cancer-inducing 'oncogene' is looking increasingly like a phantom – and SMT no more than an epiphenomenon. A new paradigm is, therefore, called for [5, 6, 51].

3. Source of carcinogenesis maybe outside the nucleus, away from genes

As early as 1975, it was reported that the carcinoma cells, after introduction into normal blastocysts, can give rise to a large variety of normal tissues – mostly strikingly, sperms – in mosaic mice, thereby showing that tumorigenesis may not involve damage to genes, but only aberrations of gene expression [52].

A study in 1987 showed that when cells are reconstituted by fusing karyoplasts from malignant cells with the cytoplast of normal cells, the tumorigenic phenotype was extinguished [53]. In 1988, the same authors reported that in cells derived by fusion of cytoplasts from malignant cells with karyoplasts of normal cells, tumors were seen in 97% of the animals injected [54]. Figure 1 is a visual depiction of their findings:
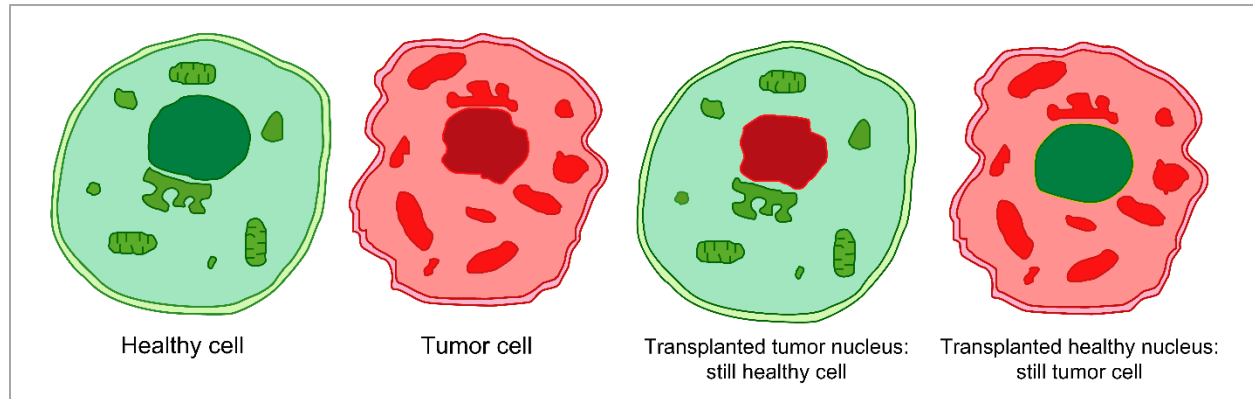
Figure 1: Transplanted nuclei (and genes within) do not hold the key to tumorigenesis

At the end of that 1988 article, one can see:

EDITOR'S STATEMENT

This is the first description of cytoplasmic mediation of tumorigenesis. There is a clear indication that cytoplasmic elements play a role in the expression of the malignant phenotype.

This addendum was highly unusual, and for a good reason. It was a clear demonstration that genes may play little or no role in carcinogenesis – contrary to the prevailing view of cancer as a genetic disease. Even after 33 years, such evidence is being ignored. It is hard to shake the belief of the vast majority of cancer researchers who cannot take their eyes off genes [6].

Subsequent researchers have confirmed this phenomenon. For example, in 2003, it was reported that blastocysts derived from medulloblastoma nuclei form embryos with typical cell layers, showing normal patterns of tissue differentiation [55]. Interestingly, these results were interpreted as "epigenetics reprogramming abrogating tumorigenic phenotype", which is a stretch since even the most ardent proponents of the 'epigenetics model of carcinogenesis' state that genetic mutations are secondary "critical by-products", not absent [21]. Therefore, how could the transfer of nuclei make those genetic mutations go away?

A more plausible explanation was hinted at earlier: the root of cancer may not be malfunctioning genes, but some biochemical processes in the cytoplasm that may be triggering unrestricted cell growth. The remainder of this article will delve into the biochemistry of cancer.

3.1. Looking for the origin of cancer in the cytoplasm's biochemistry

Due to the conceptual limitations of the cancer gene mutation theory, and the accumulated evidence against it – as described in the previous sections – researchers have started looking outside the nucleus to unravel the mechanisms underlying cancer development.

In recent years, most of the attention has been paid to the mitochondria. The century-old Warburg hypothesis has been revived which posits that mitochondrial dysfunction is the root cause of cancer, resulting in glucose fermentation even when enough oxygen is present. In the updated version, a plethora of random somatic mutations in tumors are seen as downstream effects of insufficient respiration with compensatory fermentation [56]. Examples of potent mutagens like ROS are given which are produced in damaged mitochondria.

Unfortunately, this carcinogenesis theory cannot explain what attracts carcinogens (or their metabolic products) to mitochondria and why uncontrolled multiplication of cells occurs when there is mitochondrial malfunction. Therefore, this theory is as weak as the genetic theory in explaining some basic facts about carcinogenesis.

Among those frustrated at the glacial pace of progress on the cancer-front is one of the founding fathers of molecular biology, Dr. James Watson, who spent three decades exploring the genetic aspects of cancer as director of Cold Spring Harbor Laboratory, NY. On May 12, 2016, in the New York Times, he stated:

> …locating the genes that cause cancer has been "remarkably unhelpful" - the belief that sequencing your DNA is going to extend your life is "a cruel illusion". If he were going into cancer research today, he would study biochemistry rather than molecular biology [57].

To seek mechanisms of cancer-causation in biochemistry is far from counter-intuitive. After all, most cancers are caused by toxic chemicals and the earliest drugs designed to treat cancer, just after World War II, were based on the knowledge of biochemistry [58]. Most of the chemotherapeutic drugs, synthesized ever since, often target some biochemical pathway implicated in cancer.

To fully understand the biochemistry of cancer, we must look at the activity of various enzymes involved in cancerous proliferation, as virtually all transformations in a biological cell are mediated by one or more enzymes.

4. Pivotal enzyme in cancer growth may demystify cancer

Ribonucleotide reductase (RnR) converts the building blocks of RNA into the building blocks of DNA, as shown in Figure 2. Besides catalyzing the *de novo* production of DNA precursors, RnR is also involved in DNA repair. It is the rate-limiting enzyme for DNA synthesis, without which no cell can replicate, and no cancer can grow [59].
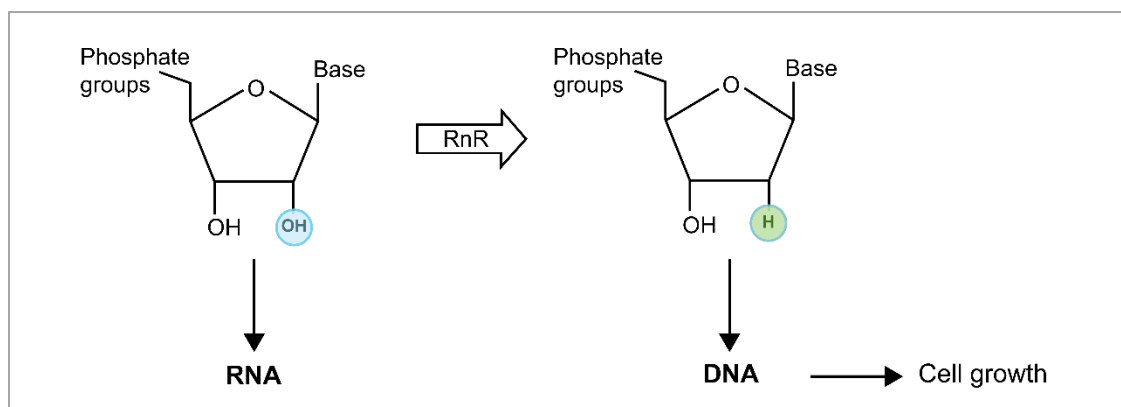

Figure 2: Ribonucleotide reductase (RnR) converts the building blocks of RNA into those of DNA

The activities of prominent enzymes in healthy and cancerous tissues are compared in a Table (as Figure 3). In a growing tumor, the activity of the enzyme ribonucleotide reductase jumps up

exponentially, much more than that of any other enzyme – almost eight-fold higher than even DNA polymerase [60].

Comparison of activities of pyrimidine- and DNA-synthentic and -catabolic enzymes in liver and in rapidly growing hepatoma Data are expressed as specific activity and as percentages of the normal liver values. In calculations, the values 200 mg of protein per g, wet weight, of tissue for homogenates and 80 mg of protein per g for supernatant fluids were used. Enzymic activities were those determined in this laboratory and in other centers.			
Enzymes	EC no.	Normal liver (pmol/hr/mg protein)	Rapidly growing hepatoma 3683F (% of liver)
Anabolic enzymes			
Ribonucleotide reductase	1.17.4.1	23	18,348
DNA polymerase	2.7.7.7	56	5,806
dTMP synthase	2.1.1.b	180	2,860
dTMP kinase	2.7.4.9	420	7,000
Deoxycytidine kinase	2.7.1.74	800	1,400
Thymidine kinase	2.7.1.21	900	3,920
CTP synthetase	6.3.4.2	5,500	1,122
Carbanmoyl-phosphate systhe- tase II	2.7.2.9	10,000	950
dCMP deaminase		12,000	750
Uracil phosphoribosyltransferase	2.4.2.9	19,000	760
Ornithine-5'-monophosphate decarboxylase	4.1.1.23	34,000	889
Orotate phosphoribosyltransferase	2.4.2.10	47,000	599
Uridine phosphorylase	2.4.2.3	164,000	671
Uridine-cytidine kinase	2.7.1.48	156,000	694
Dihydroorotase	3.5.2.3	246,000	418
Aparatate carbamoyltransferase	2.1.3.2	448,000	706
UDP kinase	2.7.4.6	444,000,000	298
Catabolic enzymes			
Dihydrouracil dehydrogenase	1.3.1.2	26,000	9
β-Ureidopropionase	3.5.1.6	144,000	
Thymidine phosphorylase	2.4.2.4	234,000	31
Dihydropyrimidinase	3.5.2.2	276,000	

Figure 3: (Table taken from Weber G. Biochemical strategy of cancer cells and the design of chemotherapy. Cancer Res. 1983; 43, 3466-3492.)

The enzyme RnR consists of two dissimilar subunits, proteins RRM1 and RRM2. The larger RRM1 is a dimer and binds substrates as well as allosteric effectors. The smaller RRM2 is also a dimer, and contains a tyrosyl free-radical which is stabilized by an adjacent oxo-bridged binuclear iron center [61].

$$[Tyr\text{-}O\bullet \text{ - - - } (Fe^{3+}\text{-}O\text{-} Fe^{3+})]$$
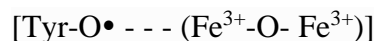
The free-radical at the core of the RRM2 subunit is essential for any enzymatic action. The levels and activity of RnR are tightly regulated via multi-layered mechanisms that involve intricate interplay between gene expression, cell cycle checkpoints, proteolysis, together with allosteric effects via two allosteric sites, the specificity site (s-site) and the overall activity site (a-site) [59]. Exquisite controls of RnR activity are necessary to optimally regulate cell multiplication.

Obviously, this critical enzyme for cell-division is known to impact cancer susceptibility [62]. Lately, the RnR-complex has been called "oncogenic" in the sense of proliferation-inducing (no genes are there, only unique proteins) [63]. *The next small step needs to be taken to view this enzyme as the site where, in all probability, cancer is initiated.*

The RnR-based model of carcinogenesis proposes that the RRM2 subunit of this enzyme, containing a diferric-tyrosyl-radical active site, is the primary, and perhaps the only, target of all types of carcinogenic chemicals. Various characteristics of tumor cells – anchorage independence, dedifferentiation, metastasis, angiogenesis, genetic aberrations, chromosomal anomalies, genomic instability, etc. – all result from the cascade of events that is initiated at the RRM2 subunit by adverse stimuli.

It is noteworthy that RnR resides in the cytosol. The deoxynucleotides produced by it diffuse into the nucleus or are transported into the mitochondria [64]. Thus, this model is in accordance with the observations depicted in Figure 1.

The mechanism of initiation of cancer at the RRM2 subunit of RnR in a variety of malignant neoplastic transformations is elucidated below: (The first two sections are based on circumstantial evidence while direct experimental proof exists for the remaining two.)

4.1. Chemicals

Carcinogenic chemicals, thought to be culpable in a large number of cancer cases, fall into two broad categories: direct-acting and indirect-acting. Direct carcinogens, of which there are only a few, e.g., dimethyl sulfate, are reactive electrophiles, i.e., they seek out and react with negatively charged centers in other compounds. Indirect carcinogens such as highly inert polycyclic aromatic hydrocarbons, can attain even more reactive electrophilic centers by going through any of the various metabolic oxidative pathways in the body, involving powerful cytochrome P-450 enzymes [13].

In addition to being or becoming electrophilic, chemical carcinogens are, in general, hydrophobic in nature. Molecules with these characteristics are especially suited to access the RnR active site since Glu/Asp residues around ferric ions constitute a negatively charged environment [62, 65], and the tyrosyl free-radical is located in a hydrophobic pocket [62, 66].

According to this mechanism of cancer induction, carcinogenic chemicals, and/or their metabolic products, are attracted to the electro-magnetically charged active site of RnR, and once there, would disturb the finely tuned rhythmic controls in place. The accumulation of such miscreant/irritant molecules may go on for years, until a threshold is crossed, resulting in persistent overstimulation. A chain of events is then set in motion culminating in the production of outlaw tumor cells. Responding to the "non-self" antigens on the surface of these cells, the immune system would eliminate them. However, over a period of time ("the latency period"), weakly antigenic cancer cells, capable of evading immune surveillance, would evolve – and cancerous growth gains a foothold.

4.1.1 Re-evaluating the chemical structure of a compound for carcinogenicity

The currently established tool Quantitative Structure–Activity Relationship (QSAR) to test the carcinogenicity potential of a compound is predicated on the affinity of its electrophilic center to nucleophilic moieties in four bases of DNA [67]. However, such an approach is highly inadequate, if not problematic, because of its lack of any specificity. The human genome consists of billions of bases – and most are not part of any protein-coding genes. As mentioned in Section 2.1.2, to a carcinogenic molecule, one section of the DNA strand is no different from any other, and therefore, it can cause genetic damage or mutations only in an entirely random fashion. How can such a process lead to uncontrolled cell growth – and at the same time, cause no other harm?

This shortcoming may be overcome if we view the diferric-tyrosyl-radical-containing active-site of RnR as the target-site of carcinogens. The vulnerability of this site should be different for different exogenous compounds (or their metabolic products), depending on their structures – quite likely in line with their carcinogenicity.

4.2. Asbestos and Radiations

Extremely fine asbestos fibers are known to cause malignant tumor growth after a latency period of 20 to 40 years. After uptake by lung-cells, phagocytic cells that engulf asbestos fibers produce large amounts of ROS and other free radicals due to their inability to digest the fibers. This model provides for these oxygen radicals a singularly sensitive target-site to initiate, albeit unwarranted, cell proliferation – in a manner similar to carcinogenic chemicals. A slow struggle with the immune system would commence then on, which may be lost only after a few decades. It is notable that epidemiological studies indicate that iron-containing asbestos fibers appear more carcinogenic [14].

The cases of UV light and ionizing radiation are very similar, since both generate elevated levels of ROS in the human body [15, 16]. However, their latency periods are considerably shorter.

4.3. HPV-related cervical cancers

High-risk human papilloma viruses (HPVs) are causal agents for human cervical cancers. The viral proliferation activity is completely dependent on its genes *E6* and *E7*, the latter of which is more potent and induces upregulation of the RRM2 subunit of RnR in the host [68]. Exogenous activation of RnR, which was initially meant to help make copies of only the invading virus, over time ("latency period") starts building unneeded copies of the cells of the human host.

Diferric-tyrosyl-radical containing RRM2 has now become a molecular marker for the diagnosis and clinical outcomes of cervical cancer [69].

4.4. Retinoblastoma

While studying the mechanism of cancer causation by HPVs, researchers discovered that the E7 protein of the virus targets and inactivates the retinoblastoma gene (*RB*) [70]. This results in the release of active E2F transcription factors which then bind to the RRM2 promoter region, putting RnR in overdrive – and causing the improper proliferation of cells [68]. These findings make it possible to understand why non-functional or missing *RB* genes in infants are responsible for retinal cancer, mediated by unchecked activity of RnR.

Thus, we have seen that in various types of cancer, persistent over-stimulation or over-expression of the active-site-containing RRM2 subunit of the enzyme ribonucleotide reductase may be the trigger that sends the entire elegant cell-division machinery spinning out of control.

This RnR-based model of carcinogenesis answers the hitherto unanswerable questions about cancer: What is the immediate cause of unrestrained cell growth? How do carcinogens cause cell replication to go out of control?

5. Disabling ribonucleotide reductase will defeat cancer

Whether or not cancer is initiated, in all cases, at the enzyme ribonucleotide reductase (RnR), it is beyond dispute that if you stop RnR, you stop cancer. Therefore, this enzyme is considered a classical target for cancer therapeutics [71, 72].

Chemotherapeutic compounds aiming to block this enzyme have been synthesized since the early 1970's [73]. They fall in three broad categories: iron chelators inhibitors, radical scavengers and nucleoside analogues. Unfortunately, these drugs have limited potency and produce toxic side effects. Despite this, several U.S. Food and Drug Administration–approved RnR inhibitors are used clinically to treat various forms of cancer [62].

A novel way of inhibiting this enzyme is suggested by the fact that the free-radical (unpaired electron) at the active-site of RnR can be destroyed (paired-up) by a stream of electrons. Thus, gentle electrotherapy would disable RnR and interrupt cancer growth [74]. This concept is strongly supported by the results of several animal studies on cancer electrotherapy reported over the years [75-77]. The most remarkable of these was the 1985 study which showed up to 98% reduction in tumor mass – a virtual cure – after only 5 hours of gentle electrotherapy over 5 days [77].

Lately evidence is accumulating of the effectiveness of this therapy on human patients as well [78, 79]. In the case of both animals and humans, there is indisputable experimental evidence that this treatment selectively targets malignant cells since the normal growth of intervening tissues – like hair follicles – remain unaffected. This is almost certainly due to the fact that the active-site of RnR is well-shielded in healthy cells [61], whereas that is not likely to be the case when RnR is in overdrive or frenzied in cancerous tissues.

6. Conclusions

Using the somatic mutation theory (SMT), which posits that cancer is caused by genetic mutations or 'oncogenes', researchers have been unable to determine the immediate cause of unrestrained cell proliferation, or suggest a pathway for the initiation of the disease by any carcinogen. By focusing on ribonucleotide reductase (RnR) – a pivotal enzyme in DNA synthesis and in cancer growth – these and other aspects of the disease are demystified. For example, this viewpoint reveals the proximate cause of uncontrolled cell growth: the hyperactivity of RnR, as confirmed by studies of retinoblastoma and HPV-related cervical cancers. This perspective also suggests a way to defeat cancer, as the free-radical – essential for the activity of RnR – can be quenched by a stream of electrons.

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Declarations

Conflicts of interest

The author declares that there are no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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