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Cancer Prevention? Fundamental Genomic Alterations Are Present in Preneoplasia, Including Function of High Frequency Selected Mutations (HFSMs)

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Abstract

In a series of publications a special, tetraploid diplochromosomal division system to only two types of progeny cells (4n/4C/G1 and 2n/4C para-diploid) has been suggested to initiate preneoplasia that can lead to a cancerous pathway. Colorectal and other preneoplasia are known with the pathogenic, histological phases of hyperplasia to arrested adenoma/nevi that can give rise to dysplasia with high risk for cancer development. The present theme is to find solutions to tumorigenic unsolved, biological problems (queries), explainable from the tetraploid 4n-system, which would support its operation in the cancerous pathway. Presently admitted, the mutational sequencing of the cancer genome (cancer chemistry) cannot discover so-called "dark matter", which herein is considered to be the queries. The solutions from the 4n-system were largely supported by mutated APC-induced same type of tetraploidy from the mitotic slippage process. But importantly, these behaviors and consequences could be linked to the beginning of hyperplastic lesions and their development to the arrest-phase of preneoplasia (polyps/nevi). Function of HFSMs is mostly unknown, but for Barrett's esophagus, HFSMs (p53, p16ink4a) caused inactivation of the Rb gene, leading to dysplasia with 4n, aneuploid, abnormal cell cycles. *In vitro* models of the 4n-system from normal human cells recapitulated preneoplasia-like histopathological changes. It was speculated that the "cancer-crucial" step to dysplasia could be therapy-vulnerable to CRISPR-caspase editing, and perhaps antibody treatment. Additionally, the 4n-system with spontaneous cell-behaviors together with preneoplasia molecular data promises construction of a more truthful cancer-paradigm than from sequencing data alone.

Keywords

DNA/Breakage/Repair, Mitotic Slippage, Cohesin, Tetraploid System, Segregation/Orderly,

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1. Introduction

Science reporter Jean Marx [1] interviewed well known cancer research scientists (~16) on how cancer development occurred. The scientists gave many suggestions; they only agreed on the fact that common cancers (colon, breast, and lung) showed colossal amounts of genomic changes. The old-old question of cause or effect from a malignant process was revived. However, the most hotly debated issue was whether there was an underlying, inherited genomic instability mechanism (loss/gain of chromosomes) that caused these changes. Vogelstein said "You may need the instability to ever get to a cancer", which he maintains [2], but the originator mechanism is still unknown (see below). In these early debates mutated APC gene (adenomatous polyposis coli), was not known to cause mechanistic tetraploidy; it was considered a point mutation in sporadic and in inherited colorectal cancers [3], which showed the diagnostic, familiar, histopathological changes from hyperplastic lesions to small benign tumors (polyps/-adenoma). But noteworthy, these latter lesions were arrested in a senescence phase caused by tumor suppressor p53 gene [4]. This sequence of preneoplastic gross pathology was shown in reconstruction of archived, biopsy specimens from several types of tumors, some of them not assessable to such diagnosis e.g., ovarian cancer [5]. The big question however, is how cells escape from the senescence-arrest, which has scanty if any credible information on how such arrested-growth gives rise to dysplasia for progression-start to potential cancer, *i.e.*, tumorigenesis. For example, inherited adenomatous polyposis coli may show adenomas in teenagers, but these do not develop to cancers before patients are 40 to 50 years of age [6], which is inclusive of a rare event in the transition to dysplasia and the regular latency-period. This mysterious puzzle has been thought of in terms of barriers prohibiting progression [7]. But, hitherto the general concept has been: "—that virtually all cancers result from the accumulated mutations in genes that increase the fitness of a tumor cell over that of the cells that surround it—", implying a mutational event for the arrest-escape in adenoma [6], but with other scientists, involving tetra-polyploidy in this rarer process [8] [9]. Tumor sequencing data have not revealed such special mutations, unless the driver mutations are involved, specifically, the HFSMs? But today, there is also the question of whether chromosomal instability can initiate tumorigenesis [10]. This basic view of accumulated mutations, associated with genomic instability, can just as well be happening from tetraploid, diplochromosomal cell division, which would have more likelihood of chromosomal miss-segregations [11] [12]. Importantly, this suggestion does not disqualify mutations (genomic alterations) as the principle event in tumorigenesis. The recent conclusion that the cancerous process is far more complex than originally thought [13] will be challenged with this new paradigm from the 4n mechanistic *system* with orderly cell divisions, mildly "aneuploidal" and, inclusive of spontaneous *cell-behavior* [12] [14] [15].

2. Treatment

2.1. Today's New Proposal to Solve the Cancer Issue

Officially, there is also a new approach to solve the complex cancer problem, which on the NIH list is called: Precision Medicine Initiative (Collins, 2015) [16]. It has two parts, one immediate concentration on cancer therapy and prevention, and later followed by inclusion of various other diseases. The big change is that all diseases will be treated on patient, individual bases for targeted therapy. This program is supposed to revolutionize the US healthcare-system with better treatment- and prevention-methods, plus being a health-cost reduction system. The program has the president's budget-OK and, obviously with great belief of success when the President in his State of the Union Address (2/12/16, "cancer moonshot") refers to this study, and the vice president promises to eliminate "cancer-politics". An interesting part of the cancer "program" is asking for volunteers to give blood samples (later other samples) for genomic sequencing and other genomic, analyses methodologies, supposedly revealing somatic "cancer" mutations attained during life-times. Carriers would get risk calculations for cancer development, and "hopefully" would receive treatment from "matching" new drugs (Science, Mutation issue 2015, 349). Biotech companies are joining for big-data analyses, which they "expect, combined with individual health data will reveal rarer genetic variants that influence disease, and suggest new drug targets—" (Science News, 2016, 352). This "expectation", is it not similar to the rational for the "war" on cancer, which

has lasted 4 decades? And, how is one to interpret that two leading cancer-genome sequencing experts have withdrawn, saying that there was nothing more to gain from continued cancer genome sequencing, which is part of this Initiative [2] [13]? Two advising cancer-gurus proclaimed that cancer prevention is now a "10-year moon shot".

Who wants to know if they are carriers of "genetics" for cancer? This ethical concern was expressed for inherited colon cancer: it can be good for some (non-carriers in a kindred), but anxiety provoking for others [17]. The public, increasingly being informed from various sources with cancer in the high-chair of interest, ought to be detailed informed as to specific use, before volunteering their DNA, the most private self.

2.2. Other Views of the Cancerous Process

Is it or isn't it strange that preneoplasia were not mentioned in this comprehensive revision of cancer prevention and cure-type therapy? But, what is clear, is that initiation of cancer is still assumed to arise from random, somatic mutations, which is said to be an accumulation-process. Is this in a stem or a progenitor cell, or in the latter tissue, where the type of mutation, would determine proliferative advantage (fitness)? Herein, preneoplasia developments are reviewed, and seen as the necessary foundation for start of tumorigenesis (see above), which is the successful cell-escape from senescence arrested preneoplasia. This very rare event, ought to be targeted for prevention, which can become real by accepting the 4n-diplochromosomal-system, as the originator of cancer-diagnostic, histopathological developments, *i.e.*, hyperplasia to dysplasia.

Other skeptical scientists of the mutation theory have settled on other concepts of cancer initiation, one being aneuploidy [18], another is tissue response from disrupted, growth-controlling tissue organization that would liberate G1 cells for multi, clonal proliferation [19] [20]. Injury to tissue structure can be from extrinsic and/or intrinsic causes, the latter, for example, from faulty waste-disposal, producing focal, toxic tissue areas with result of DNA breakage [21], the basic condition for the route to the 4n mechanistic system. But, truly remarkable is: in the absence of carcinogens/mutagens/infectious agents, broken bone-injury in growing points of bones, from falls of young boys, showed linkage to osteosarcoma [12] [22]. Tissue damage with DNA breakage and a repair response (DDR), normally recruit the wound healing programs, which include a phase of tetraploidy with 4-chromatid chromosomes (diplochromosomes) and, it has long been known that the wound healing system can take a cancerous pathway [23] [24]. The frequent presence of such tetraploid cells in plant and animal cells was discussed [25]. Thus, DNA double strand breakage in association with a repair process alone, appears to have tumorigenic potential. Although, DNA-breakage could be mutational, breakage *per cee* has its own pathway for repair, and, it is the fidelity of this pathway which can lead to the diplochromosomal 4n-system (see below).

2.2.1. An *in Vitro* Model System for Induction of Tetraploid Diplochromosomal Initiation of *in Vivo* Preneoplasia-Like Cellular Happenings

Spontaneously occurring diplochromosomal tetraploidy associated with genome damage from telomere attrition was observed in pre-senescence from normal human cells [14] [26] [27]. Accordingly, young normal human cells with normal telomeres, were exposed to a carcinogen-free induction of genomic damage (chromosomal breakage) to test an aberrant telomere-requirement. The cells were exposed to growth medium deficient in amino acid glutamine, previously shown to induce polyploidy [11] [28]. Exposures for 2 - 5 days were followed by 2 - 5 days in recovery, complete medium, and *in situ* chamber slide examination. Generational growth in flask cultures were intermittently also sampled on chamber slides. Chromosomal analyses (no treatments) showed cells with 46 diplochromosomes (4n/8C/M), and their division to only two types of offspring cells: cell cycle arrested 4n/4C/G1 cells, and rarer split(s) in two halves (no segregation) of such telophases to 2n/4C para-diploid cells (para-homozygous?). The unexpected, was immediate hyperplasia-like, morphological growth patterns (streaming growth) from the para-diploid cells, out-growing surrounding normal cells, *i.e.*, gain of a proliferate advantage (GPA) [11]. But most intriguing, was rarer proliferating foci/areas with multilayered (3-D), disoriented cells from cell polarity change, which was reported earlier [29].

Several of these in vitro happenings were almost duplicated from mutation of the APC gene, which interestingly, induced the same type of tetraploidy from the mitotic slippage process [30] [31]. Although, this extraordinary discovery was reported nine years ago, the response from cancer-scientists has not been forthcoming. Is this because tetraploidy and polyploidy cannot be identified by cancer genome sequencing [32], or is it that teaching of "cancer biology" in reality is "cancer chemistry"? One chemical sequencing, educated cancer-scien-

tist discovered that credible cancer research was in re-education in biology, and in cellular pathological happenings in cancer-development [33]. They described origins of cancer stem cells, and a spontaneous, single cell, disposal-mechanism from multinucleated ovarian cancer cells, also observed *in vitro* [34], which truly cannot be described by sequencing data of cancer genomes. The significance of these observations is already apparent in suggested therapy, potentially prohibiting some metastasis [35]. And, biological, cellular behavior is becoming a big issue in metastasis (Science 2016, 352).

2.2.2. The Route to Special Diplochromosomal Tetraploidy through the Mitotic Slippage Process in Early Preneoplasia

Human lung hyperplasia, nevi and other preneoplasia showed DNA-damage repair foci (γH2AX) [36], which when lasting into late G2, the cells went into the mitotic slippage process [37] resulting in 46 diplochromosomal, 4-chromatid structures. Mitosis for late G2 repairing cells is prohibited from disintegration of the mitotic entry proteins cyclin B and cdk1, such that cohesed bichromatid chromosomes ends-up in an S-period. In other words (see above), for DNA breakage and repair, it is not the potential mutations from abnormal repair processes that are the issue for proposed tumorigenic initiation, but the resulting diplochromosomal 4n-*system.* It is a system, because it creates predictive, different, repeatable, cellular happenings, which is rooted in a unique event, special for late G2 breakage-repair that is: during the S-phase of the mitotic slippage process, activation of genome-wide down-load of extra cohesin occurs [38] [39] giving stability to the 4-chromatid chromosomes. This unique situation was found to be evolutionary conserved in mammalian cells [39], pointing to an ancient, inherited system for orderly resolution of DNA-breakage/repair. For example, there are sequential separations of the centromeres: the oldest first with co-segregation of whole complements, then the newly replicated once from slippage-S-phase [12] [14].

Contrary to this stable 4n-system is tetraploidization from spindle poison treatment, which also goes through the mitotic slippage process. However, these 4n-cells are highly unstable with asymmetric chromosomal segregations [40], which has made the poisons questionable in cancer-therapy. This unstable behavior is expected, because there is little or no down-load of extra cohesin in this mitotic slippage S-phase [39]. Therefore, such poison-associated tetraploidy is not a valid comparative methodology to present DNA-breakage/repair (faulty) induced stable mechanistic tetraploidy.

2.3. Some Definitions

Foulds [41] has pointed out that the use of pre-cancer terminology "—can only mean that the lesions are not neoplastic whereas I maintain strongly that they are neoplastic and that this should be recognized in their designation—".

A recent report suggested, *unfounded* that "—a the majority of cancers arise without a histologically discernible premalignant phase, —and that different modes of tumor evolution are operative here—a", chromotripsis was suggested [42], (a pro-sequencing article). However, until otherwise proven, it is assumed that the "majority" of solid tumors are preceded by pathological, benign preneoplasia. One important mutation theory change is the acknowledgement that the cancer-genome may contain "dark matter", not identifiable by sequencing technology [43]. This new sentiment is positive for a cancer paradigm, constructed from both cellular behavior and molecular data of the diplochromosomal system. Evidential material for this 4n-system operating in the cancerous pathway is evident from it being the solutions to certain ongoing, biological queries (dark matters) in cancer observations, as for example, an inverse quantitative relationship between cancer progression and loss of cell adhesion molecules (see below).

2.3.1. Common Queries in Cancer Biological Research—Dark Matters

1) Preneoplasia with an arrest phase (polyps/nevi) from activation of senescence, has no explanation for how cells escape from arrest, and neither how such cells can give rise to dysplasia, which is the high risk growth-condition for solid cancer-developments.

2) From karyology of most solid cancers it has been amply reported that these cells, cycle in the trip-tetraploid range [44], but how this ploidy-level-change occurs has no valid explanation (until recently).

3) "—you may need the (inherited) instability to ever get to a cancer—" (Vogelstein, above), and as pointed out, this happening has no clear causative mechanism, but still is a popular subject [45]. No one however, has

mentioned man's evolutionary conserved inheritance.

4) Expected SAC control to prevent aneuploid cell cycles in tumorigenesis proved not to be correct, neither the search for SAC inactivating mutations, which is a big unexplained phenomenon in cancer research, still very active.

5) How does a normal cell acquire freedom from growth-controlling tissue organization? Cells are tied to each other by a web of adhesion molecules, which for in vitro cells is known as contact inhibition.

2.3.2. Preneoplasia Developmental Course from Hyperplasia to High Cancer Risk Dysplasia, Query # (1)

Two BE patients with matched adenocarcinoma showed from sequencing data 65 and 31mutations in BE, and 78 and 39 mutations, respectively, in the cancers. This demonstrated that the "majority of the mutations"—were already present in "—benign precursor lesions—" [46]. Cellular events in BE and ulcerative colitis preneoplasia both showed accumulation of 4n cells in hyperplastic lesions, preceding cycling of 4n-cells in dysplastic lesions [12] [47]-[50]. These 4n cells with a G2 DNA content, "4N (G2 tetraploidy)", were not in G2, but in G1, cell cycled determined from division of special tetraploidy, 4n/8C/M to 4n/4C/G1 cells [12] [51]. This misconception has led to the belief of a G2 checkpoint in preneoplasia [52].

These early works on hyperplasia risk for change to dysplasia revealed that the HFSMs for BE were p53 and p19ink4a (CDKN2A), which were found to prevent phosphorylation of the Rb protein, rendering it inactive for control of G1 to S-phase entry [53]. The 4n/4C/G1 cells in hyperplasia (above), if cell cycle capable, would need to gain these two mutations in a single 4n/G1 cell. This would be an occurrence with very low probability if at all happening, which is consonant with "years" for adenoma change to proliferative cells. This transition from arrested pre-cancer, is herein advocated to be 4n aneuploid cell cycling, giving rise to dysplastic lesions. This senescence escape-change was referred to as "the origin of tumorigenesis" [54]. Cycling of cells with 3 or more chromosomal copies was considered a form of CIN in lung cancer [55]. For colorectal and breast cancers the HFSMs were APC, p53 and K-RAS, but no function was suggested [56]. However, the HFSM of the PIK3CA gene was ascribed the function of increased kinase activity, affecting PTEN-normal operation [57]. Finally, whole-exome sequencing of BE and its matched adenocarcinoma revealed loss of CDKN2A (p19ink4a) followed by p53 inactivation in early preneoplasia before dysplasia development [58], confirming earlier cellular associated findings.

2.3.3. *In Vitro* Support for Rb Dysfunction in 4n Aneuploid Cell Cycling, Query # (2)

Normal human cells in telomere crisis, and with inactivated p53 and Rb from SV-40 large T antigen, showed endo-re-replication to diplochromosomal cells and tetraploid cell-cycling in the trip/tetraploid chromosomal range [59]. Moreover, inactivation of the Rb gene is a frequent event in cancers, [60] and was sufficient for immediate cycling of quiescent cells [61]. The present paradigm for a tumorigenic initiation, noteworthy, begins with one type of tetraploid cell cycling to hyperplasia, and ends in dysplasia with another type: 4n, aneuploid cell cycles. Importantly, more and more sequencing scientists are admitting to: "—copy number changes—affect a larger fraction of the cancer genome than any other type of alteration does—" [62] [63]. This is well known from "forgotten" karyology studies of early to late tumorigenic lesion-studies [42] [64]-[66].

2.3.4. Inheritance of Special 4n Cell Cycling, Query # (3)

Strangely, cytometry isolation of 4n/8C cells (4n/4C cells are not distinguishable from 2n/4C) from BE hyperplastic lesions, followed by in vitro culturing for "enrichment" showed after some 20 days, a big 4n and a much smaller 2n peak [49]. This unexpected, proliferation of 4n cells has no other explanation than rounds of special 4n/8C/M tetraploidy (diplochromosomes) with equational divisions to 4n/4C/G1 and reductive division to 2n/4C/M cells. But, with the latter cells, "capable" of initiating special tetraploidization from the mitotic slippage process. Barrett and co-workers [49] from oligo-array and FISH studies of upregulated genes in 4n cells in G2 and G1, concluded that their studies showed "—spontaneously arising '4N' cell fractions in the absence of aneuploidy, —in a premalignant tissue—". If this claim of 4n enrichment from culturing of 4n/8C cells is true, it can only mean that the para-diploid (2n/4C/M) cells have inherited "genetics" for change to mechanistic tetraploidy, which was found to be a stable source for mild genomic instability (chromosome loss/gain) [11].

The genesis of the special tetraploid division-system is evident from several cell behavioral peculiarities, which started (spontaneously) with a perpendicular re-orientation of the 4n nucleus relative to the cell's cy-

toskeleton axis before division. The two progeny products became perpendicularly oriented relative to the surrounding normal cells [29]. The unexpected, was that this peculiarity occurs in some extent unicellular organisms, pointing to an evolutionary conserved trait. For example, from the evolutionary record, Raikow [67] wrote: "—chromosomes were not on plate as in regular mitosis, but perpendicular to it—", and D'Amato [68] for plants, saw the segregation as "parallel" as opposed to axial, and emphasized the presence of diplochromosomal cells. The extent unicellular radiolaren *Aulachanta scolymantha*, divided perpendicularly to its own axis, lacked centrioles, co-segregated genomes, and showed actin, myosin and motor proteins presence in the cytoplasm [69]. Fission yeast divide in the absence of a spindle apparatus [70]. Thus, the question is whether there is special "genetics" (a program from several genes?) evolutionary conserved in man's genome for this to happen? The fact that this division system is an abnormal happening in somatic human cells, which only comes alive from DNA breakage and prolonged repair, indicate a primitive ancestry when environmental conditions easily caused genomic damage [15] [39]. Aggressive oral cancers were observed with skewed cytoskeletons relative to the axis, which indicate inheritance of this trait to descended cells from 4n perpendicular division(s) [71] [72]. This tumor fact of all cells with skewed cytoskeletons, not only support suggested activation of a conserved primitive genetics, but "tumorigenesis" (see above) may be vulnerable to CRISPR-caspase editing therapy [73]. This of course, would depend on molecular identification of the special, relic genetics, which for a trial search would be present in GPA-cells in the in vitro model system from normal human cells (see above).

2.3.5. Bypass of Spindle Assembly Checkpoint Control (SAC), Query # (4)

As mentioned nine years ago mutated APC was shown to induce tetraploidization, "—via mitotic slippage with non-separated chromosomes—" [30] [31]. These authors also described that the 4n division proceeded without anaphase anchoring at the cortex, and that centrioles were not present, nor was a functionally, structured spindle apparatus, which is in likeness with the radiolaren division-system [69]. These abnormalities in APC mutated crypt and mice cells led to disoriented cell growth with changed cell polarity axis (cytoskeleton). Coldwell and co-workers [31] measured the degree of altered cell orientations relative to basal cell membrane with normal variation up-to 30˚, and found that cells could show up-to 90˚ orientation-change. Thus, these axial changed cells were preceded by perpendicular orientation of the 4n division system, and as for BE, these authors also reported "—a constant low frequency of change in ploidy is ongoing in dysplastic and tumor tissue—" [31]. These divisions of tetraploid cells in the absence of a spindle apparatus for certain, would not activate a SAC-response. SAC avoidance was also observed for PtK-1 cells, which showed that spindle fibers did not come to a polar-point in meiotic-like division, because of centriole absence [74], and similarly, there is no spindle assembly in genome reductive divisions of mammalian trophoblastic cells, whole complements co-segregate [75].

2.3.6. Consequences of the Perpendicular Division, Query # (5)

The perpendicularly oriented tetraploid nucleus affected cell-to-cell adhesion, known to be gradually reduced in tumorigenesis, which here is shown to be caused by cell-behavior. The 90˚ changed orientation of 4n cell-divisions, led to a mid-zone stretching of the mother-cell, that physically drew the basal and apical regions cell-inward, which tore the mother-cell lose from adhesion molecules. At cytokinesis-stage, the mother-cell was a flattened, oblong structure, and the daughter cells as mentioned for mutated APC, became oriented in a perpendicular orientation relative to the normal surrounding cells [72]. Firstly, these progeny cells had gained freedom from proliferation contact inhibition, and secondly, their cytoskeleton had to be rebuilt [71]. E-cadherin is a major adhesion molecule linked to cell internal catenin, which normally, bridges an attachment to the cytoskeleton. This tri-part structure likely, became destroyed for the progeny cells, and interestingly, in tumorigenesis with example from BE, "—there is an inverse relation between E-cadherin expression and neoplastic progression—" [53]. Moreover, when the nucleus in *Drosophila* brain stem cells were induced to a 90˚ orientation- change, cell proliferation led to cancerous growth: "—to tissue overgrowth and transplantable tumors—" [20]. Maintenance of normal cell-axis-polarity was questioned as to being the gateway to neoplasia. Importantly, this is a highly, meaningful idea regarding present evidential material for an axial cell-change and, it was based on its own referenced literature.

2.3.7. Do Diplochromosomal Tetraploidy Exist *in Vivo*?

Cancer cell cytogenetics by the Therman-school revealed a direct linkage of diplochromosomal cells to tumorigenesis [76]. They observed in lymphocytes from Bloom's patients (BS) chromatid exchanges within the

4-chromatid chromosomal complex. However, the exception was that BS patients, showed excessively high recombination by chiasma counts [77]. The frequencies of chiasmata were in BS 2500/1000 cells compared to normal, 100/1000 cells, which was not understood at that time. Bloom's syndrome has long been considered to be the proto-type, cancer model system, because homozygous individuals are highly prone to cancer-development. The identification of the causative mutation, being dysfunction of a RecQ helicase, (a DNA-strand unwinding enzyme) solved the chiasma-observations [78] [79]. This enzyme caused chromosomal breakage and excessive chromatid exchanges and, slow and aberrant repair processes of the double strand DNA breaks. This latter observation is the recipe for special tetraploidization with extra cohesin-down-load in the mitotic slippage process.

All in all there is operational persistence of the special, mechanistic 4n-system when data are available from preneoplasia. Moreover, these in vivo happenings are supported from in vitro experiments. The predictive behavior and consequences of this system, becomes deterministic for a potential cancer initiation program. This suggestion fits into the idea of cancer being a pre-programmed development [7] [80] [81].

3. Conclusions

The diplochromosomal tetraploid *system* is a formidable challenge to the mutation theory. It is supported from various preneoplastic developmental phases in four different *in vivo*, cancer related conditions, and from non-carcinogenic induction in normal human cells. The best known example, is Bloom's syndrome, long-time acknowledged to be the prototype for tumorigenesis. From this and other preneoplasia, it is clear that identifying tumorigenic driving mutations, and perhaps their functions, is not informational sufficient for a construct of the cancerous pathway. Cell-behavior and consequences have to be considered. For example, an innate cell ability, orients the 4n-diplochromosomal nucleus, perpendicularly relative to the cell's axis before division, leading to progeny freedom from proliferation, inhibiting tissue organization (*in vitro*: loss of contact inhibition). Increasingly now, there are skeptics that question the soundness of a fifth decade with cancer genomic sequencing, in spite of help from constant improvements in technological sophistication from the sequencing-industry. Who is winning, the scientist or the industry? Two rather prominent "sequencing" scientists have withdrawn from this project, but the new "Precision Medicine Initiative", guarantees genomic sequencing for one decade to complete the new cancer moonshot project. Promise?

The rational for attention with analytical action to preneoplasia is: the end product, the complex cancer genome with hundreds to thousands genomic alterations, did not give the desired result, but beginning preneoplasia with significantly less genomic heterogeneity would have considerable better chance of revealing cancer-related, therapy-vulnerable, genomic alterations. The possibilities are that cells with such early genomic/epigenetic changes may have immunological competence, making antibody treatment an early choice besides vaccine probabilities, and as mentioned the growth from the progeny cells of the special tetraploid system might be sensitive to CRISPR-caspase editing. This hopeful out-look, although again theoretic, is on a better platform than the old "war" and perhaps the moonshot idea, because of a known initiating beginning, which can give rise to a testable *in vitro* model system from note, normal human cells. Hesitation against a preneoplasia focus for extended research (molecular and cellular), may come from uncertainties regarding its general occurrence across solid tumor-types. But as for cancer and other diseases, what is "cool" at one time becomes over-shadowed by what is cool today, and presently, genomic catastrophe with chromotripsis is cool. But note, as an originator mechanism, excluding telomere crisis in immortalization (an *in vitro* phenomenon), the evidential material is not there, but preneoplasia is, which is an ongoing, serious warning of a potential cancer development.

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