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Mitotic Slippage Process Concealed Cancer-Sought Chromosome Instability Mechanism (S-CIN)

Kirsten H. Walen

Cromos, Richmond, USA
Email: kwalencromos@gmail.com

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Abstract

Official (NIH) cancer investigation is on identification of inherited cancer genes in you and me for early interventions, and for use of such knowledge in therapy. In this review the emphasis is on the unknown cancer initiation, and on the question of a mechanism for inherited CIN (chromosomal instability). Evidence for fitness increased cells from the mitotic slippage process (*in vivo*/*in vitro*) originated from genome damaged diploid cells in G2/M, skipping mitosis to G1, which illegitimately permitted S-phase re-replication of the chromatid cohesed-2n cells to 4n-tetraploidy. During which, down-load of genome-wide cohesin occurred, producing 4-chromatid diplochromosomes, evolutionary conserved in repair of DNA. This type of 4n cells divided 2-step meiotic-like, leading to diploid aneuploid cells with increased fitness, and expression of gross chromosomal anomalies in proliferation. The diploid cohesed chromatids during re-replication would hinder replication of sticky heterochromatic regions, resulting in their under-replication, and known from *Drosophila*. The human chromosomes are longitudinally differentiated into satellite DNA regions, folic acid sensitive sites and the primary constriction (centromere); they are breakage sensitive regions and being heterochromatic. This strongly suggests, multiple, chromosomal regional under-replication-cites, translated to origin of slippage, S-CIN, a genome inherited destabilization mechanism. Logically, S-CIN would affect genes differentially depending on chromosome location, for example, the high frequency in cancers of mutated p53 on the small 17p-arm, which with centromere breakage would be preferentially lost in mitosis. This likely S-CIN mechanism in cancer evolution can be studied *in vivo* for APC mutated crypt cells with demonstrated mitotic slippage process.

Keywords

Biorhythm, Microscopy, Reversible Poly-Tetraploidy, Fitness Increase,

Inherited Cin, Under-Replication, Cancer Genes, Tumor Relapse,
Cancer Predisposition, DNA Damage/Repair, Aneuploid Diploidy

1. Introduction

The advantages/odds of eradicating cancer are the highest for knowledge of how cancer can arise: *i.e.*, cellular mechanism(s) that can give rise to number one hallmark of cancer: fitness increased genome-changed cells [1]. Descriptive knowledge of such biological happenings from abnormal cytology/cytogenetics has been the base for vaccine approaches (immunologically). But, a new development is a molecular approach to identify colon cancer mutations in pre-cancer adenoma, and how such data can be used in vaccine development [2] [3] [4].

Cancers arising from normal human somatic cells is a very rare event, considering that there are billions of cells in an adult body, but the appearance is that cancer is rising in frequency, because more individuals are "hit" by a cancerous-event [5]. Epidemiologically, does this mean that something in the external/endogenous environment that was not there 3 - 4 generations ago then can induce a cancerous response? This question has been linked to modern, fast-track life-styles, which often refer to lack of exercise, obesity and poor diets. In the "old days" exercise came naturally in the course of day to day living, and diets then were as now in expensive stores: "organic home-made". Unfortunately, this issue is deeply divided as to nutritious and non-nutritious food and also fraught with politics [6] [7]. In our *smart lives* today, with work at our fingertips, freezers full of ready packed dinners, and shelfs stacked by rainbow colored bottles, there is little or no incentive to change the *status quo*. But, only you are in charge of your own health, and a saying is "you are what you eat", which with other criteria should promote regularities in biorhythm (KW) Thus, the aim in *living*, should include not to get cancer.

The cancerous process, mostly un-curable, were proposed to happen by multiple, accumulating mutations (MT) [8] [9] in a normal body cell, despite the fact that the mutation rate for such cells is exceedingly low. To accommodate this fact, a changed MT-theory proposed initiation by a mechanism of chromosomal instability (CIN) with the special feature of being inherited [10]. There is also the suggestion of a mutator phenotype (semantics?), causal of cancer (different from microsatellite instability) [11]. The goal/aim for this review is to evaluate the "old" and recent literature in cancer research for a paradigm consistent with the CIN-inherited theory, passing the mechanism to offspring cells, capable of leading to "transformed" cells. It should be recognized that any unveiled genomic/CIN mechanism may have attached cellular behavioral consequences, which rather recently was called "dark matter" for genomic sequencing identification [12] [13]. However, such cell responses, to some degree revealed by microscopy (KW) [14], has also more recently been revealed by improvements in sequencing technology, showing chromosome and molecular anoma-

lies (indels) as "copy number alterations across human cancers" (CNAs) [15]. Interestingly, these different types of CNAs were shown to enter into therapy decisions [16] [17].

Presently, the core principle for a paradigm different from "simple" MT, but inclusive of CIN inheritance, is "difficult" repair of DNA double strand breakage (DSBs), and how such a process can lead to genome and chromosomal CIN, derived from polyploid cells reversing to mildly, unstable, aneuploid, diploid CIN cells, an evolutionary conserved process. The origin of this thesis is based on a series of *in vitro* experiments from observations associated with natural telomere "breakage" and carcinogen-free, induced chromosomal breakage with a visual response of induced tetra- and endo-polyploid cells [18]-[27]. These polyploid cells mechanistically, underwent genome reductive divisions, culminating in fitness increase (KW) of near-diploid human cells, as mentioned, a first required hallmark for tumorigenesis [1]. Thus, the purpose of this review is to bring into tumorigenesis, cellular consequences of reversible polyploidization (KW) in the context of current "cancer" thinking-and-doings in the search for novel, cancer therapy targets.

2. Current "Official" Cancer Research

Several cancer investigators have brought-up the question of whether the MT merits the central role in cancer-research today, we see, as suggested (above) that together with an early gained mechanism for inherited CIN, indeed, a cancerous process is possible. But, decades of molecular sequence analyses of cancer genomes and other investigations have neither shown expected mutation commonality among cancers nor the suggested inherited CIN mechanism (KW). There has however, been revealed so-called cancer genes (KW), occurring with higher frequencies than "passenger" mutations, and are supposed to drive cancer evolution [28], but they are functionally in "the dark". The enormous sequencing project uncovering such mutations, was more or less led by two sequencing pioneers that recently withdrew from "more of the same". Vogelstein claimed that nothing more to gain from continued cancer mutational sequencing. And Weinberg said that the complexity of cancer development lacked a viable paradigm [13] [29].

From this latter happening many scientists expected an "official" (NIH) policy-change regarding genome sequencing analyses, and it came, but with a shift from cancer-type sequencing to you and me. We are now the targets for findings of inherited cancer genes (germline) by sequencing of voluntary blood samples in a project called Precision Medicine Initiative (see NIH meeting 6/24, 2015) [30] [31]. In this new cancer theory, man is predisposed to cancer (KW)from inheritance of cancer genes, and positive individuals will be given a probability score, put together from mutation-type and medical record, meaning, high or low chance of cancer. The identification of such cancer genes are expected to be used in development of new cancer-targeting drugs. Moreover, previously used cancer cell lines in cancer research will be replaced by a thousand newly estab-

lished models from fresh tumor-types, because the old cell lines (HeLa, etc.) have acquired "laboratory mutations". (Such happenings occur quickly, largely depended on "the out-of-incubator" handlings, Walen, unpubl). Then, should the old "contaminated" cancer-information be disregarded? Furthermore, the Initiative policy becomes an ethical issue, discussed earlier for hereditary colon cancer: there would be relief for some, but anguish for others [32], translated to: who wants to know? There are also needed extra genomic sequencing and data analyses for success of the Initiative [33] [34] [35] [36]. Vogelstein [13] remarked that the probability of a cancerous event is much higher from carcinogen exposure than from predisposition. These reconstructions leave questions of mechanism(s), showing reversible polyploidy in tumor relapse (KW), obtained from live biopsies, not cell lines [37] [38] [39].

But much more complex research, in the name of cancer and other bad diseases, is already in the making, from construction of the complete human genome from scratch, the nucleotides (The Genome Project-Write) [35]. This is an outcome from the concluded "Human Genome Sequencing Project"—Encode [40]. Encode concluded that in man's genome there were 21,000 protein-coding genes, but that 98.8% of a cell's DNA was non-coding and "unexplored". They also reported that only 4% of the non-coding DNA showed: "signs of having experienced strong natural selection", the rest they called "baggage being dragged along". But, one suggestion was that during evolution, mutations caused inactivation of genes, meaning inability to code for proteins, and became "effectively dead". They called these genes "pseudo-genes", and estimated that there are 10,000 to 20,000 such "pieces" of DNA. If true, it might be a bonanza for evolutionary information, and perhaps, reveal present core principle of an awaking of tumorigenic evolutionary conserved "dead genetics".

The key issue is access to these "dark" DNA regions, which apparently is being developed from CRISPER technology [41] [42]. But the sure enormity of such unveiling will most likely be a multi-generational project. Perhaps, it is not surprising that cynicism over any cancer-solution is growing, murmuring that the economic wealth of the gigantic industrial world, surrounding "cancer", has its own momentum that keeps the cancer-issue alive (too big to fail?). But worse, seems to be cancer (sequencing) scientists unwillingness to assess whether mutational search "is still relevant", closing the gap between "data-collection" and clinical application [43].

3. Genomic Damage and Repair

Since access to pseudo-genes in the human genome is not possible, another way would be to compare cancer related cellular happenings to primitive unicellular haploid/diploid organisms' dealings with "life" in stressed environments. Especially, for DNA damage (KW) in an ancient volatile environment, there was evolved survival-associated repair mechanism(s) consummate with "life" existence [44]. Evolutionists have drawn attention to primitive organisms' use of genomic doubling in DNA-recombination repair [45] [46] [47], which at con-

clusion, would have had to genome-reduce back to constitutional, vegetative reproductive, genomic condition. Following meiotic development from mitosis [48], there would still be need for such an ancient system, because of vegetative reproduction, and that meiotic reproduction most often, was/is relegated to specific environmental conditions [49] [50]. Cancer cell proliferation is a form of vegetative reproduction, and by some considered to be a development to cancer genome speciation with "genetic cohesiveness" [11] [51] [52] [53]. This latter feature has been "dramatically" shown by automated, computer-assisted 3D karyotype analyses, revealing cancer clones having specific, "stable" karyotypic phenotypes, others showing "on-going" instability [54] [55]. Although, this genetic cancer-trend was previously obtained by labor-intensive karyotyping [56] [57], the 3D *image* of average 30 cells' karyotypes has brain "cognitive" effect (see last paragraph). And the message is that rate of genome instability may have quiet periods in mature cancers, somewhat at odds with a recent evaluation of "genomic instability in cancer" [58].

However, more pertinent to present cancer-thesis is a provocative discussion of phylogeny, population genetics, environmental stress-survival, cancer species development, and the basic involvement throughout cancer evolution of the "life" fundamental genes, Wnt and Notch [11] [59]. Vincent [11] concluded that anti-life "essential genes" [60] might have to be "drugged" in cancer therapy, because of revolving "bursts" of speciation. And, related to present theses, he sees cancer initiation from some type of mutator phenotype: "conceivably as a retained or revealed characteristic from early life forms".

Speciations in phylogeny (systematics) are organisms having evolutionary reached sexual isolation. Cancer cells are not sexual, and the species-label is a concept of "quasi" stable karyotypic clones operating in a system's biology concept in mature cancers, contrary to earlier thinking of single mutational effect [61]. The quasi genomic stability is not, however, characteristic of early beginnings of tumorigenesis, which require CIN/mutator mechanism(s) for on-going selectable aneuploidy that von Hansemann saw as increasing cancer-cell "independent existence" [62].

Genomic damage "then" and now, in a repair process, today visualized from stained $^{\gamma}$H2AX foci [63] in pre-neoplasia (before p53 inactivation), can have many causes, for example, naturally aging "broken" telomeres, tissue reactive oxygen species causing genomic damage, genotoxic lesion associated with phagocytic "garbage-bags" not properly discarded in tissues [64], and surprisingly, from injury of bone breaks in *growing* bone tips, which could be linked to osteosarcoma [27]. Furthermore, all life's molecule, DNA, is not a stable molecule [65]. It undergoes significant, replication-associated faulty base-pairings, and interestingly, nucleotide and base excision repair leave normal cells with mutations without a neoplastic phenotype [66]. There are several mechanisms for repair of DNA damage [67], which could have differential cellular effects. The most primitive mechanism most likely being homologous recombination [47], but cancer therapy-associated "sick cells" invoking a repair process can show

endo-polyploidization avoiding apoptosis and senescence [68]. And, the wound healing structured programs can also show tetraploidization (KW) and occasional related cancer-development [26] [27] [69]. In Barrett's esophagus from acid reflux disease causing areas of damaged epithelial cells and like-wise in ulcerative colitis, bacteria caused cell damage, the preneoplasias showed tetraploid-dization with division to 4n/4C/G1 accumulating cells, most peculiar [70] [71]. A suggested step for gain of S-phase entry of these cells is their gain of p53 and p16ink4a mutations plus in-activation of Rb (frequently negatively affected in cancers), which would lead to trip-tetraploid cell cycling, a feature observed for both diseases [14].

In primitive time, tolerated, incomplete DNA-repair for unicellular organisms was suggested to be a source for mutational genome evolution [72] [73]. But, normal human cells having "difficult" DNA-repair processes, starting in S-phase of the cell cycle with continuation into late G2, was associated with abnormal cell cycle events. The prepared mitotic program degenerated (Cyclin B & Cdk-1), and the G2 cells did not divide, they entered G1, which is the process of mitotic slippage [74] [75]. Remarkably, these G2 cells (chromosomes) in G1 entered S-phase, and re-replicated to 46 four-chromatid, diplochromosome tetraploidy. These special chromosomes were observed in near-senescence telomere "damage" associated growth [18] [19] [76] [77] (**Table 1**).

Table 1. Sequence of events in cell cycle mitotic slippage process from genome damaged cells.

Cells	Cell Cycle Phase	REFS
1. 2n/2c	Double strand DNA breakage in S-phase	44, 63, 67, 68, 74, 75
2. 2n/4c	Prolonged repair into late G2 gap	67, 74, 75
3. 2n/4c	No mitosis: No Cyclin B2 and kinase Cdk-1	74, 75
4. 2n/4c	Entry into G1 with cohesed chromatids	current idea
5. 2n/4c	Illegal entry into S-period: re-replication with cohesin download	74, 75, 76, 77, 83, 84, 85, 86, 87
6. 4n/8c	43 diplochromosomes in G2: under-replicated sticky heterochromatic chromosome regions causing inherited slippage chromosome instability (S-CIN)	88, 90, current idea, 89, 91
7. 4n/8c	Primitive two-step meiotic-like division	11, 19, 22, 23, 46, 47
8. Progenies	tetraploid 4n/4C/G1 and fission division of 4n/4C to aneuploid diploid cells with gained fitness	22, 92, 93
9. Chromosome instability (CIN) in cancers		8, 9, 10, 15, 17, 58

Comment: Tetraploid 4n/4C/G1 arrested cells are selection accumulated in pre-neoplasia [14] [70] [71]. Cohesin download and sticky heterochromatic chromosome regions lead to under-replicated chromosomal "cites", causing destabilization (breakage) of the genome [22] [87] [88] [89].

The importance of a genomic doubling in the DNA-repair process (G2 cells to tetraploidy) is reflected in an evolutionary conserved, genome-wide download of cohesin, which would occur during slippage re-replication [78] [79]. For eukaryote repair-associated genomic doubling [47], the extra cohesin would greatly, facilitate chromatid-closeness for recombination-efficient repair, which would have selective value in the evolutionary tree. Timely expression of enzymatic

"release" from four-chromatid cohesed structures (separase) was observed as a two-step orderly, meiotic-like division system with resolution of the oldest cohesed centromeres first to 4n/4C/G1 cells, and infrequent telophase fission-division of these, to near-diploid cells, having gained fitness increase [22] [23]. In the establishment of female and male marsupial cell lines (PtK-1&2), their gained fitness compared to normal cells, was shown to be from a time-wise shorter cell cycle, shown by that times popular technique of tritiated thymidine autoradiography [80] [81]. Later PtK1 cells were shown to have inherited the capacity of producing tetraploid cells that underwent "meiotic-like", genome reduction to aneuploid, diploidy (KW) [82].

As mentioned in the title, a (slippage) S-CIN mechanism is concealed in the mitotic slippage process. This mechanism is a result from two suggested events: 1) the G2 (chromosomes) in interphase cells entered S-period with cohesed chromatids and centromeres, and 2) being in a DSB-repair process, has been shown to "trigger" genome-wide download of cohesin during replication [78] [83] [84], here meaning re-replication. These crucial events are supported by diplochromosome structure, which showed non-random, tritiated thymidine labelling of the 4 chromatids (an old unanswered observation), suggested at that time, to be caused by sticky heterochromatic centromere regions [85] [86]. Glued together heterochromatic regions from stickiness [87] would prevent access of helicase for re-replication and consequently such regions would be *under-replicated* (KW). But most interestingly, in a more recent discussion of "one hit wonders of genomic instability" [88], one such "wonder" was suggested to be under-replication, leading to "heritable genome destabilization", mentioned, to be lacking in paradigms of the cancerous process. This report being theoretical, also emphasized genomic damage as a first "hit" with DNA under-replication-consequences. The fitness-gained aneuploid, diploid cells showed centromere-associated abnormal rosette figures, laggards in divisions as chromosome loss, centromere breakage to arms and dysmorphology of centromere region, bent or stretched, clearly observed for acrocentric chromosomes [22].

The Therman-school of cytogenetics/cytology in the book "Human Chromosomes" [89] dedicates a whole chapter on "Longitudinal differentiation of eukaryotic chromosomes" with structural and behavioral effects in mitosis. Examples in the human genome of chromosomal regions different from unique, gene-rich regions were the nucleotide repetitive satellite hetero-chromatic regions with late replication and out of phase condensation. Additionally, chromosomes have folic acid sensitive sites, believed to correspond to structural gaps prone to breakage. Therman and college refer to numerous discoveries of heterochromatic stickiness, associated with satellite DNA. It's also a well-known feature of repetitive DNA for short telomeres with rearrangements and dicentric bridges in anaphase [90].

Interestingly, support for the present S-CIN mechanism with likely differential chromosomal affects (breakage) is from early adenoma studies in colorectal tumorigenesis [91]. This study produced a genetic model for tumorigenesis from

early chromosomal occurring abnormalities in hyperplastic/dysplastic (mild) growth in adenomas. The hyperplastic growth showed certain gene mutations that occurred more frequently than others, and note, from centromere and regional chromosomal breakage. Interestingly, p53 a tumor suppressor gene, on chromosome #17p was not mutated/lost in the adenomas, but was mutated in carcinomas. Furthermore, specific chromosomal arms (1q, 4p, 6p, 8p, 9q and 22q) showed regional breakage-loss. These events are here interpreted to be from chromosomal "sites" being under-replicated and prone to breakage, and the high frequency of mutated p53 in cancers in general, can be explained by a "bad" location on 17p. From under-replication of the #17 centromere region with breakage the p-arm would be lost more frequently than the q-arm, because of smaller size. The authors [91] suggested for the absence of p53 mutation in adenomas that the initiating mechanism for fitness increase over normal cells, not being depended on tumor suppressor loss, as assumed today. For this suggestion at that time, another more recent discovered suppressor gene could well be the solution. In the adenoma studies, CIN mechanisms for their observations were suggested to act "dominantly at the cellular level", which can also be said for S-CIN.

But very surprising to this author was the realization that the suggested mitotic slippage-tetraploid division-system for reversible tetraploidy, had been documented ten years earlier for *in vivo* APC (adenomatous polyposis coli) mutant, colon crypt cells, which not only, was associated with a hyperplasia, but that the further growth led to dysplasia and malignancy [92] [93]. These data in short, completely verified the *in vitro* experimental sequence of events, including new cell growth with loss/change of cell polarity with observation of βcatenin move to the nucleus [24] [92]. Aggressive oral cancer cells showed skewed cytoskeletons relative to the cell-axis, which is indicative of a needed re-building [94]. Loss/change of cell polarity is by some considered to be critical in early installation of tumorigenesis [95] [96] [97].

4. The Mutator Phenotype

An interesting fact is that normal cells display significant presence of mutations without a preneoplastic phenotype [66], which supposedly originate from repair-associated break induced replication (BIR) [65] [98]. These events are far from accurate; producing micro duplications, deletions, inversions and translocations documented in cancer cells [65], and has become likely occurrences in chromothripsis [99]. The sudden bursts of such micro events, fit the concept of "bursts in cancer speciation" [11], and are increasingly being identified: breast cancer showing multiple chromothripsis occurrences [100]. But, there is also non-cancer-associated BIR happenings, identified in germ-lines, giving rise to inherited disease conditions [101], which has probability of being a mutational process in normal cells [66]. To these events an "yesterday" article from Vogelstein' group on the etiology of cancer, showed calculated correlation data from "all things considered", with the conclusion that replicative mutations were re-

sponsible, and that two thirds of the cancers could be avoided [102]. Adding S-CIN caused gross chromosomal changes to replication and BIR-type nucleotide changes (indels), the route in potential carcinogenesis to malignancy becomes similar to observed cancer-cell revealed molecular and gross chromosomal "disarrays", also called chaos [15] [16] [17] [58]. Furthermore importantly, tumorigenesis with operating S-CIN can renew itself whenever, accidental genomic damage goes into a prolonged repair process causing repetition of the mitotic slippage process. This is supported by observation of diplochromosomal cells in cancer cytogenetics ([103], fig. 2H). This sudden renewal might initiate "bursts" in genomic instability, feeding the mechanism(s) for genomic restructure [11] [99] [104]. But to remember, these "bad" cell occurrences in probable etiology of cancer can largely be avoided (Introduction) [102].

5. Conclusions

The conclusion is that cancer development can indeed be a complex process. Herein, old and current cancer-related observations have been brought into cancer "thinking and doing", and where current "official" research is in relationship to prevention and therapy. In contrast however, is the present emphasis on cancer initiation that supposedly is the best information for prevention of cancer? *In vitro* genome damage of *normal* diploid human cells with repair ongoing in a hostile environment, were found to be associated with a survival system, the mitotic slippage process, that led through special chromosomal tetraploidization to genome changed aneuploid, fitness increased, diploid cells. These observations were supported from similar cellular events *in vivo* from APC mutated colon crypt cells. The slippage process for genome damage repairing cells showed four features, rarely mentioned if at all: 1) illegitimate passage of diploid G2/M cells into S-phase for re-replication to 4n diplochromosomes, 2) genome-wide download of cohesin during re-replication, 3) orderly meiotic-like reduction-division to the aneuploid, fitness increased diploid cells, and 4) as a result of cohesed chromatids of the G2 cells during re-replication, sticky heterochromatic chromosome regions, scattered longitudinally over the human chromosomes , became under-replicated. These structurally weaker regions were breakage prone, and would be an inherited trait for slippage-induced S-CIN. The aneuploid diploid cells showed gross chromosomal segregation anomalies with loss/gain of chromosomes and breakage to arms. This S-CIN is a major "missing link" in the cancerous process to malignancy. Predictably, from locations of under-replicated regions and of genes, certain genes would be mutational more affected than others as for example p53. The location on the small #17p-arm with centromere-breakage would be preferentially mitotic-lost. Importantly, this S-CIN mechanism can be addressed *in vivo* for APC mutated colon crypt cells with demonstrated mitotic slippage process.

Now, the challenge is, to put the observed, various, sequential cellular events in the mitotic slippage process into molecular signaling networks that can reveal cancer druggable targets (KW). The very latest in such decision making is rec-

ognition of visualization, which apparently, trigger a cognitive brain response. Visualization is increasingly a demand for job applicants in cancer biology (see Science). This very interesting approach, might on the cell level, promise a come-back of simple microscopy, giving "life" to current test-tubes. What goes around comes around: "a picture speaks a thousand words", which may lead to surprising decisions in cancer therapy.

Note: Having encountered re-replication to diplochromosomes in 1965, this author has a significant library (data-base) of complete reprints of "possible" related facts/ideas, used herein for older references. More recent ones were obtained from Science, colleges and Google based, Pub Med Central.

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