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Review

Genomic instability in human cancer: Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition

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ABSTRACT

Genomic instability can initiate cancer, augment progression, and influence the overall prognosis of the affected patient. Genomic instability arises from many different pathways, such as telomere damage, centrosome amplification, epigenetic modifications, and DNA damage from endogenous and exogenous sources, and can be perpetuating, or limiting, through the induction of mutations or aneuploidy, both enabling and catastrophic. Many cancer treatments induce DNA damage to impair cell division on a

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global scale but it is accepted that personalized treatments, those that are tailored to the particular patient and type of cancer, must also be developed. In this review, we detail the mechanisms from which genomic instability arises and can lead to cancer, as well as treatments and measures that prevent genomic instability or take advantage of the cellular defects caused by genomic instability. In particular, we identify and discuss five priority targets against genomic instability: (1) prevention of DNA damage; (2) enhancement of DNA repair; (3) targeting deficient DNA repair; (4) impairing centrosome clustering; and, (5) inhibition of telomerase activity. Moreover, we highlight vitamin D and B, selenium, carotenoids, PARP inhibitors, resveratrol, and isothiocyanates as priority approaches against genomic instability. The prioritized target sites and approaches were cross validated to identify potential synergistic effects on a number of important areas of cancer biology.

1. Cellular mechanisms that prevent or promote genomic instability

Genomic instability plays critical roles in both cancer initiation and progression. This instability can manifest itself genetically on several different levels, ranging from simple deoxyribonucleic acid (DNA) sequence changes to structural and numerical abnormalities at the chromosomal level. This section will briefly outline the mechanisms that maintain the stability of nuclear and mitochondrial DNA and how these mechanisms may become corrupted in cancer cells.

1.1. Telomeres foster chromosomal stability and can inhibit or promote malignant transformation

The chromosome stabilizing role of intact telomeres was recognized as early as the 1930s from independent research by McClintock [1] and Muller [2] and more recent work has further strengthened the connection between telomere dysfunction and chromosomal instability (CIN) [3,4]. Telomeres, which are located at the ends of each chromosome, consist of approximately 5–10 kbp of specialized, tandem repeat, noncoding DNA complexed with a variety of telomere associated proteins [5,6]. These elements create a protective cap that prevents the recognition of the chromosomal termini as DNA double strand breaks (DSBs) and their consequent aberrant repair via nonhomologous end joining (NHEJ) or homologous recombination (HR) [7–10]. Due to the inability of DNA polymerase to fully replicate the ends of linear DNA molecules, in the absence of compensatory mechanisms, telomeric DNA is lost at the rate of approximately 100 base pairs (bp) per telomere per cell division [11–17]. In normal somatic cells, this telomere erosion is used by the cell to monitor its division history, with moderate telomere shortening triggering either irreversible cell cycle arrest, termed replicative senescence, or apoptosis [18–21]. This block to continued proliferation is thought to have evolved to prevent the development of cancer in long-lived organisms by restricting the uncontrolled outgrowth of transformed cell clones, and also by preventing further telomere erosion which would accompany such abnormal growth and eventually destabilize the telomeres leading to CIN [13,22].

A current popular model for the involvement of telomere shortening in carcinogenesis posits that increasing numbers of cells experience telomere shortening as a person ages, which increases the pool size of cells that are in danger of experiencing eventual telomere dysfunction and prooncogenic CIN. In the vast majority of such cells, the senescence and apoptotic blocks are strictly enforced [23–28]. However, this process eventually fails in rare cells which continue to replicate and eventually experience CIN due to critical telomere shortening [15,29–37]. Notably, such cells may be more tolerant of rampant genomic instability due to their previous abrogation of the tumor suppressive telomere length checkpoints. However, if left unchecked, this instability will eventually reach lethal levels in the transforming cells, thereby presenting a second block to the development of cancer [37–40]. This escalating telomere driven CIN creates a strong selective pressure for telomere maintenance in incipient cancer cell populations; a problem that is solved in one of two ways: activation of telomerase or alternative lengthening of telomeres (ALT). In the majority of human cancers, the telomere specific reverse transcriptase telomerase, which is stringently repressed in normal somatic cells, is activated, thereby restabilizing the telomeres, although cancer telomeres on average seem to remain very short [32,41–45]. Whereas most cancers use telomerase to maintain telomere length, a significant minority of cancers (typically non-carcinomas) utilize ALT, a telomerase independent, homologous recombination based mechanism [46–48]. This mode of telomere maintenance results in extreme telomere length heterogeneity and, interestingly, better patient survival compared to their telomerase positive counterparts in several tumor types [49–52]. These observations suggest that cancer cells utilizing ALT may have compromised their vitality in exchange for the unlimited replicative potential conferred by this telomere maintenance mechanism.

1.2. Centrosomes, the spindle assembly checkpoint, and tumorigenesis

The centrosome is the primary microtubule organizing center in dividing mammalian cells and is composed of a pair of centrioles surrounded by a cloud of proteins that promote microtubule nucleation [53,54]. The centrosome is duplicated in a semiconservative fashion with one daughter centriole formed next to a preexisting mother centriole, and this process only occurs once in every cell cycle [53,55]. Centrosome amplification, the presence of greater than two centrosomes during mitosis, is a common characteristic of most solid and hematological tumors that may induce multipolar mitoses, chromosome missegregation, and subsequent genetic imbalances that promote tumorigenesis [54,56].

Centrosome amplification may be caused by diverse mechanisms, including centrosome overduplication [53,57–59], de novo assembly, [60–62] and mitotic failure downstream from mono- [63] or multipolar division [64–69]. The end result of these structural abnormalities is often cytokinesis failure, which can give rise to tetraploid binucleated cells and genome instability downstream. Over time, the net result is a small population of cells that harbor the ability to manage extra centrosomes, which could account for the accumulation of cancer cells with centrosome amplification and aneuploidy.

Catastrophic aneuploidy and nonviable daughter cells are a possible tumor suppressive consequence for centrosome abnormalities [70]. However, cancer cells have developed mechanisms that overcome this fate by clustering multiple centrosomes into a “pseudobipolar” state [59,70–72]. Cancer cells may utilize this mechanism to dampen high level aneuploidy and extreme CIN, leading to better prognostic outcomes [73,74]. Centrosome