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A Review on Malignant Transformation

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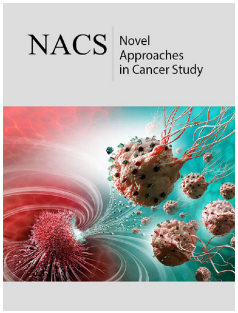

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Abstract

Multiple genetic alterations must accumulate within a cell in order for it to become malignant throughout the development and growth of a tumour. One must identify as many of the genetic changes that occur during cancer development in order to comprehend the biology that underlies the disease. Our current understanding of the chromosomal basis of cancer was built on that chromosome aberrations play a crucial role in the malignant transformation of a normal cell. Numerous genomic tools, the transcriptional activity of protein-coding genes is regulated by these tiny non-coding RNA molecules in mammals. When present in amounts above a particular threshold, the heavy metals cadmium, arsenic, and nickel are all cancer-causing.

Keywords: Malignant transformation; Genetic; Chromosome; Genomics transformation; Heavy metals

Introduction

Malignant transformation is the process by which cancerous characteristics are acquired by cells. This might happen either directly as a primary process in healthy tissue or indirectly as the malignant degeneration of an earlier benign tumour.

Primary malignant transformation, often known as tumorigenesis, has a wide range of reasons. The majority of human malignancies in the United States are brought on by outside sources, most of which can be avoided [1-3]. These components were assembled by Doll & Peto [1] in 1981and represent prevalent underlying causes of cancer symptoms.

Mutations

Cancers are caused by genetic mutations acquired either by inheritance or somatic DNA over time [4]. These mutations alter protein coding genes (exome) and confer no selective growth advantage. Cancers also have genome instability, with an average number of DNA sequence mutations in the entire genome of breast cancer tissue of 20,000 [5] and 80,000 in an average melanoma [6].

Epigenetic alterations

Transcription silencing: Cancers have a higher frequency of epigenetic transcription silencing (caused by promoter hypermethylation of CpG islands) than mutations [7]. In colon tumours, there are 600 to 800 heavily methylated CpG islands in promoters of genes, which fully silence gene expression, just as a mutation would [7]. In addition, the promoters of several hundred genes are hypomethylated (under-methylated), which makes these genes active when they should be inactive [8].

Post-transcriptional silencing: MicroRNAs (miRNAs) are also involved in epigenetic modifications. The transcriptional activity of protein-coding genes is regulated by these tiny non-coding RNA molecules in mammals to a degree of about 60% [9]. In cancer cells, abnormal DNA methylation of the promoter regions governing miRNA genes' expression results in their epigenetic suppression or overexpression [10-12]. In breast cancer cells, it was discovered that about one-third of the miRNA promoters active in healthy mammary cells

were hypermethylated, while other microRNA promoters were hypomethylated [13-14]. BRCA1 is generally produced in breast and other tissue cells, where it aids in the repair of broken DNA or, in the event that DNA repair is not possible, the destruction of cells [15-16].

Only 3-8% of all breast cancer patients have a BRCA1 or BRCA2 mutation. The majority of high grade, ductal breast tumours exhibit diminished or undetectable BRCA1 expression [17]. Additionally, BRCA1 is inhibited by miR-182, miR-146a, and/or miR-146b-5p, whose overexpression renders BRCA1 inactive [18]. The target mRNA is either translated into silence or degraded as a result of complementary binding to specific sequences in the target gene's three primary untranslated regions. This process is known as post-transcriptional regulation by microRNA [19]. The RNA-Induced Silencing Complex (RISC) implements the mechanism of target mRNA degradation or translational silencing.

DNA repair gene silencing: The RNA-Induced Silencing Complex (RISC) implements the mechanism of target mRNA degradation or translational silencing. Cancers of the colon, head and neck, stomach, prostate, breast, thyroid, non-Hodgkin lymphoma, chondrosarcoma, and osteosarcoma all have WRN hypermethylation, which ranges from 11% to 38%.

Similar to a germ-line mutation in a DNA repair gene, such silence probably predisposes the cell and any offspring to developing cancer [20]. Another review [21] notes that DNA repair is likely to be insufficient and DNA damage can build up when a gene required for DNA repair is epigenetically silenced. Increased DNA damage can result in more mistakes being made during DNA synthesis, which can result in cancer-causing mutations.

Induced by heavy metals

When present in amounts above a particular threshold, the heavy metals cadmium, arsenic, and nickel are all cancer-causing [22]. It is well known that cadmium causes cancer, presumably through slowing down DNA repair. Five DNA repair genes were examined in rats by Lei et al. [23] after the rats were exposed to low amounts of cadmium. They discovered that three DNA repair genes-XRCC1, OGG1, and ERCC1-necessary for base excision repair, nucleotide excision repair, and nucleoside excision repair-were repressed by cadmium. The methylation of these genes' promoters did not cause their repression.

Bhattacharjee et al. [24] reviewed the carcinogenicity of arsenic. They provided an overview of how arsenic and its metabolites contribute to oxidative stress and DNA damage. Arsenic not only damages DNA, but it also suppresses a number of DNA repair enzymes in the base excision repair route as well as the nucleotide excision repair pathway. Further reviews of the involvement of arsenic in telomere dysfunction, mitotic arrest, faulty apoptosis, changed promoter methylation, and altered miRNA expression were provided by Bhattacharjee et al. Each of these modifications may have a role in the development of cancer caused by arsenic.

Because nickel compounds are cancer-causing, occupational exposure to nickel is linked to a higher risk of developing lung and nasal malignancies [25]. Nickel compounds have only modest mutagenesis potential, but they significantly change the transcriptional landscape of exposed people's DNA [26]. Eight employees of a nickel refinery and ten non-exposed employees' peripheral blood mononuclear cells were studied by Arita et al. [27]. With 770 up-regulated genes and 1986 down-regulated genes, they discovered 2756 genes that were differentially expressed [28]. DNA repair genes were repressed in nickel refinery workers, whereas two were over expressed. DNA repair genes were significantly overrepresented among the differentially expressed genes. The changes in gene expression seem to be caused by histone epigenetic modifications, methylation of gene promoters, and at least hypermethylation of microRNA miR-152 [24-28].

Clinical signs

Malignant transformation of cells in a benign tumour may be detected by pathologic examination of tissues. Often the clinical signs and symptoms are suggestive of a malignant tumor. The physician, during the medical history examination, can find that there have been changes in size or patient sensation and, upon direct examination, that there has been a change in the lesion itself.

Risk evaluations are possible and well-known for specific benign tumour forms that are known to change into malignant tumours. One of the better-known examples of this phenomenon is the progression of a nevus to melanoma.

Conclusion

Tumour formation requires numerous genetic changes within cells for malignant growth. Understanding the biology behind cancer requires identifying these genetic alterations. Chromosome abnormalities are crucial in malignant transformation, and chromosomal basis of cancer is based on these abnormalities. In mammals, RNA molecules control protein-coding gene transcription through genomic tools. Heavy metals like Cadmium, arsenic, and nickel can cause cancer when present above a specific threshold.

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