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Poly Comb Group Proteins A Dual Player in Ageing and Cancer

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Introduction

Maintenance of health at middle age is more important to have a longer disease free life. Every human stem cells are exposed continuously to several genotoxic stimuli from younger age, which are repaired by DNA repair process using DNA polymerase δ1, at some point during ageing, the ability to repair the damage was exhausted followed by instability in genome, causing cancer in elderly. This confirms the association of longevity to repair process. Ageing is a common factor, which occurs due to the damage in the macromolecule, organelle, cells, tissues and it is not a disease. Ageing is a key risk factor in the development of cancer among 60% of the people. Most of the mutations leading to cancer are linked with ageing. Ageing process weakens mitochondrial functions, creating more ROS and cause mutations in DNA of nuclear and mitochondria, improper DNA repair process, loss of replication leading to defective or oxidized protein synthesis and cancer. Altered functional enzymes linked with the activation of carcinogens make aged tissues more accessible to the effect of carcinogens that reside in the cell for a long time. The ageing and cancer are linked through the effect of endogenous stress (ROS) on DNA. The telomere shortening that takes place with each cell division makes the cell to enter in to a senescence stage, thereby cell cycle arrest, a normal process that is essential for tumor suppression. There are also reports of shorter telomere and telomere malfunction as well as more senescence cells accumulation formed by irreversible arrest of cell growth during ageing offers conducive tissue environment that enhances tumor promotion. Usual telomere loss is balanced by telomerase, which adds telomeric repeats per cell division but stem cells lack telomerase to do its function and hence more chromosomal damage via telomere. Short telomeres increase the risk of breast cancer [1]. Senesence cells also fuel pre malignant keratinocytes, epithelial cells (mammary gland) to malignant. Thus senescence is playing a dual role. In young age, it is a normal mechanism helps to survive against cancer but in older age, the same is tumorigenic. Genetic modification like point mutation, DNA hypermethylation and chromosomal translocation prepares ageing tissues toward tumor [2-6].

Poly Comb Group Pproteins

DNA methylation takes place through an enzyme DNA methyl transferase in order to add methyl groups to cytosine residues which are placed next to guanine. In human being, almost 90% of CpG sites are methylated and the balance 10% is nonmethylated CpG sites are grouped as island, situated in the promoter region towards 5' end. Changed methylation occurs in cancer cells DNA through hypo and hypermethylation at promoter region of CpG Island. Increased cytosine methylation of tumor suppressor gene causes natural deamination and thymine synthesis, followed by point mutation and uncontrolled cell proliferation. Many tumor suppressor genes contain CpG repeats as islands in their promoter region, which is normally unmethylated but its methylation lead to downstream gene transcription failure, enhancing gene silencing. These epigenetic changes in hematopoietic stem cells are regulated by polycomb group proteins that determine the functions of normal and cancer stem cells. The fate of the cell before birth until death was decided by cell fate transcription factors (Hox, Sox, Pax, Fox, Gata etc.). More than thirty abnormal/altered transcription factors are required for tissue specific cancer growth. So, they form a main regulatory role in attaching and detaching poly comb group proteins to specific target gene [7]. These proteins bind to their respective domain in the promoter region of genes for effective repression to takes place or silencing. In order to maintain its suppressor function at the time of cell division, poly comb group proteins binds to chromatin, DNA throughout the process of DNA replication, such binding have an effect on availability of DNA strand for transcription and its subsequent altered translation. Because DNA packaging in to the chromatin structure is a key factor for gene accessibility for its transcription and regulation. Poly comb group proteins are first discovered in Drosophila, regulating the Hox gene expression starting from flies to human beings [8,9]. These polycomb proteins are

essential for the maintenance of identity in a cell by chromatin preservation [10,11]. As well as to maintain a balance between hematopoietic stem cell aging and cancer growth because any interruption in poly comb group proteins will affect cellular process like fate, senescence, DNA repair and apoptosis. In hematopoietic cancer this protein was misregulated. Mutant embryos of mammals lacking polycomb group proteins are committed to death during implantation stage [12-14]. Nearly 3-4% of genes regulated by polycomb group protein are transcription factors and target genes in embryonic stem cells are prone to be hypermethylated 12 times in aged somatic cells [15]. According to studies, 50% genes are hypermethylated in colon, prostate cancers are premarked by poly comb proteins. Poly comb protein BMI 1 (Poly combring finger protein 4 or 51) is a subunit of polycomb repressive complex1 (PRC1) encoded by gene BMI 1, control the differentiation of stem cells. PRC 1 includes Bmi-1, Me118, cb, mph, ring. BMI1 regulate senescence and proliferation by regulating cell cycle inhibitor genes such as p16 and p19, essential to hold the self renewing capacity of stem cells, in case of any modification in the cell cycle inhibitor genes, it permit BMI1 to transform normal stem cells into cancerous (oncogenic) and also it inhibits neuronal ageing via p53 suppression [16]. BMI 1 was altered in few cancers like squamous cell bladder, leukemia, brain and thus marker for cancer [17-20]. Its loss leads to defective DNA repair system. Various processes such as oncogene activation, DNA damage, telomere shortening stimulate the onset of cellular senescence are delayed by BIM1, CBX7, CBX8 (polycombgroup proteins) in fibroblast embryo of mouse and human [21] by reducing p16 and p14 levels. All senescence cells are active metabolically and alive but the ability to divide is lost so as to prevent the growth of damaged cells. Proliferation of cancer, normal cells is altered via an interaction between polycomb group proteins and cyclin dependent kinases. CDKN2A and 2B encoding three cellular senescence inducers (p14, p15, p 16) were repressed by BMI 1. Another polycomb group protein is Mel 18. Increased expression of Melanoma nuclear protein 18 (a tumor suppressor protein) was found in cancer of medulla, melanoma, hodgin lymphoma [22-24]. Polycomb repressive complex 2 (PCR2), begins silencing via (H3K27) histone H3 Lisine-27 methylation, enclosing Ezh2, Suz12, Eed [25,26]. H3K27 methylation engage PRC1 binding to chromatin for stable gene silencing [27,28]. PCR2 also functions by interacting with long non coding RNA (HOTAIR) and aid enzymes of histone modification that bind DNA/RNA to engage polycombgroup proteins to its gene of specific target.

Conclusion

This review depicts the relationship between ageing and cancer and role of poly comb group proteins. In tissues at young age, the growth factors, inhibitory signals prevent tumor cell proliferation but during old age, accumulated senescence cells synthesize enzymes of disruptive nature, altered growth factors, cytokines that destroy tissue structure creating a conducive for cancer development. But, the exact mechanism linking these two factors has to be dealt a lot and require in depth research. It is obvious, that genes of poly comb group protein targets are more silenced through DNA methylation and also poly comb group proteins have dual role in senescence, gene silencing, ageing and cancer.

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