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Review

Epigenetic Regulation of Telomere Maintenance for Therapeutic Interventions in Gliomas

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Abstract: High-grade astrocytoma of WHO grade 4 termed glioblastoma multiforme (GBM) is a common human brain tumor with poor patient outcome. Astrocytoma demonstrates two known telomere maintenance mechanisms (TMMs) based on telomerase activity (TA) and on alternative lengthening of telomeres (ALT). ALT is associated with lower tumor grades and better outcome. In contrast to ALT, regulation of TA in tumors by direct mutation and epigenetic activation of the hTERT promoter is well established. Here, we summarize the genetic background of TMMs in non-malignant cells and in cancer, in addition to clinical and pathological features of gliomas. Furthermore, we present new evidence for epigenetic mechanisms (EMs) involved in regulation of ALT and TA with special emphasis on human diffuse gliomas as potential therapeutic drug targets. We discuss the role of TMM associated telomeric chromatin factors such as DNA and histone modifying enzymes and non-coding RNAs including microRNAs and long telomeric TERRA transcripts.

Keywords: telomere maintenance; high grade glioma; epigenetic therapy; CpG DNA methylation; chromatin modification; histone methylation and acetylation; histone deacetylase; miRNA; telomeric repeat-containing RNA

1. Introduction

Genetic information and the pattern in which genes are expressed are both important for properties of cells. Human cell types show broad diversity and specialization although, in a given person, cells share identical genetic information. Gene expression patterns important for cell phenotype and function need to be both adaptable and heritable. Adaptability allows that specialized cell types and functions such as telomere maintenance mechanisms (TMMs) arise from common cell precursors in response to specific signals from the environment, whereas heritability ensures that the integrity of cell type lineages can be maintained through cell divisions. Adaptable gene expression patterns are often responses to stimulation and based on non-genetic determinants that are summarized as epigenetic mechanisms (EMs) with fundamental implications for cancer especially in combination with heritable mutations [1,2]. These EMs currently include covalent modification of DNA, covalent modification of histones, non-protein-coding RNAs (ncRNAs) such as short microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Genetic mutations that target epigenetic modifiers of EMs probably cause genome-wide epigenetic alteration in cancer (reviewed in [2]).

EMs are important for providing the proper regulation of telomerase activity (TA) in several biological states, such as embryonic down-regulation of the limiting factor hTERT contributing to aging and upregulation of hTERT to gain immortality in most cancers [3]. Moreover, EMs form condensed heterochromatin structures at telomeres and subtelomeres densely compacted by repressive
DNA methylation and histone modifications [4]. Differential abundance of epigenetic modifications at