Chapter VI:

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Short Communication

A comparative study on regulation of HLA-G expression in bad obstetric history and in head and neck squamous cell carcinoma from Northeast India

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ABSTRACT

The expression of immunomodulatory molecule HLA-G is tissue restricted with abundant expression in placenta, mediating immune tolerance to fetus. Tumors hijack HLA-G to establish nutrient supply and evade host immune response. 14 base pair Insertion/Deletion polymorphism (rs371194629) and + 3142 G/C SNP (rs1063320) of 3′UTR of HLA-G were investigated in conjunction with miR-148A, miR-152 and HLA-G expression in SAB (Spontaneous abortion) history placenta and HNSCC tumor in a hospital-based case control study. Higher frequency of G allele of rs1063320 was seen in study participants as reported in other global populations. Both miR-148A and miR-152 were downregulated in tumor tissue. Predominance of 14 base pair "IN" allele of rs371194629 was noted in SAB placental tissue ($p =<0.0001$) with lower expression of HLA-G levels. In conclusion, 14 base pair Insertion/Deletion in linkage with + 3142 G/C SNP was related to lower HLA-G protein expression in SAB tissue, contradictorily HLA-G protein level was manipulated by tumors by suppressing microRNAs.

1. Introduction

The nonclassical major histocompatibility (MHC) class Ib HLA-G is an immunomodulatory molecule with distinct structure and function, first reported at the maternal-fetal interface [1]. Studies have subsequently reported the expression of HLA-G in immune-privileged tissues such as pancreas, cornea and thymus [2]. Optimal HLA-G expression in the feto-maternal surface favors successful pregnancy as it confers maternofetal immunotolerance and has a role in establishing proangiogenic microenvironment [1,2]. Recently HLA-G expression has been reported in different tumors where it exhibits exemplary role as an immune checkpoint molecule [3]. HLA-G binds to inhibitory receptors expressed on the surface of T cells, NK cells, and B cells thereby promoting a tolerogenic loop for placentation as well as tumor growth [2,3]. The polymorphisms at 5′ upstream regulatory region (URR) [4] along with methylation of CpG islands of HLA-G promoter 5 is involved in transcript level expression regulation of the HLA-G gene while the 3′ untranslated region (UTR) regulates its post-transcriptional expression [4,6]. A unique 14 base pair insertion/deletion (IN / DEL) polymorphism (rs371194629) at position + 2960 of exon 8 is associated with differential expression of HLA-G. 14 bp IN removes 92 base pair sequences from mature mRNA, affects transcript stability, suppresses translation of HLA-G and is associated with low HLA-G levels. DEL allele is related to more stable mRNA and higher HLA-G expression [7].

The + 3142C > G SNP (rs1063320) at 3′UTR of HLA-G provides a binding site for microRNAs such as *miR-148a*, *miR-148b*, and *miR-152*. These microRNAs bind to mutant "G" allele at 3'UTR with strong

Abbreviations: BOH, bad obstetrics history; SABm, spontaneous abortion; HNSCC, Head and Neck Squamous Cell Carcinoma; HLA, human leukocyte antigen; miRNA, MicroRNA; IN/DEL, Insertion/Deletion; UTR, untranslated region; PE, Pre-eclampsia; RSAB, recurrent spontaneous abortion.

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Chapter

Genomic Instability and DNA Repair in Cancer

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Abstract

Mutations in genome are essential for evolution but if the frequency of mutation increases it can evince to be detrimental, for a steady maintenance there exist a detailed complex system of surveillance and repair of DNA defects. Therefore, fault in DNA repair processes raises the probability of genomic instability and cancer in organisms. Genome instability encompasses various aspects of mutations from indels to various somatic variants. The chapter tries to present an overview of how cancer puts up several ways to ensure suppression of the fidelity in our DNA repair system. Cancer cells assure failure of efficient DNA repair mechanisms by innumerous ways, by mutation and epigenetic modifications in repair genes themselves or genes controlling their expression and functions, other by some catastrophic events like kataegis, chromothripsis and chromoplexy. These are clustered mutations taking place at a particular genomic locus which deluge the repair process. Cancer generation and evolution is dependent largely on genome instability, so it applies many strategies to overcome one of its basic obstacles that is DNA repair, targeting these DNA repair genes has also demonstrated to be helpful in cancer therapy; but an intricate understanding of recalcitrant process and mechanisms of drug resistant in cancer will further enhance the potential in them.

Keywords: genome instability, DNA repair, cancer, epigenetic modifications, clustered mutation

1. Introduction

Genome is the basis of life of an organism and mutation in genome is essential for adaptation [1]. A mutation is a change in genomic sequence, they are the result of mistakes a cell makes while copying a piece of genome during replication or sometimes mutation is influenced by exogenous agents. Mutations have the capacity to influence gene expression depending on their location in the genome, gene structure and intergenic region. They possess this power to affect with such consequences because mutation in coding region of the genome might give rise to a truncated protein with no use or might compromise its fidelity. Alternatively, it can also endow the protein with some advantages with its function. Their presence in the regulatory region may increase or decrease its expression. This change in level of expression also affects cellular mechanisms since proteins are required by the cell in specific amounts. Therefore, these changes give either an advantage or a disadvantage depending on the effect it may produce but with a higher rate of mutation cell loses