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REVIEW ARTICLE

CO-EXPRESSION AND REGULATION OF P53 AND MUC1 IN HUMAN CARCINOMAS

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ABSTRACT

Mucin 1 (MUC1) is polymorphic transmembrane protein containing large extra cellular domain with variable number of highly conserved tandem repeats, aberrantly over expressed in most human carcinomas. Tumor suppressor protein, p53 is highly conserved, expressed in normal tissues and integrity of p53 function is essential for the maintenance of the non-tumorogenic phenotype of cells. Thus, p53 plays a vital role in suppressing the development of cancer. Tumor suppressor activity of p53 is reported by growth arrest of cells, DNA repair, senescence, differentiation or by apoptosis. It is reported that MUC1 promotes the arrest of growth to DNA damage by p53 dependent mechanism. The expression and regulation of p53 and MUC1 could be useful markers for metastatic potential tool for human carcinomas including breast and colorectal carcinomas.

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INTRODUCTION

Mucin 1 (MUC1) is an integral membrane glycoprotein contains an extracellular domain consisting of a variable number of highly conserved tandem repeats (each tandem repeats contains 20 amino acids) (Gendler *et al*., 1990; Lan *et al*., 1990). It is reported that MUC1 expression is up-regulated in most of the carcinomas including colorectal cancers and breast cancers (Nakamori *et al*., 1994; McGuckin 1995 *et al*., 1995). It is found that, MUC1 with aberrant glycosylation, expressed on the surface of different carcinomas (Lavrsen *et al*., 2013) and aberrantly glycosylated is reported in almost 90% of human breast carcinomas. As a process of neoplastic transformation and loss of epithelial cell polarity, MUC1 gene product enters into the bloodstream. Generally circulating MUC1 concentration are measured by Cancer antigen 15-3 (CA15-3) assay. CA15-3, a product of MUC1 gene, is well known diagnostic and prognostic biomarker of breast cancer and utilized to monitor the response to therapy with the stages of breast cancer (Lauro *et al*., 1999; Ebeling *et al*., 2002; Kumpulainen *et al*., 2002; Uehara *et al*., 2008). The MUC1 amino terminal subunit (MUC1-N) contains variable numbers of tandem repeats that are heavily modified with O-linked glycans. The MUC1 carboxyl-terminal subunit (MUC1-C) contains a 58–amino acid extracellular domain, a 28–amino acid transmembrane domain, and a 72–amino acid cytoplasmic tail (Gendler *et al*., 1988; Merlo *et al*., 1989). It is reported that overexpressed MUC1-C is sufficient to induce transformation along with resistance to apoptosis induced by stress (Yin *et al*., 2004; Raina *et al*., 2006).

Tumor protein p53 or transformation-related protein 53 (TRP53) is involves in the regulation of cell cycle and hence functions as a tumor suppression protein. The integrated form of p53 is very important for cells in multicellular organisms to suppress cancer (Surget *et al*., 2013). Different mechanism have been involved for anticancer property of p53 including role in apoptosis, genomic stability and inhibition of developmental process of blood cells (Aylon and Oren, 2011). In this study we demonstrate the function of MUC1 with p53 regulation in human carcinomas.

MUC1 aberrant Glycosylation and it's products

Mucin1 (MUC1) is a large glycoprotein contains 1255 amino acid (Accession # P15941) with theoretical protein molecular weight 122 kDa without any post translational modification. MUC1 have 3 domains includes extracellular topological domain containing 1-1161 amino acid residues, transmembrane region containing 1162-1179 amino acid residues and a cytoplasmic topological domain containing 1180-1255 amino acid residues (Parry *et al*., 2001).

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The best characterized MUC1 gene product are MUC1/REP, MUC1/SEC and MUC1/Y. MUC1/REP contains large extracellular domain, primarily consist of 20 amino acid tandem repeats, transmembrane domain and cytosolic tail of 72 amino acid. MUC1/SEC has an extracellular domain identical to MUC1/REP but it is devoid of hydrophobic region. MUC1/Y is a transmembrane protein that contains transmembrane and cytoplasmic domain as identical to MUC1/REP but devoid of tandem repeat and its flanking region (Obermair *et al*., 2002; Baruch *et al*., 1999; Oosterkamp *et al*., 1997; Kufe, 2013).

Antibody against recombinant MUC1/Y is reported to detect section of breast cancer tissue, suggested using this antibody for the diagnosis of breast cancer with CA 15-3 (Gupta *et al*., Jan-2015). Polymorphic epithelial mucin (PEM), a product of MUC1 gene is expressed on the surface of epithelial cells. In breast carcinoma condition, PEM is aberrantly glycosylated and found distinct antigenic property as compared to normal mammary epithelial cells (Girling *et al*., 1989; Burchel and Taplor-Papadirnitriou, 1993). The aberrant glycosylation of MUC1 products is also found in several types of carcinomas (Desmetz *et al*., 2009; Kufe, 2009).

P53 mutations

Human gene TP53 is responsible for encoding p53 transcription factor and mutations in TP53 gene is reported in almost every type of cancer (Peller and Rotter, 2003; Petitjean *et al*., 2007). In most of the human cancer, the TP53 gene is often found to undergo missense mutations, so a full-length protein may contain only a single amino acid substitution and most of the mutations result in loss of p53's ability to bind DNA to activate transcription of p53 target genes (Hainaut and Hollstein, 2000; Bullock and Fersht, 2001). It is reported that, mutations in TP53 are distributed in all coding exons of the TP53 gene, with predominantly found in exons 4 to 9, which is responsible for encoding of DNA-binding domain of the protein and it is frequent in most of the cancer (Cho *et al*., 1994).

It is reported that, mutations in TP53 causes, loss of function of p53 and it is able to actively promote tumor development by several way. In a heterozygous situation, both wild and mutant alleles exist. Mutant p53 can reverse the wild p53 tumor suppressor functions (Milner *et al*., 1991; Milner and Medcalf, 1991; Sigal and Rotter, 2000). It is reported that mutation of p53 occurred in late stages of cancer as in case of breast cancer (Olivier *et al*., 2006) and hepato-cellular carcinoma (Cohen and DeRose, 1994; Oda *et al*., 1992).

P53 and Programed cell death

Different studies demonstrated that p53 induces apoptosis by both transcription-dependent and transcription-independent mechanisms (Caelles *et al*., 1994; Wagner *et al*., 1994; Yan *et al*., 1997; Gao and Tsuchida, 1999). In transcription dependent apoptosis, p53 target genes PUMA and NOXA having specific importance in apoptosis process. It is reported that hematopoietic progenitor cells (thymocytes) from the developing nervous system from PUMA knockout mice are approximately fully impaired for p53-dependent apoptosis to a levels equivalent to p53 knockout mouse, but partially impaired in other cell types of PUMA knockout mouse (Jeffers *et al*., 2003; Michalak *et al*., 2008).

It is reported that, p53 mutant containing only the first 214 amino acid residues induces apoptosis and suppresses the transformation of rat embryo fibroblasts by several oncogenes, but it does not induce trans activation of p53 target genes (Chen *et al*., 1996; Haupt *et al*., 1997). The addition of recombinant p53 to nuclear-free cytosolic extract of irradiated cells leads to the release of cytochrome C, activation of caspase (cysteine-aspartic proteases) and induce apoptosis. That means p53 can directly activate apoptotic machinery which involves translocation of p53 to the mitochondria (Ding *et al*., 1998; Schuler *et al*., 2000).

Mechanism of regulation of p53 by MUC1

MUC1 cytoplasmic domain directly interacts with p53 and this interaction is proportional with response to DNA damage. MUC1 is also detectable with p53 on promoters of the p53-responsive p21 and Bax genes. The cytoplasmic tail of MUC1 is function as site for direct interaction with the p53 regulatory domain (Wei *et al*., 2005). p21 is functions as a regulator of cell cycle progression at G1 and phase which inhibits the activity of cyclin-CDK1, CDK2, and -CDK4/6 complexes (Gartel and Radhakrishnan, 2005). Bax gene is function as apoptotic activator and expression of this gene is regulated by the p53 and shown to be involved in p53-mediated apoptosis (Miyashita *et al*., 1994). The interaction of MUC1 and p53 co-activates the transcription of p21 in response to DNA damage or genotypic stress (Wei *et al*., 2005; Barlev *et al*., 2001; Liu *et al*., 2003; Mujtaba *et al*., 2004).

It was found that MUC1 possession of the p53-responsive element in the Bax promoter is very limited or no binding to Bax promoter in cells by p53 is lesser as compared to p21 promoter in response to genotypic stress or DNA damage (Kaeser and Iggo, 2002).

MUC1 and expression of p53 in breast cancer

In breast cancer, p53 is one of the most common mutated gene and its expression in nucleus is associate with tumor progression at early stage and it reduce survival rate of patents (Moll *et al*., 1992). Immunohistochemical analysis for P53, MDM-2 and MUC-1 shows that tumors that is over expressing p53 did not expressing MUC-1 which had a significantly shorter median time to progression (TTP) and median overall survival (OS). These result suggested that expression of p53 and MUC-1 may be act as good marker and may represent novel therapeutic targets in such patients (Resetkova *et al*., 2004).

Human MCF-7 and ZR-75-1 breast cancer cells infected with a retrovirus expressing a MUC1 is RNA. Immuno-blot analysis showed that silencing MUC1 was associated with increases in p53 as compared with that in wild type cells. Immunoblotting analysis of purified nuclear and cytosolic fractions from the MCF-7 and ZR-75-1 cells also showed that the silencing of

MUC1 was associated with increased expression of p53 expression in the cytoplasm and nucleus. These results and analysis of p53 mRNA levels indicate that MUC1 down-regulates p53, at least in part, by transcriptional mechanism (Wei *et al*., 2007).

MUC1 and expression of p53 in colorectal cancer

The over expression of p53 and MUC1 in colorectal cancers is reported in very few reports (Matsuda *et al*., 2000). Up regulation of MUC1 (Zotter *et al*., 1987) and over expression of p53 (Yamaguchi *et al*., 1992) is seen in colorectal cancer. Immuno staining analysis of colorectal carcinoma tumor section shows that the frequency of MUC1 positivity was proportional to depth of tumor invasion, hepatic involvement and found more frequently in Dukes C, D as compared to Dukes A, B. But there is no correlation found for p53 frequency with depth of tumor invasion and Dukes stages or hepatic involvement (Matsuda *et al*., 2000).

Immunohistochemical analysis of expression of MUC1, p53 along with MUC2 shows that co-expression of MUC1 and p53 were associated with higher frequency of lymph node metastasis with more positivity of MUC1 with right colon. These results suggested that co-expression of MUC1 with p53 are involved in regional lymph node metastatic and could be useful markers for metastatic potential in colorectal carcinomas (Jang *et al*., 2002).

MUC1 and p53 in multiple myeloma

Multiple myeloma is a cancer of plasma cell in which abnormal plasma cells collected in bone marrow and interfere with normal blood cell production. In this condition, abnormal plasma cells travel form tumor to several bones caused bone lesions and hypercalcemia (Chiriva-Internati *et al*., 2008). MUC1 is heterodimer protein expressed in multiple myeloma patients (Takahashi *et al*., 1994). MUC1-C terminal subunit (MUC1-C) is found in cytoplasm of multiple myeloma patients and it is targeted to nucleus (Li *et al*., 2003). In myeloma cells, silencing of MUC1-C, slowing the proliferation of cells along with enhanced sensitivity to programmed cell death and expression of MUC1-C is linked with the activation of NF-κBRelA and Wnt/β-catenin pathways (Kawano *et al*., 2008).

It is found that multiple myeloma cells is sensitive to reactive oxygen species (ROS) oxidative stress and MUC1-C terminal subunit (MUC1-C) protects myeloma cells from ROS and oxidative stress hence interfere with treatment with agents responsible for increases in reactive oxygen species (ROS) and oxidative stress-induced cell death (Yin *et al*., 2004). The treatment of multiple myeloma with GO-203, a MUC1C inhibitor, is associated with increase in reactive oxygen species (ROS) along with substantial down-regulation of the p53-induced glycolysis and apoptosis regulator. It is also found that inhibition of MUC1-C inhibition in multiple myeloma cells is associated with depletion of NADPH and GSH, which is responsible for the initiation of apoptosis/necrosis in response to oxidative stress (Yin *et al*., 2012).

MUC1 and p53 in pancreatic cancer

Pancreatic ductal adenocarcinoma is reported as fourth leading cause of death by any cancer and it is characterized by very aggressive growth with early development of metastases (Jemal *et al*., 2010; Ellenrieder *et al*., 1999). Met, a receptor tyrosine kinase that regulates cell growth, invasion, and cell survival. A ligand of Met, Hepatocyte growth factor (HGF) stimulates phosphorylation process at different residues of Met. Overexpression of Met causes carcinogenesis effects and has been reported in different carcinomas, including pancreatic adenocarcinoma (Galimi *et al*., 1993, Gao *et al*., 2005; Di Renzo *et al*., 1995).

MUC1 cytoplasmic tail (MUC1CT) is having multiple threonine, tyrosine and serine amino acid residues which are reported to phosphorylate in response to variable condition of cell surface by stimulation induced by cytokines and growth factors (Singh and Hollingsworth, 2006).

In pancreatic cancer cells, the Met receptor tyrosine kinase interacts with Mucin 1 (MUC1) followed by induction of phosphorylation of the MUC1CT in response to stimulation by hepatocyte growth factor (HGF). It is reported that MUC1 over-expression in pancreatic adenocarcinoma cells down-regulate Met-mediated signaling and inhibits the invasion and motility. Stimulation of hepatocyte growth factor enabled interaction of MUC1CT with p53 along with p53-mediated suppression of transcriptional activity of activator protein 1 (AP1) and reduce the expression of the Matrix metalloproteinase-1 (MMP1). So in Pancreatic cancer, Met-mediated phosphorylation of MUC1 modulates signaling related to motility and invasion (Singh *et al*., 2008).

Concluding remarks

The Mucin 1 (MUC1) is transmembrane glycoprotein, over-expressed with aberrantly glycosylation in different human malignancies. MUC1 is positioned at the cell membrane as a complex of N-terminal (composed of 20 AA tandem repeats) and C-terminal subunits. Tandem repeats, expressed in mammalian cells mimic native CA15-3 suggested to use recombinant protein for the diagnosis of breast cancer (Gupta *et al*., July-2015). MUC1 C-terminal domain (MUC1-CT) is a part of MUC1 includes a 58 AA extracellular domain with 72 AA cytoplasmic domain (Merlo *et al*., 1989). It is reported that phosphorylation of MUC1CT by Met enhanced its interaction with p53 which is responsible for tumor formation and metastasis in several carcinoma, including pancreatic adenocarcinoma (Gao *et al*., 2005; Di Renzo *et al*., 1995; Singh and Hollingsworth, 2006; Singh *et al*., 2008; Corsoe *et al*., 2005).

Integrity of p53 is required for the non-tumorogenic phenotype of cells and tumor suppressor functions of p53 in response to stress inducing growth arrest, apoptosis, DNA repair. MDM2 is reported to inhibits and degrade the p53 hence tumor suppression function of p53 (Levine, 1997; Momand *et al*., 1992; Oliner *et al*., 1992). Mutation of the MUC1-C cytoplasmic domain at 60^{th} position (Y60F) activates ARF gene transcription and stabilization of p53 indicated that MUC1 suppresses activation of the ARF-MDM2-p53 pathway (Raina *et al*., 2008). Up-regulation of MUC1 with high expression of p53 is reported in colorectal carcinoma whereas MUC1 down regulate p53 in breast cancer. These all studies

suggested that co-expression and regulation of p53 and MUC1 play a crucial role in carcinogenesis and could be useful markers for some malignancies.

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