Review Article

Genomic instability in obesity-associated colon cancer

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Abstract: Epidemiological studies have demonstrated the association between obesity and colon cancer. Many studies using animal models have also confirmed that obesity increases colon cancer incidence. Multiple cancer risk factors in obesity have been identified, which can activate multiple signalling pathways to promote cell proliferation and decrease apoptosis. The mechanisms for obesity-associated colon cancer, however, are not fully elucidated. In this review, the possible roles of genomic instability in obesity-associated colon cancer are summarized. It is known that genomic instability is critical for the carcinogenesis of colon cancer. Recent studies have provided convincing evidence that obesity can increase genomic instability. Therefore, it is highly possible that genomic instability has an important role in obesity-associated colon cancer. Particularly, the activation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen activated protein kinases (MAPK) signalling pathways in obesity may mediate genomic instability in obesity-associated colon cancer.

Keywords: DNA repair; cell cycle; phosphoinositide 3-kinase/protein kinase B (PI3K/Akt); mitogen activated protein kinases (MAPK); telomere

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Introduction

Colon cancer is caused by various genetic and environmental factors. The most common genetic defects include *APC*, *TP53*, *KRAS*, beta-catenin, *PIK3CA* and *BRAF* mutations (1). Environmental factors include red meat, high-energy diet, alcohol, HPV infection and obesity. As obesity is increasing worldwide and accounts for a large proportion of the population, its role in cancer has been investigated. However, how it is incorporated into the previously proposed carcinogenesis model for colon cancer is still not well understood. A well-known model proposed previously for the carcinogenesis of colon cancer assumed that *APC* mutation is the initial factor followed by *KRAS* and *TP53* mutations (2,3). *APC* is mutated in 95% of familial adenomatous polyposis (FAP) (4). *APC* mutation is also found in 34-70% of sporadic colon cancer. Several studies showed that *APC* is highly mutated in colon cancer cell lines (5-7). However, a recent study showed that the most mutated genes in colon cancer cells are *TP53*, *KRAS*, *PIK3CA* and *BRAF* (8). Therefore, *APC* model can only explain part of colon cancer cases. Models for the carcinogenesis of other colon cancer cases are needed.

Epidemiological studies showed that obesity not only increases colon cancer incidence (9-11) but also is an independent factor for colon cancer survival (12). This has been confirmed by studies in animal models. The common animal models for obesity-associated colon cancer include leptin deficiency, leptin receptor deficiency and high-fat diet feeding. Studies showed that obesity increased colon cancer incidence in these models (13-15). Although gene knockout model of obesity by leptin deficiency has been used, high-fat diet-induced obesity is more similar to that in humans. The animal models have also been employed for the studies to elucidate the mechanisms of obesity-associated colon cancer.

The mechanisms for obesity-associated colon cancer have been studied extensively. Many cancer-risk factors in obesity have been identified such as insulin, IGF-1, leptin, adiponectin, Interleukine(IL)-6, IL-17, TNF-alpha and vascular endothelial growth factor (VEGF) (16-18). Many more cancer-risk factors have been identified, revealing the complex nature of obesity-associated cancer. For example, adipokines visfatin, omentin-1, and vaspin have also been shown to have effects on increased cancer incidence in obese people (19). These factors are known to cause cancer via activation of multiple signalling pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen activated protein kinases (MAPK) pathways (20-22). The mechanisms for the involvement of obesity in colon cancer are not fully elucidated. In this review we hypothesise that genomic instability may be of importance and summarize the relevant evidence particularly the involvement of the PI3K/Akt and MAPK in genomic instability. Genomic instability is one of the major hallmarks of cancer as described by Hanahan and Weinberg (23). The important role of genomic instability in obesity-associated colon cancer is suggested by the fact that genomic instability is increased in obesity and has been recognised as a key step in the carcinogenesis of colon cancer. Genomic instability can facilitate accumulation of multiple mutations necessary for carcinogenesis of various cancers. HPV-caused cancer and HBV-associated HCC have been associated with genomic instability (24-26). Chemical carcinogens and radiation have also been associated with genomic instability (27,28).

Genomic instability as a hallmark of colon cancer

Genomic instability refers to decreased ability of the cells to maintain DNA sequences (29). As replicating DNA in fidelity is necessary for normal physiological activities, genomic instability can lead to many diseases including cancer. Several systems have been employed to maintain genomic stability including cell cycle check points, DNA repair system and cell death (30). The checkpoint proteins can detect damaged DNA and slow down cell cycle progression so that mistakes in DNA sequences are not carried forward. DNA repair system can get mismatched DNA sequences repaired if DNA damage is not severe. Apoptosis and cell death may be stimulated by severe DNA damage which cannot be repaired. Failure in these defence systems results in genomic instability and thus increases gene mutations.

Colon cancer is considered to be caused by progressive accumulation of gene mutations and epigenetic changes. Usually 6-10 gene mutations are needed to initiate cancer. Genomic instability plays a key role in this process as it can allow gene mutations to accumulate gradually to be sufficient for carcinogenesis (31-35). Mutations in DNA repair genes such as *CHEK2*, *BRCA1*, *BRCA2*, and *BLM* have been associated with increased colon cancer incidence (36,37). In familial colon cancer, DNA repair gene defects are also increased (38-40).

Genomic instability include chromosomal instability (CIN), microsatellite instability (MSI) and gene mutations (29). CIN can be changes of chromosomal structures or altered numbers of chromosomes. MSI refers to production of novel microsatellite fragments due to impaired DNA mismatch repair system, leading to accumulation of DNA sequence errors, i.e., gene mutations. In colon cancer, both types of genomic instability have been identified. CIN accounts for about 85% of sporadic colon cancer (32,41,42). MSI happens in about 15% of colon cancer (32,35). Another form of genomic instability could be caused by the epigenetic changes, i.e., abnormal methylation of DNA sequences in colon cancer (43,44). Ahmed *et al*. [2013] characterised 24 colon cancer cells for genomic instability and found that 9/24 have MSI and 15/24 have CIN. CIN and MSI are mutually exclusive (8). In 24 colon cancer cell lines, *TP53* mutation is the most frequent genetic alteration, accounting for 17/24; next is *KRAS*, 15/24, *PIK3CA* 11/24, *BRAF* 5/24 (44). However, Goel *et al*. [2003] examined 209 cases of CRC and showed that 37.8% of colon cancer patients were neither MSI nor CIN, indicating other types of genomic instability may be involved (45). This study also showed that CIN and MSI could overlap (45). It was found that 6.5% of CIN patients also had high MSI and 23.3% of patients with high MSI had CIN.

Increased genomic instability in obesity

Obesity has been shown to have increased genomic instability. A study that used lymphocytes from lean and obese subjects to investigate CIN after being challenged with DNA mutagens found higher chromosome abnormalities in obese subjects (46). Obesity has also been shown to have increased micronuclei (47). Polycystic ovary syndrome, which has increased insulin was shown to have increased genomic instability (48). This may indicate that increased blood levels of insulin in obesity could also cause genomic instability. Indeed, addition of insulin, to cultured colon cancer cells has been shown to increase DNA damage.

In addition, weight loss in obese men can increase telomere length and thus reduce genomic instability (49).

It has been demonstrated that activation of PI3K/Akt and MAPK play key roles in obesity-associated colon cancer (50). Below we discuss the roles of these two pathways in genomic instability and summarize evidence for the involvement of genomic instability in obesity-associated colon cancer.

PI3K/Akt/mTOR pathway in genomic instability

Activation of PI3K/Akt pathway in obesity-associated colon cancer

PI3K/Akt pathway plays a key role in many cancers and has been extensively studied. The pathway is increased in obesity and has been demonstrated to play a key role in increased carcinogenesis of obesity-associated colon cancer (50). The pathway can be activated in obesity by increased insulin, IGF-1, cytokines and leptin. Activation of this pathway also plays a key role in insulin induced drug resistance (51,52). In animal model of colon cancer with high-fat diet induced obesity, tissues from colon polyps showed increased phosphorylated Akt (15). Activated Akt could lead to increased carcinogenesis of colon cells via several downstream pathways, one of which is genomic instability.

Activation of PI3K/Akt pathway and genomic instability

Phosphatase and tensin homolog (PTEN), an inhibitor of the PI3K/Akt pathway, has been regarded as an important guard for genomic stability (53-55). PTEN can convert PIP3 into PIP2 and thus reduce activation of PI3K. Activation of the PI3K/Akt pathway due to *PTEN* mutation has been demonstrated to increase genomic instability (56).

Stimuli of PI3K/Akt pathway such as IGF-1 and insulin have been associated with genomic instability. It has been found that activation of Akt by IGF-2 can cause genomic instability (57). Fernandez *et al*. showed that the oncoprotein YAP can increase genomic instability (57). This is mediated by IGF-2 as silencing of IGF-2 by siRNA resulted in the loss of association of YAP with genomic instability. Othaman *et al*. treated colon cancer HT29 cells with insulin and showed that insulin increased DNA damage as detected by comet assay (58). Insulin also increased micronucleus frequency, indicating increased genomic instability. Reactive oxygen species (ROS) were also found to be increased and inhibition of mitochondrial ROS production decreased insulin-induced DNA damage.

The mechanisms for Akt-caused genomic instability

Akt and DNA repair

Akt can affect BRCA1 which is important in genomic instability. DNA damage response pathway is necessary for maintaining genomic stability. One of its mechanisms is homologous recombination (HR), which is regulated by BRCA1 (59,60). Activation of Akt has been shown to cause a deficient phenotype in BRCA1 and HR (59).

Akt can also cause inactivation of Chk1, leading to genomic instability and double-strand breaks (53). Chk1 is important in genomic instability because it can delay cell cycle progression from S to G2 phase. DNA damage can cause activation of ATM or ATR which phosphorylates Chk1 at positions serines 317 and 345, leading to activation of Chk1. Activated Chk1 can phosphorylate cdc25A, resulting in the degradation of cdc25A and cell cycle arrest. However, Akt can phosphorylate Chk1 at serine 280, leading to Chk1 ubiquitination and thus sequestrated in cytoplasm, losing contact with nuclear ATM or ATR (53). Inhibition of ChK1 has been shown to increase DSBs detected by gamma-H2AX.

Activation of Akt has also been shown to suppress Rad 51. Rad51 can repair double stranded DNA breaks (61). Akt has been shown to increase Rad51 transportation into cytoplasm and thus reduce its role in genomic stability (59). It has also been found that *PTEN* loss is also associated with decreased Rad51 (62).

Akt and telomere length

Telomere is a region of repeated sequences, which can protect DNA in the end of chromosomes from damage and thus plays a key role in genomic instability (63). Decreased telomere length is known to cause genomic instability. Obesity has been associated with shortened telomere length and loss of weight in obesity increases telomere length (64,65). The short length of telomere could be mediated by activation of Akt. Over-expression of Akt has been shown to decrease the length of telomere. Activated Akt can directly phosphorylate telomeric repeat binding factor 1 (TRF1) but not mutated TRF1 (66).

Akt and cell cycle

Cyclin D1 is an important regulator in G1/S transition (67). Increased cyclin D1 can increase G1/S transition. Akt can increase cyclin D1 via mTOR, FOXO, c-myc and GSK-3beta (68). Akt can directly phosphorylate GSK-3beta, leading to its degradation, and thus the inhibitory role

of GSK-3beta on cyclin D1 is lost (69). mTOR has been demonstrated to regulate translation of cyclin D1 (70). Akt decreases FOXO which repress the expression of cyclin D1 (71). PI3K/Akt pathway has been shown to increase genomic instability by reducing the effect of genotoxic stress-induced destabilization of cyclin D1 (72). Short term over-expression of cyclin D1 is sufficient to cause genomic instability like aneuploidy (73).

Akt has been demonstrated to decrease p27 and p21 which are blockers of cell cycle (74,75). P27/p21 can block cyclin E/cdk2 pathway (76). It has been shown that knockout of p27kip1 increased high-fat diet-induced colon cancer (77). Knockout of p21 can also increase *APC*-initiated tumour formation under high-fat diet (78). In colon cancer model, Akt has been shown to increase cyclin E to increase genomic instability (79). Obesity due to leptin and leptin receptor deficiencies has been shown to have decreased p27 (80). In addition, blood levels of glucose, insulin and branched chain amino acids are also inversely associated with p27 expression, indicating decreased p27 levels could play an important role in obesity-increased colon cancer (80).

Inactivation of Rb can increase E2F, which is also sufficient for genomic instability (81). HPV infection has been shown to cause genomic instability. E7 oncogene can inhibit Rb and thus increase E2F. A study showed that pRB is inactivated in hypothalamus accompanied activation of E2F (82). However, the change of E2F in colon cells is not investigated. As inactivation of Rb in hypothalamus is caused by high-fat diet, it is also possible that Rb is inactivated in colon cells.

Akt and cell death

It has been shown that DNA damage response occurs before genomic instability and malignant conversion (83). This could be a counter-response to eliminate cells recognized as hazardous cells. This system is increased in colon cancer precursor lesions but not normal tissues. The molecules detected include H2AX, p53 and ATM/chk2. Mutations in ATM/chk2/p53 thus will facilitate accumulations of mutations and carcinogenesis (83).

P53 is an important tumour suppressor that induces cell death when DNA damage is severe. Akt can decrease the expression of p53 and thus reduce cell death. The reduction of p53 by Akt will facilitate the accumulation of mutations through the continuing replication of these defect cells. It has been shown that p53 can cause CIN which is accelerated by MAPK activation (84). P53 and MAPK activation also have synergistic effect in cancer transformation. Virus can decrease p53 via various ways to increase genomic instability (85).

MAPK pathway and genomic instability

MAPK pathway is an important survival pathway and activated in many cancers. It has also been shown to be activated in obesity-associated colon cancer. Park *et al*. demonstrated that high-fat diet-induced obesity increased AOM-induced colon polyp formation in A/J mice. The increased MAPK indicated by pErk is one of the mechanisms (15).

Activation of MAPK could also cause genomic instability in obesity-associated colon cancer. It has been demonstrated that RAS/RAF/MEK/MAPK can cause genomic instability (86,87). In colon cancer, KRAS was demonstrated to cause genomic instability via MAPK (88,89). *BRAF* mutations in colon cancer have been associated with mismatch repair (90). MAP activation in colon cancer has also been associated with MSI (91). Activated MAPK can increase genomic instability and DSBs (92). MAPK can also regulate cyclin D1 to cause genomic instability (69).

KRAS is found to be mutated in one third of CRCs. The mutations are located in codons 12, 13 and 61. *KRAS* mutation is considered to play a key role in carcinogenesis in Vogelstein's adenoma carcinoma sequence model. *BRAF* is also mutated. Mutation of *KRAS* and *BRAF* together account for 20/24 of the colon cancer in that study (44).

Prevention implication

Diet has been associated with genomic instability. In an epidemiological study, Satia *et al*. showed that fine carbohydrate and red meat increased MSI while beta-carotene reduced risk of MSI (93). Grape seed extracts and curcumin have been shown to decrease genomic instability in animal models (94). Tea components such as epigallocatechin gallate (EGCG) have also been shown to maintain microsatellite stability (95,96). Lycopene can also reduce genomic instability in colon cancer cells (97).

In obesity-associated colon cancer, phytochemicals such as lycopene, genistein, EGCG and curcumin have been proposed to be used for the prevention. These phytochemicals could inhibit multiple signalling pathways activated in obesity and thus reduce obesity-increased colon cancer. They may also inhibit genomic instability in obesity-associated colon cancer and this is warranted for

further studies.

Conclusions and future directions

Genomic instability is important for colon cancer. This may be also the case for obesity-associated colon cancer. Obesity may increase genomic instability via several signalling pathways. The study of genomic instability in obesity-associated colon cancer is still in a very early stage although evidence has been provided that genomic instability is increased in obesity and it is known that genomic instability plays a key role in colon cancer. The detailed mechanisms for genomic instability in the initiation and progression of obesity-associated colon cancer are largely unknown. How changed cancer risk factors and activated signalling pathways mediate genomic instability are warranted for further studies. As both PI3K/Akt and MAPK pathways are activated in obesity-associated colon cancer. It will be interesting to investigate if these two pathways have co-ordinated effect on genomic instability. It is known that activation of these two pathways have co-operatively induced carcinogenesis (98,99). Therefore, inhibition of both pathways may have better preventive effects. Although, inhibition of both pathways has been tested for treatment of cancer, no studies have been carried out for the prevention of obesity-associated colon cancer. Inhibition of these pathways by small inhibitors or phytochemicals may prevent obesity-associated colon cancer.

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