E. coli and colon cancer: Is mutY a culprit?

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Abstract:

The recent demonstration of a role of *E. coli* in the development of invasive carcinoma in mice ushers a new era of bacterial involvement in cancer etiology. It has been shown previously that the colonic mucosa of colorectal carcinoma (CRC) is exclusively colonized by intracellular *E. coli* instead of extracellular form found in normal colonic mucosa. Surprisingly, the DNA repair gene MUTYH, which is a homologue of the *E. coli* gene mutY, is responsible for CRC. The current paper discusses the potential role of mutY in CRC etiology and concludes that research in this area can bring together the diverse threads of the CRC etiology puzzle.

Keywords: *E. coli*, mutY, MUTYH, chronic inflammation, carcinogenesis

1. Introduction

The enigmatic relationship of *E. coli* with colorectal cancer (CRC) has always raised suspicions for cancer researchers in the role of this bacterium in cancer development. Recently, an article published in the August 2012 issue of *Science* revealed that *E. coli* has the capability to promote invasive carcinoma in mice [1]. Although verification of its etiological potential in humans is still awaiting a legitimate appraisal, a logical mechanistic explanation for this association has been provided through chronic inflammation. Induction of proinflammatory cytokines and highly reactive chemical species during chronic inflammation leads to oxidation, nitration and chlorination of DNA, RNA and proteins. [2]. Khan *et al* suggested that the frequent association of *E. coli* with CRC may allow the bacteria to serve as an indicator of cancer development [3]. *E. coli* infection is involved in chronic inflammation of the intestine during inflammatory bowel disease (IBD). It has been observed that the pathogenesis of IBD involves a consistent increase in mucosa-associated *E. coli* with an "adherent and invasive" phenotype. Although many other bacterial species are also involved in IBD [4], the recent demonstration of *E. coli* induced carcinogenesis in mice attracts our attention towards this organism as a possible CRC etiologic agent in humans. Two forms of IBD, including Crohn's disease (CD) and ulcerative colitis (UC), are associated with an increased risk in the development of colon cancer [5,6].

2. *E. coli*: a host cell cycle modulator

Several studies have considered the potential role of microbes in CRC etiology [7,8]. A role for *E. coli* in CRC etiology gained much interest after finding mounting evidence for this association [9]. It has been verified in many studies that *E. coli* has an enormous potential for cell cycle modulation, thus increasing the chances for the development of cancer. Some *E. coli* strains produce cyclomodulins which interfere with the host cell cycle and may serve as a possible link for the association with *E. coli* and CRC [10]. In addition, cytotoxic necrotizing factor (CNF) is a cyclomodulin produced by *E. coli*; CNF activates rho GTP binding protein

and prevents apoptosis. CNF modulates both mitochondrial homeostasis and the expression of Bcl-2 member of apoptotic regulators. It acts as an apoptosis inhibitor and cell cycle stimulator due to the induction of DNA replication and G1/S transition [11-13]. Another *E. coli* cyclomodulin, known as cycle inhibiting factor (Cif), has the ability to cause irreversible arrest of the cell cycle at the G2/M transition [14]. Cif, which is produced by enteropathogenic (EPEC) and enterohaemorrhagic (EHEC) *E. coli* strains [15], activates G2/M arrest by activating a DNA damage independent pathway through sustained inhibitory phosphorylation of mitosis inducer CDK1 [14]. Cif also causes unique alterations in the actin cytoskeleton leading to its anchoring to the host cell membrane and cellular and nuclear enlargement. Nuclear enlargement occurs due to continuous DNA replication in the absence of nuclear division [16]. This endoreduplication increases cellular DNA content and also increases gene copy number and proteins including growth factors leading to rapid growth of cells and possibly cancer [13,17,18]. Moreover, *E. coli* also produces cytolethal distending toxin (CDT), which causes cell cycle arrest by inflicting DNA damage [19,20]. CDT is a tripartite complex with the CdtB subunit homologous to human DNAse I [21]. The role of CDT in the carcinogenic process has been investigated in a microbial induced hepatocarcinogenesis mouse model. In this model it was observed that *Helicobacter hepaticus* CDT promoted the development of dysplasia from hepatitis and increased proliferation of hepatocytes [22].

It has been reported recently that host cell mismatch repair activity of *E. coli* infected cells is reduced in colon cancer cell lines as well as CRC patients [23]. A reduction of DNA repair activity is directly related to an accumulation of mutations and is a suspected reason for *E. coli* driven cancer. Besides these attributes of cell metabolism in *E. coli* induced cancer etiology, this bacteria have little or no capacity for the conversion of N-hydroxy-4-acetyl-aminobiphenyl (N-OH-AABP) to 4-acetylaminobiphenyl, which reverses activation of the

parent carcinogen in the gut [24]. It has been known for some time that the gut microflora have the capacity to convert several carcinogens to harmless products in the intestine and thus minimize the cancer risk [25]. However, during IBD *E. coli* is generally present as a prominent organism and can reduce this attribute of the gut microflora. Although many pieces of evidence support a proposed carcinogenic activity of *E. coli*, a satisfactory consensus cannot be achieved on any single mechanism. This situation demands the detection of firm evidence and the identification of specific mechanism for the *E. coli*-CRC association.

3. *E. coli* and CRC: a peculiar association

In addition to the mechanistic link between chronic inflammation and CRC development, it is also worthy of note that the colorectal carcinoma mucosa, but not normal colonic mucosa, is colonised by intracellular *E. coli* [26]. Chronic inflammation and consequent tissue damage induces a cascade of pro-inflammatory and anti-inflammatory molecules. The equilibrium between these two groups of regulators controls cell death and repair of tissue damage caused due to cell death. However, any problems with this equilibrium may lead to the development of cancer [27]. Cellular mutations are additional factors in regulating the development of CRC. Several cellular mutations have been identified as etiologic factors for colon cancer and these have been reviewed in many recent articles [28]. Among the mutations linked to CRC, MUTYH, which encodes for DNA glycosylase, is one of a number of genes involved in regulating oxidative DNA damage repair [29]. Although germ line mutations in MUTYH are linked to hereditary CRC, somatic mutations in this gene are also associated with cases of CRC [30]. It is noteworthy that the cellular MUTYH gene is a homologue of the *E. coli* gene mutY, which is also responsible for regulating DNA damage repair [29]. Thus it offers an additional target for investigating the *E. coli*-CRC association.

4. Possible role for the involvement of mutY in CRC etiology

Considering the diverse lines of evidence described above for the microbial etiology of CRC, it is interesting to consider a potential role for the *E. coli* mutY gene in the development of colon cancer. *E. coli* can exist as a chronic intracellular pathogen in colon cells and this intimate association between the bacteria and colon cells provides an opportunity for the bacteria to grow for many generations and for the old bacterial cells to release their contents into the colon cell cytoplasm. Thus, we can speculate that the intracellular *E. coli* will release their DNA and mutY gene products into the colon cell.

This hypothesis raises three interesting questions. *First*, due to the high degree of homology between mutY and MUTYH, can horizontal gene transfer (HGT) events take place, which might affect DNA glycosylase performance? *Second*, can *mutY* gene products interfere with the activity of human MUTYH gene products? *Third*, do epigenetic factors that regulate *mutY* gene expression also influence MUTYH expression? Although remote, each of these three events could lead to an abnormal DNA repair pathway and ultimately promote the development of colon cancer (Figure 1).

4.1 Horizontal gene transfer of mutY and CRC

Indirect support for the involvement of HGT in CRC progression comes from the demonstration of extensive horizontal gene transfer from intracellular bacterial pathogens to their multi-cellular eukaryotic hosts. For example the intracellular bacterial endosymbiont, *Wolbachia pipientis*, has the ability to transfer genes horizontally to its host [31]. The intracellular residence of *E. coli* within colon cells during CRC may thus lead to a similar horizontal gene transfer [26]. Furthermore, several bacteria, particularly intracellular bacterial pathogens, can influence host metabolism and gene expression in order to sustain them within the host cellular environment. Several reports have been published on the subversion of host

cellular responses by intracellular pathogens [32]. There is some skepticism about the transfer of genetic material between intracellular bacteria and the eukaryotic host cell due to the physical barriers that exist between the intracellular bacterium and host cell. However, in one comparative genomic study approximately 40 genes were identified that were consistent with lateral transfer between bacteria and humans [31]. During intracellular bacterial infection, the bacterial DNA acts as a symbiotic DNA molecule similar to mitochondrial or chloroplast DNA. It is reasonable to propose that these bacterial DNA fragments can affect the host MUTYH through horizontal gene transfer (HGT). The mechanism of HGT from bacteria in cancer etiology has been reviewed in a recent article [32]. However, it can be argued that MUTYH mutations are generally bi-allelic whereas *E. coli* induced events lead primarily to mono-allelic mutations. It is relevant to note that bi-allelic mutations are 10 times more prone to result in CRC compared to mono allelic mutations. Thus, bi- and mono-allelic mutations could be responsible for early and delayed onset cancers respectively [33].

4.2 Direct effects of mutY protein or its epigenetic regulators and CRC

Due to the high degree of homology between the bacterial *mutY* and eukaryotic MUTYH genes, both functional and structural analogies between the gene products are likely. It has been observed previously that the same enzymes from different organisms can differ in their degree of substrate specificity. This phenomenon is evident even for equivalent enzymes isolated from different bacteria. In the case of the equivalent enzyme from humans and *E. coli*, which are evolutionary distant, it is reasonable to propose that the presence of both enzymes in the same cell at one time can interfere with each other's activity. This latter scenario raises the possibility that DNA repair can be impaired, allowing the accumulation of mutations that ultimately lead to CRC. As discussed earlier, *E. coli* has the ability to reduce host cell DNA mismatch repair (MMR) in colonic cell lines and this has also been observed in CRC patients. This process has been suggested as a possible mechanism for *E. coli*

induced colon carcinogenesis [23]. Enteropathogenic *E. coli* (EPEC) has been shown to secrete an effector protein (EspF), which is responsible for the reduction of MMR proteins [34]. However, the role of mutY in reducing the DNA repair activity of *E. coli* infected eukaryotic cells also requires a detailed appraisal.

It is relevant to note that microbes posses the ability to carry out epigenetic alterations of their host eukaryotic cells and induce pathological changes through epigenetic reprogramming [35]. Epigenetic changes leading to cancer include DNA methylation, histone modification and modulation of micro RNA expression [36,37]. Consequently, based on their sequence homology, mutY and MUTYH could share similar epigenetic regulators and thus cause comparable epigenetic alterations in the host cell DNA repair machinery. Micro RNAs are small RNA molecules involved in translation inhibition and silencing of many genes including those responsible for cell proliferation, differentiation and cell death. Gut microbiota have the capacity to modulate micro RNA expression thus influencing several biological processes in the host cell as recently reviewed by Masotti [38]. *E. coli* is a gram negative bacterium within the gut microbiota and has the potential to modulate the expression of micro RNA through it lipopolysaccharide (LPS). In macrophages, the LPS of gram negative bacteria can induce the expression of mir-155 but down regulate the expression of mir-125b micro RNAs [39]. The resident colonic microflora is responsible for the production of short chain fatty acids (SCFA) through fermentation of non digestible carbohydrates; these SCFAs include butyrate that is an inhibitor of histone deacetylase enzyme and can affect histone modification and DNA methylation [40,41]. DNA methylation is known to affect the expression of several cancer associated genes [42]. Since the pattern of DNA methylation varies between different organisms, it is possible that the presence of *E. coli* epigenetic regulators can lead to reprogramming thus altering the expression of host cell genes including MUTYH. Altered patterns of DNA methylation is a common molecular alteration observed

in human cancers including CRC [43]. This scenario has already been described during epigenetic reprogramming of host genes by viruses and intracellular bacteria [44].

It is well-documented that enteropathogenic E. coli (EPEC) synthesise a variety of effector molecules that are capable of influencing cellular DNA repair [34]. The cytosolic localization of *E. coli* within colon cancer cells allows the bacteria to release the effector molecules directly into the host cell cytoplasm, although to affect host cellular processes these bacterial effector molecules must enter in the host cell nucleus. *E. coli* generally uses a Type III Secretion System (T3SS) to transfer the bacterial effector molecules into the eukaryotic host cell. However, when the bacteria are residing intracellularly the nuclear localization of the bacterial proteins depends upon the presence of nuclear localization signals (NLS) on the bacterial proteins [45]. Nuclear localization signals are required for the active transport of proteins from the cytoplasm to nucleus, although proteins with molecular weights < 40 kDa can transfer to the nucleus *via* a passive transport mechanism [45,46]. Surprisingly, the mutY protein (NCBI Accession number EGT70329) has a molecular weight of 39.18 kDa giving strong support for its nuclear localization *via* the passive transport mechanism. Similar to the possible mutY nuclear transport, the epigenetic regulators have a high propensity for an intracellular localization due to functional relatedness. For example, *E. coli* replication terminator protein Tus, an *E. coli* epigenetic regulator, has both a NLS and nuclear export signal (NES), and can therefore target the host cell nucleus. Although research in this area is in the early days, Tus protein was one of the first proteins shown to possess both NLS and NES, thus supporting a role in epigenetic targeting of the host cell nucleus [47]. However, future research on bacterial epigenetic regulators will, no doubt, identify similar host nuclear targeting potential for many *E. coli* proteins, perhaps including mutY. Therefore, chronic *E. coli* infection may create a situation where chronic inflammation, caused by the *E. coli*

infection, leads to mutY mediated cellular alterations in the host cell DNA repair machinery that controls the development of CRC.

5. Concluding remarks

Our current understanding of CRC pathogenesis raises suspicion for a potential role of *E. coli* mutY in colon cancer and research in this direction is uncovering several aspects of CRC pathogenesis. Further research is required to address the potential role of *E. coli* in colon cancer development. Several aspects of the proposal outlined above, specifically the intracellular growth of *E. coli* in colon cancer cells, the homology between the mutY and MUTYH genes, possible horizontal gene transfer from the intracellular *E. coli* during colon cancer, and the presence of *mutY* and MUTYH gene products in same cell provide clues for linking these threads. Further research will provide new avenues to understand CRC etiology and help us to plan and implement infection control measures to control CRC. Managing an infection is much easier than managing the cancer itself; hence the role of *E. coli* mutY in CRC should be investigated further.

Conflict of Interest: Authors do not have any potential conflict of interest related to this work.

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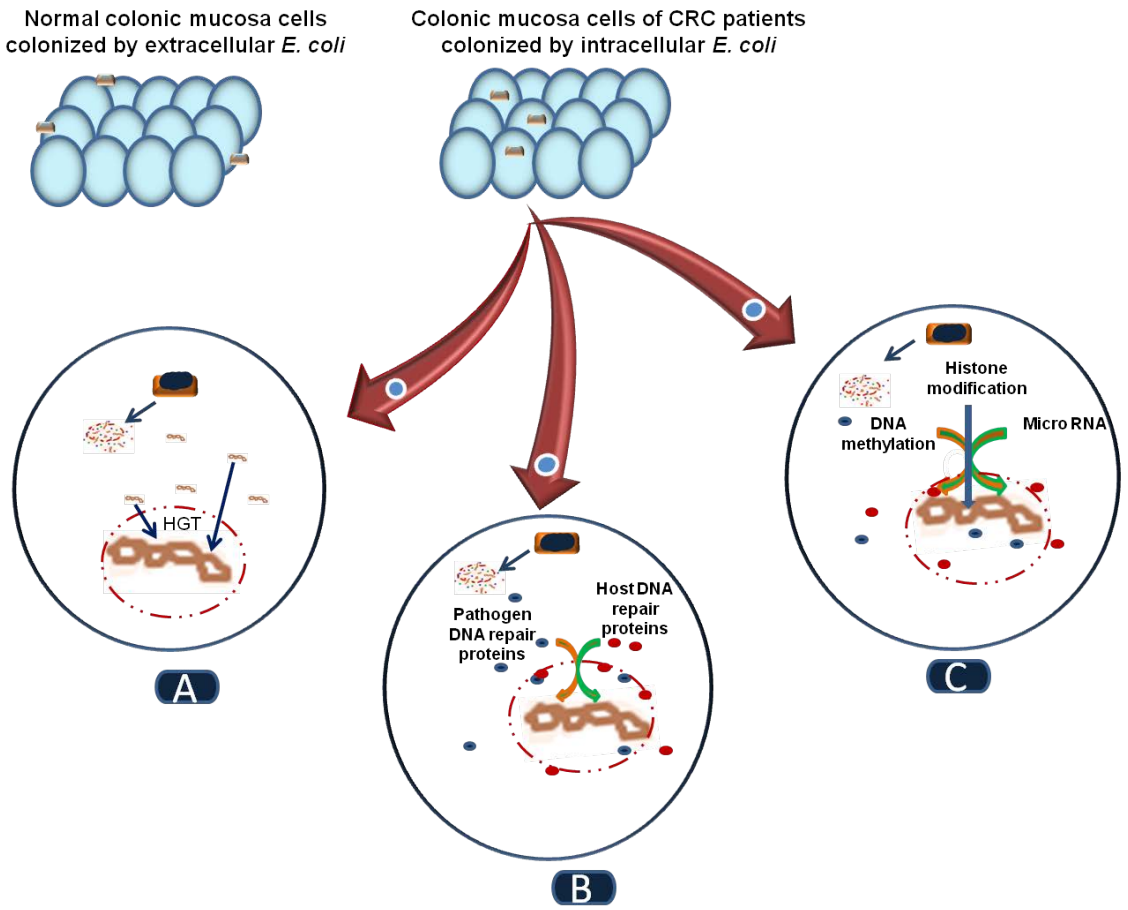

Figure 1: Proposed explanation for the potential involvement of *E. coli* mutY in CRC etiology. During chronic *E. coli* infection, the bacteria establish an intracellular residence of bacteria in associated colon cancer cells. (A) Shedding of the bacterial DNA into the host cell and due to sequence homology between mutY and MUTYH, horizontal gene transfer events may occur, which can lead to the development of CRC. (B) Products of *E. coli* mutY and human MUTYH can also affect the ability of DNA repair in host cell (C) Epigenetic regulators of the bacterial mutY gene can also affect human MUTYH leading to abnormal expression of MUTYH and ultimately the development of CRC.