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Potential role of *Escherichia coli* DNA mismatch repair proteins in colon cancer

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ABSTRACT

The epithelium of gastrointestinal tract organizes many innate defense systems against microbial intruders such as integrity of epithelial, rapid eviction of infected cells, quick turnover of epithelial cell, intrinsic immune responses and autophagy. However, Enteropathogenic *Escherichia coli* (EPEC) are equipped with well developed infectious tricks that evade the host defense systems and utilize the gastrointestinal epithelium as a multiplicative foothold. During multiplication on and within the epithelium, EPEC secrete various toxins that can weaken, usurp, and use many host cellular systems. However, the possible mechanisms of pathogenesis are still poorly elusive. Recent study reveals the existence of EPEC in colorectal cancer patients and their potential role in depletion of DNA mismatch repair (MMR) proteins of host cell in colonic cell lines. The EPEC colonised intracellularly in colon mucosa of colorectal carcinoma whereas extracellular strain was detected in mucosa of normal colon cells. Interestingly, alteration in MutS, MutL complexes and MUTYH of mammalian cells may be involved in development of CRC. These data propose that MMR of *E. coli* may be potential therapeutic targets and early detection biomarkers for CRC. This article reviews the potential role of *E. coli* MutS, MutL and MutY protein in CRC aetiology.

1. Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and fourth most common reason of malignancy death in the world. About 693,933 deaths and 1360,602 new cases were recorded

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worldwide due to high prevalence of CRC according to the GLOBOCAN estimates in 2012 (Parkin et al., 2005). Aetiology of CRC is multifaceted and very complicated. The association of infectious agents in the etiology of cancer has focused the interest of scientists in recent years. The microbial communities of intestine known as "microbiota" have crucial role in health and disease of human and other living beings. The microbiota normally controls the host in a beneficial style through altering the immune and gastrointestinal functions, applying defence against pathogenic microbes (Neish, 2009). The gut microbiota is probably associated with growth of colorectal carcinoma through different mechanisms. This is due to the effective role of inflammation in creating conditions that can intensely change local immune responses and, subsequently, tissue homeostasis. At present, an association between bacterial, viral and other infectious agents has been established with cancer, and it has been reported in almost 15–20% of the entire malignancies (de Martel and Franceschi, 2009; Shahanavaj et al., 2015).

Primarily commensal inhabitant *Escherichia coli* is a member of the mammalian intestinal microbiota, colonizing the gut after birth and persisting throughout the life of the host. *E. coli* isolates can be classified into five major phylogenetic groups including A, B1, B2, D and E. The B2 group of *E. coli* are retrieved less frequently although, however it can remain existing in the colon, comparing to other groups it's present in almost 30–50% of isolates separated from the feces of healthy persons residing in high-income states (Touchon et al., 2009). Pathogenic strains belong to B2 and D phylogroups are involved in intestinal and extra-intestinal diseases, whereas most fecal strain A1 and B1 phylogroups are non-pathogenic. Subgroup B2 and D generally carries virulence factors that are lacking in subgroup A and B1 strains. The colonic mucosa of CRC patients showed cyclomodulin-producing *E. coli*, mostly belonging to B2 phylogroup (Buc et al., 2013). The potential role of the human gut microbiota including *E. coli* for colon cancer has not received serious attention. Furthermore efforts are needed to completely understand the possible role of pathogenic *E. coli* in progression and development of CRC.

2. Pathogenesis of EPEC in colorectal cancer

Pathogenic bacteria EPEC have the capability of causing attaching and effacing lesions on the surface of the host's intestinal epithelium through distinct colonization adeptness. (Tjalsma et al., 2012). *E. coli* act as commensal bacteria in human intestine, although several pathogenic isolates have acquired the capability to encourage chronic inflammation and generate many toxins including cyclomodulin, which may be involved in carcinogenesis (Raisch et al., 2014). The mysterious relationship of colorectal cancer (CRC) with *E. coli* has attracted the attention of cancer researchers in the role of this particular bacterium in cancer growth and development. *E. coli* is mainly classified as a commensal bacterium and begins to colonize the human gut with little abundance just after birth (Fanaro et al., 2003. *E. coli*) produce a broad range of proteins into the cells and tissues of host to promote their replication, transcription, survival and dissemination potential. The awareness that these effector proteins can disclose novel pathogenic properties of *E. coli* has led researchers to identify novel and effective approaches to rapidly characterize and identify these proteins. Recent research confirmed that pathogenic strain of *E. coli* could also play crucial role in pathogenesis of colorectal cancer (Bonnet et al., 2014). Extremely elevated levels of *E. coli* may be related to alterations in colon and intestinal permeability, inflammatory responses associated with inflammatory bowel disease (IBD) (Bonnet et al., 2014; Vajro et al., 2013). There is a broad variety of *E. coli* genotypes in common serotypes such as pathogenic strains that are responsible for various diseases, infection, and nonpathogenic strains that could be linked with many disease phenotypes. For instance, colonization of mucosa-associated *E. coli* was identified to induce local inflammation in patients with colon cancer, but not Crohn's disease whereas another subset of adherent-invasive *E. coli* was generally observed in individuals with IBD including Crohn's disease and ulcerative colitis (Rolhion and Darfeuille-Michaud, 2007; Martinez-Medina and Garcia-Gil, 2014; Barnich et al., 2007; Martin et al., 2004).

2.1. DNA repair genes and colorectal cancer

The highly conserved region of MutS, MutL and MutY are present in many eukaryotes including yeast, mice and humans in addition to many prokaryotes such as *E. coli*, *Helicobacter pylori*, *Deinococcus radiodurans*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Neisseria gonorrhoeae* and *Neisseria meningitides* (Slupska et al., 1996). Recently, published papers demonstrated that *E. coli* has the potential to promote invasive carcinoma in mice (Bonnet et al., 2014; Arthur et al., 2012; Cougnoux et al., 2014). However corroboration of its etiological capability in humans still remains a genuine appraisal, and a rational mechanistic explanation for this link has been provided by chronic inflammation. Stimulation of highly reactive chemical species and proinflammatory cytokines during chronic inflammation directs to nitration, oxidation and/or chlorination of nucleotides in RNA, DNA and proteins (Wogan et al., 2012), which may be the causes of cancer. The infection of *E. coli* is involved in inflammatory bowel disease (IBD) due to chronic inflammation of intestine. It has been studied that the cause of IBD involves a regular inflation in mucosa-connected *E. coli* through a specific manner of adherent and invasive phenotype. Although various species of bacteria are also connected with IBD (Friswell et al., 2010), the current evidence of *E. coli* mediated carcinogenesis in mice focus our interest towards this micro-organism as a potential etiologic cause in humans CRC. Two types of IBD, such as ulcerative colitis (UC) and Crohn's disease (CD), are linked with an increased threat in the growth and development of colon cancer (Gillen et al., 1994; Collins et al., 2011).

3. Idiosyncratic association of *E. coli* with colorectal cancer

It is an excellent outcome to note that the colorectal carcinoma mucosa is colonised by intracellular *E. coli*, although not normal colonic mucosa in addition to the mechanistic association between chronic inflammation and CRC growth and development (Swidsinski et al., 1998). The unique cascade of pro-inflammatory and anti-inflammatory molecules involves in chronic inflammation and consequent tissue damage. The equilibrium between these two groups of regulators controls cell death and repair of tissue damage caused due to cell death. Cell death and repair of damage tissue caused due to cell death manages by the equilibrium between these two groups of regulators, though many problems in this equilibrium may direct to the development of cancer (Lu et al., 2006). Additional factors include cellular mutations also controlling the development of CRC. Various cellular mutations have been characterised as etiologic causes for colon cancer (Markowitz and Bertagnolli, 2009).

The DNA repair systems are highly conserved with respect to their central roles in MMR among eukaryotes including human, yeast (Kadyrov et al., 2006; Kadyrov et al., 2007) and prokaryotes such as *Thermus thermophilus and E. coli* (Table 1) (Mauris and Evans, 2010; Fukui, 2010; Fukui et al., 2008; Mauris and Evans, 2009). The MSH2/MSH6 designates as a MutS homolog, while MLH1/PMS1 is considered as homologs of MutL (Prolla et al., 1996). Study of 16 exons of MSH2 in 34 unrelated HNPCC analogues has showed a heterogeneous array of mutations (Fishel et al., 1993; Lynch et al., 1993). Four MutS homologs, MSH2, MLH1, MSH6, and PMS2,