Life Sciences 180 (2017) 60–67

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Colorectal cancer-inflammatory bowel disease nexus and felony of *Escherichia coli*

Abdul Arif Khan [a,*], Zakir Khan [b], Abdul Malik [c], Mohd Abul Kalam [a], Phillip Cash [d], Mohd. Tashfeen Ashraf [e], Aws Alshamsan [a,f]

[a] Nanomedicine Research Unit, Department of Pharmaceutics, College of Pharmacy, PO Box 2457, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Baverly Blvd., Los Angeles, CA 90048, USA
[c] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh 11451, Saudi Arabia
[d] The Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, United Kingdom
[e] School of Biotechnology, Gautam Buddha University, Greater Noida, UP, India
[f] King Abdullah Institute for Nanotechnology, King Saud University, PO Box 2455, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 29 January 2017
Received in revised form 24 April 2017
Accepted 12 May 2017
Available online 12 May 2017

Keywords:
Inflammation
Intracellular pathogen
Infection
Cancer etiology

ABSTRACT

Colorectal cancer (CRC) has a multifactorial etiology. Although the exact cause of CRC is still elusive, recent studies have indicated microbial involvement in its etiology. *Escherichia coli* has emerged as an important factor in CRC development since the bacterium can cause changes in the gut that lead to cancerous transformation. A number of studies indicate that chronic inflammation induced by microorganisms, including *E. coli*, during inflammatory bowel disease (IBD) predisposes an individual to CRC. The evidence that support the role of *E. coli* in the etiology of CRC, through IBD, is not limited only to chronic inflammation. The growth of *E. coli* as an intracellular pathogen during IBD and CRC enable the bacteria to modulate the host cell cycle, induce DNA damage and accumulate mutations. These are some of the contributing factors behind the etiology of CRC. The present article considers the current status of the involvement of *E. coli*, through IBD, in the etiology of CRC. We discuss how intracellular *E. coli* infection can cause changes in the gut that can eventually lead to cellular transformation. In addition, the recent management strategies that target *E. coli* for prevention of CRC are also discussed.

Contents

* Corresponding author.
E-mail addresses: karif@ksu.edu.sa, abdularifkhan@gmail.com (A.A. Khan).

http://dx.doi.org/10.1016/j.lfs.2017.05.016
0024-3205/

1. Colorectal cancer (CRC): introduction and severity

CRC is the third most common cancer worldwide and second commonest cancer in Europe with 1,360,602 and 447,136 new cases respectively reported in 2012. It was estimated in 2012 that CRC cases accounted for 693,933 deaths worldwide, the fourth commonest reason for cancer-associated mortality, and 214,866 deaths in Europe, the second commonest reason for cancer-associated mortality [1]. Based on epidemiological data for CRC from the USA, it has been predicted that the prevalence of CRC will increase more rapidly than the US population by 2020. These data highlight the need to develop effective strategies for the management of CRC [2].

Recently, there has been a decline in CRC associated mortality due to improved early stage detection, increased screening for CRC, and improved treatment options for cancer patients [3]. However, the upward trend in the incidence of CRC calls for an urgent need to develop effective preventative strategies. Although the exact causes of CRC are unknown, the cancer is believed to have a multifactorial etiology in which different factors contribute to the varied susceptibility to CRC among different individuals. Both genetic and non-genetic factors are responsible for the etiology of CRC. Most CRC cases (65%) are sporadic and develop in response to various environmental factors. Only 3% of CRC cases are due to inherited syndromes including hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and several very rare hamartomatous polyposis syndromes. The remaining 32% of CRC cases are thought to arise due to a combination of unknown genetic and environmental factors [4]. The diet, age and lifestyle of an individual are also important risk factors that determine the development of CRC. It has been reported that high dietary intake of energy, protein, saturated fats, cholesterol and sodium increases the risk of developing CRC, whereas a diet rich in vitamin E and caffeine decreases the risk for the development of CRC [5].

Recently, a role for *Escherichia coli* (*E. coli*) has been proposed in the etiology of CRC based on data derived from a various in vivo, in vitro and in silico studies [6–9]. *E. coli* is a common gut microorganism and different *E. coli* biovars can have diverse consequences on the health of the gut. The bacterium can drive a moderate CRC risk to a high risk and ultimately the development of colorectal carcinoma. Various studies have shown that the *E. coli* biovar commonly present in the intestines of the majority of individuals differ from that isolated from CRC patients [6,10].

The following article reviews the current status of the involvement of *E. coli* in the etiology of CRC and elaborates on how *E. coli* can convert susceptibility to CRC from moderate to high risk. A specific area of interest is how future research on the role of *E. coli* in the etiology of CRC might open new avenues for developing effective preventative strategies. The control of the bacteria is likely to be far easier in comparison to the management of cancer. The current article provides an overview of this association for microbiology and cancer researchers.

2. CRC etiology: are we heading towards the root cause?

Both host and environmental factors play a crucial role in the development of CRC. Host factors can convert high and moderate CRC susceptibility to CRC depending on the host's physiology, age, lifestyle and genetic constitution [11]. Environmental factors work together with host factors to influence the development of CRC. Subtle changes in environmental factors can influence the progression of CRC in high risk individuals, whereas in moderately susceptible individuals continued environmental stimulation are required for CRC progression over a longer duration. These factors are sometimes also referred to as non-modifiable and modifiable risk factors as discussed below [12].

2.1. Non-modifiable risk factors

The chances of developing CRC increases over the age of 40 years and it is estimated that >90% of CRC cases occur in people over the age of 50 years [12]. The development of adenoma, a benign tumor of glandular epithelial tissue, increases the frequency of CRC progression. Therefore, the detection and removal of adenoma prior to the malignant transformation, which typically takes between 5 and 10 years, reduces the risk of developing CRC [13]. The development of adenomatous polyposis is also associated with a genetic condition known as MUTYH-associated polyposis (MAP), which is caused by bi-allelic mutations in the *MUTYH* gene (also known as the *MYH* gene). The *MUTYH* gene product is involved in the base excision DNA repair pathway and prevents oxidative DNA damage [14].

Although the majority of CRC cases develop without a family history, a strong family history of CRC increases the chances of CRC development and accounts for nearly 20% of CRC cases [12]. Support for the role of family history in susceptibility to CRC comes from reports of several genetic conditions that have been shown to increase the risk for CRC [15]. These inherited genetic conditions include HNPCC (also known as Lynch syndrome) and classic/attenuated FAP. HNPCC is associated with mutations in the hMSH2, hMLH1, hMSH6, and hPMS2 genes, which are involved in DNA repair, while FAP is associated with mutations in the tumor suppressor gene APC, which is involved in the WNT signaling pathway. The hMLH1 mutation is associated with 90% of HNPCC cases while mutations in hMSH2 and hMLH1 are associated with 10% of HNPCC cases. However, hPMS2 involvement in HNPCC is a rare event [14]. Less is known about the involvement of hMSH6 in CRC etiology, although a study analyzing the role of hMSH6 germline mutations in the etiology of CRC revealed that 7.1% of analyzed probands carry mutations in cases of non-HNPCC [16]. In addition, Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS) are hamartomatous polyposis found to increase the risk for CRC [17]. All of these factors influence the susceptibility to CRC, although other modifiable external risk factors also aid in normal to cancer transformation.

2.2. Modifiable risk factors

Food and eating habits are major modifiable risk factors for CRC. The consumption of high fat, mainly animal fat, leads to alterations in the host microflora that favor the degradation of bile salts into carcinogenic N-nitroso compounds. The presence of heme iron in red meat is also proposed as an underlying factor driving CRC progression. Cooking meat at high temperature results in the generation of carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons [18]. Physical activity reduces the progression of CRC. Thus, the lack of physical activity is a major etiological factor in CRC. Physical activity is associated with obesity, which is another risk factor for CRC. Individuals with a Body Mass Index (BMI) >30 kg/m^2 have a 19% increased risk of developing CRC compared to individuals with BMI values of 20–25 kg/m^2 [18–20]. Cigarette smoking and alcohol consumption are also associated with an increased CRC risk. Studies have shown that 12% of CRC cases are linked with smoking. In addition to tobacco smoking, the consumption of alcohol and male gender is also associated with the etiology of CRC [21].