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Tumor Engineering: Finding the Brakes

Rajunor Ettarh
Department of Structural and Cellular Biology, Tulane University School of Medicine, New Orleans, USA

1. Introduction

There is sufficiently detailed understanding about how an automobile works such that starting or running the engine can be selectively disabled. Applying this analogy to colorectal cancer, the question researchers and clinicians ask is: can colorectal cancer be prevented from starting? Once started, can the disease be prevented from running? These two aims fall broadly into the categories of prevention and treatment respectively. Many of the aspects of colorectal cancer that provide focal points for clinical management of patients of the disease are included in Figure 1 (below). This volume provides insights into aspects of disease incidence and presentation, some of the advances and developments in diagnosis and patient management, and examines prevention and therapeutic targets and regimes. This chapter provides a general overview of some of the aspects of colorectal cancer that affect clinical management of the disease and explores incidence of the disease, diagnosis and treatment as well as preventive screening programs.

2. Epidemiology

As a disease, the statistical data for colorectal cancer are disturbing. Every year, there are over 1 million new cases worldwide, half of them in men; over 200,000 new cases in Europe; and 1.5 million new cases in the United States (Jemal et al, 2010). Over 700,000 patients die each year.

Expanded surveys and studies show that the incidence of colorectal cancer is increasing worldwide, along with cancer detection rates. Other studies suggest that these rates may also be dependent on anatomic site along the intestine at which the cancer occurs. However, although absolute numbers of patients affected by the disease is increasing in the US, the trend for colorectal cancer is downward: age adjusted incidence has declined steadily since 1976 (Ji et al, 1998; Chen et al, 2011; Eser et al, 2010; Merrill & Anderson, 2011). Genomic instability is present in 15% of colorectal cancer, and forms the basis for those who advocate the need for screening programs for colorectal cancer patients (Geiersbach et al, 2011).

Incidence of colorectal cancer around the world per 100,000 of population varies between 3-43 and is influenced by age, gender, socioeconomic status, and ethnicity (Center et al, 2009; Hao et al, 2009). Younger patients have greater susceptibility if there is an associated family history and tend to present at a more advanced stage of the disease. Long and short-term incidence of colorectal cancer is also affected by aspirin intake and this effect may be

dependent on dosing regime and patient history (Dube et al, 2007; Flossmann et al, 2007; Rothwell et al, 2010).

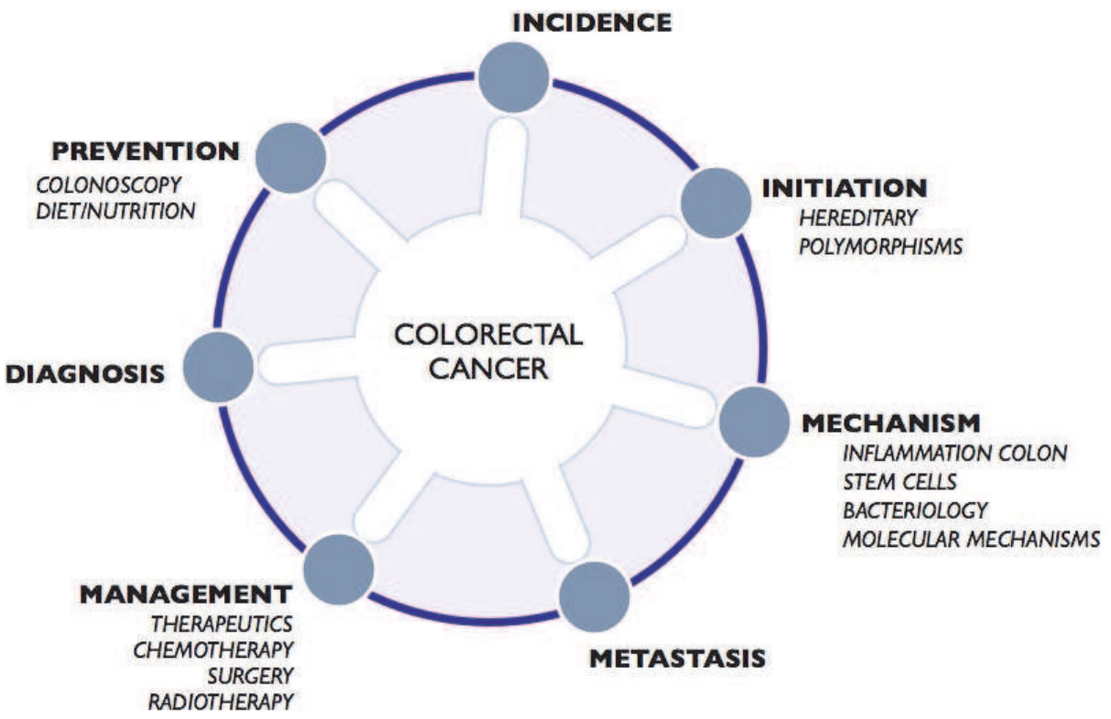

Fig. 1. Basic science studies and clinical management continue to improve our understanding of colorectal cancer. This volume considers incidence, diagnosis and clinical management of the disease as well as metastatic disease. Aspects of initiation and mechanisms are dealt with in the first volume of the book.

3. Diagnosis and treatment

There has been steady improvement in survival rates in colorectal cancers that are diagnosed early. Prognosis for patients who present with late stages of the disease remains poor. Treatment options include surgery for localized tumors, chemotherapy and immunotherapy. When resectable, surgical removal of the tumor remains the treatment of choice for localized colorectal disease. Surgery may be curative or palliative and is sometimes combined with chemotherapeutic regimes to achieve pre-operative tumor shrinkage (Zhao et al, 2010). Minimally invasive approaches such as laparoscopic surgery for colonic tumors are reported to offer improved short-term clinical outcomes (Hiranyakas & Ho, 2011). Chemotherapeutic regimes include infusional combination therapies such as FOLFIRI that combine irinotecan, 5-fluorouracil and leucovorin, and FOLFOX that combines oxaliplatin, 5-fluorouracil and leucovorin (Lee & Chu, 2007; Garcia-Foncillas & Diaz-Rubio, 2010). Studies suggest that overall survival time and progression-free survival are significantly improved with the addition of cetuximab to FOLFIRI.

Better understanding of some of the molecular mechanisms in colorectal cancer has led to the development of targeted therapy that modulate specific pathways and pathway

components. Biological treatment with bevacizumab, a recombinant antibody to vascular endothelial growth factor (VEGF) receptor, cetuximab and panitumumab has improved clinical outcomes for patients, prolonged survival times and is recommended in metastatic disease (Koukourakis et al, 2011). Despite these improvements in treatment, the number of patients who develop metastatic disease is significant and the prognosis for such patients is poor. Metastatic disease is thought to be related to epigenetic mechanisms and the development of cancer stem cell-mediated chemoresistance (Anderson et al, 2011). Treatment for metastatic disease is complex and requires careful patient evaluation and selection from single and combination treatment options that include surgery for resectable metastases, chemotherapy and biological therapy. Fluoropyrimidine 5-fluorouracil (5-FU) has been joined by cetuximab, an IgG antibody whose efficacy has been documented in several clinical trials (Lee & Chu, 2007). Improving regimes have led to better 2-year survival rates in patients.

New therapeutic approaches and targets are emerging from research studies. One promising approach currently being explored is the prospect of therapeutic vaccines to combat colorectal cancer (Kabaker et al, 2011; Kameshima et al, 2011).

4. Screening for prevention

A reduction in the morbidity and mortality from colorectal cancer can only be achieved through effective screening for the disease. Screening allows for early detection of cancer and early treatment of detected cancers. It is estimated that up to 60% of deaths from colorectal cancer could be prevented by routine screening after the age 50 years (Byers, 2011; He & Efron, 2011). Approaches to screening for colorectal cancer include stool-based tests (fecal immunochemical testing FIT, fecal occult blood testing FOBT), endoscopy (sigmoidoscopy and colonoscopy) and radiologic examinations (barium radiography, and colonography) (de Wijkerslooth et al, 2011). Studies suggest that stool-based testing is more cost effective than colonoscopy (Hassan et al, 2011; Wilschut et al, 2011).

Colonoscopy remains the gold standard for screening and while it offers advantages for treatment such as removal of premalignant lesions, this approach may not be as protective for right-sided disease as it is for left sided disease (Baxter et al, 2009; Brenner et al, 2010; Singh et al, 2010). Other advanced colonic imaging techniques include capsule colonoscopy, computed tomographic colonography, virtual colonoscopy and magnetic resonance colonography (Liu et al, 2011). All screening programs are complicated by social and community factors (such as culture, level of knowledge about the disease) that affect participation rates (O'Donnell et al, 2010; Ramos et al, 2011; Reeder, 2011).

5. Conclusion

Colorectal cancer remains a major health challenge. Trends for geographically distributed fluctuations in incidence point towards the need for developing strategies to tackle increasing colorectal disease in the population under age 50 years, the relationship of the disease with socioeconomic status, and the increasing incidence of the disease in Asia.

Treatment options are still dictated by the stage of the disease in the patient at presentation but evidence from basic science research studies are providing a better understanding of the disease process, drivers for improvements in therapeutic options for patients, and new therapeutic targets for impeding the progression of the disease.

Despite the remarkable improvement in our understanding of certain aspects of colorectal cancer, the best approach to combating the disease remains a preventive one. Prevention and screening programs need to be more efficient and more effective. Cost benefit analyses preclude early adoption of newer screening methods but advances in colonoscopic and colonographic approaches are helping to reduce morbidity and mortality for colorectal cancer.

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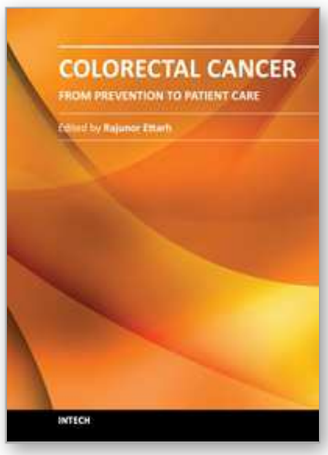

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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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