

Chapter 2

Genetic Alterations in Colorectal Cancer in Older Patients

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Abstract Colorectal cancer is typically associated with advanced age, with an estimated median age at onset which reaches 70 years of age in the western population. Limited data are available regarding the differences in genetic and epigenetic alterations in colonic carcinogenesis between younger and older patients. Some studies suggest that mutation status in critical genes, such as *KRAS*, *BRAF*, or *PIK3CA/PTEN*, is different, depending of the age at diagnosis of colorectal cancer. These data provide the evidence that distinct genetic mechanisms are implicated in the somatic development of colorectal cancer in younger and older patients.

Keywords Ageing • Genetic alteration • Colon cancer • Elderly patients

Introduction

The genetic underpinnings of CRC are especially well studied [52], and a multistep model for the carcinogenetic process in the colon epithelium, from normal mucosa to invasive cancer, has been proposed more than 20 years ago [17], as presented in Fig. 2.1.

This model implicates chromosomal aberrations, a phenomenon termed CIN for chromosomal instability and is associated with common somatic mutations, more frequently in the *APC*, *TP53*, and *KRAS* genes, followed in frequency by *PIK3CA* mutations [53] (Fig. 2.1). This model implicates the activation of the Wnt pathway,

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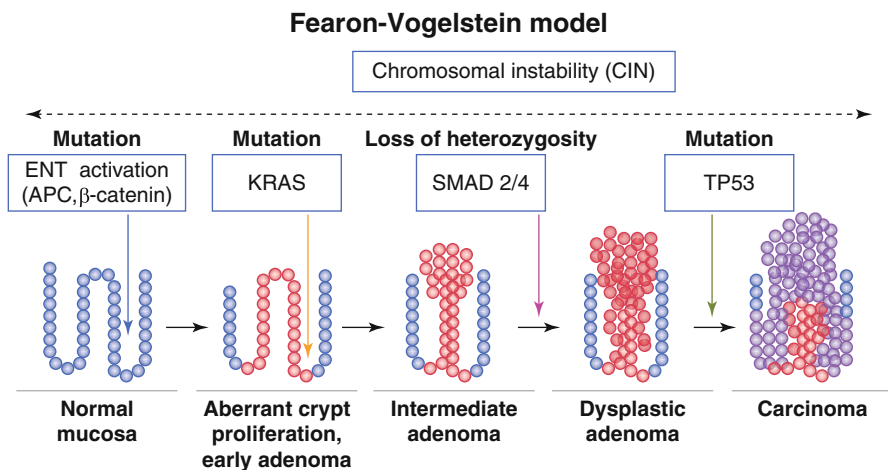


Fig. 2.1 The multistep process of carcinogenesis in the colonic epithelium with the corresponding genetic alteration in each step

through either inactivated mutations in the *APC* (more frequent) or *AXIN* genes or activated mutations of *beta-Catenin*. As a result, the aberrant proliferation of the cell in the crypt increases the level of genetic instability. The activated mutations in the *KRAS* gene lead to the formation of early adenomas. The subsequent loss of the tumor growth factor-beta (TGF- β) control on differentiation, through the loss of SMAD 2/4, leads to progression to advanced-dysplastic adenomas. Finally, the loss of the control to the genomic stability due to inactivated mutations in TP53 gene allows the formation of invasive cancers. For more than two decades, this model was considered as the only way for the initiation and progression of neoplasia in the colonic mucosa.

Subsequently, landmark experiments suggested that not all CRC present CIN. A subgroup of sporadic CRC, up to 15 %, is attributed to microsatellite instability (MSI) due to inappropriate mismatch repair (MMR) system [19]. This simplified approach suggests two paths to colon cancer, with all cases having some measurable degree of genetic instability, either CIN or MSI. The picture became more complex when it was reported that some colon cancers seemed to have neither MSI nor CIN [9]. Moreover, epigenetic changes marked by DNA methylation were increasingly described as a common event in colon cancers, and a specific pathway of intense DNA hypermethylation was identified, the CpG island methylator phenotype (CIMP) [28]. More recently, other epigenetic alterations such as histones modification and chromatin remodeling have also been described in subsets of CRC.

The potential clinical implications of multiple pathways leading to colon cancer are obvious and may change our approaches in all aspects, from prevention to screening to therapy. From a prevention standpoint, if the different colon cancers

arise from different cells, it is likely that familial predisposition and carcinogenic exposures affect each pathway differently. Such heterogeneity in the disease initiation and natural history may explain the difficulties in reproducing some associations between exposures, lifestyle, and genetic polymorphisms on colon cancer risk. By extension then, interventions to prevent colon cancer may have a preferential effect on one disease type but not on others.

The major effect of the multiple pathways to colon cancer model relates to therapy. Despite decades of research, there continues to be uniformity in thinking of and in treating colon cancer. The different colon cancers have vastly different prognoses, ranging from favorable (MSI, BRAF unmutated) to very poor (CIMP, no MSI). Until now, with the exception of *KRAS* mutations as predictor marker of resistance to anti-EGFR monoclonal antibodies [1, 31], this knowledge in the biology of the disease has limited application in the daily clinical practice. In addition, there is no current model (including the classic “Vogelgram”) that fit every patient with CRC. Finally, there are limited data regarding the differences in genetic alterations in colonic carcinogenesis between younger and older patients. These data are discussed in the next pages of the present chapter.

Human Ageing: Genetics and Biodemography

What is actually ageing and what causes it? Regardless of how much we have achieved in the ageing field, this is still a mystery. Self-evidently we can say that ageing is caused by macromolecular damage, since with age, homeostasis declines and damage accumulates. It is only relatively recently that we have discovered that ageing, like so many other biological processes, is regulated by transcriptions factors and signaling pathways. Although initial research was restricted to short-lived organisms such as worms and flies, nevertheless, it soon became evident that the findings applied to mammals as well. Astonishingly, mutational changes found to slow ageing, at the same time, postponed age-related disease, giving a whole new meaning to the field by presenting ageing as a potential therapeutic target [34]. In parallel to genes and environment, another factor which may affect ageing is chance [26].

One of the first discoveries conserved from yeast to primates was that dietary restriction extends lifespan by reducing the cellular damage accumulation rate through nutrient metabolism. But it soon became clear that dietary restriction attacks ageing by an acute and rapid decrease in the mortality rate [38]. We know now that this is accomplished through nutrient-sensing pathways involving the insulin/insulin-like growth factor (IGF-1) [3], the kinase target of rapamycin (TOR) [30], the AMP kinase [21], and the sitruins [36]. Other conditions that can increase lifespan are chemosensory and thermosensory signals, heat and oxidative stress, low ambient temperature, signals from the reproductive system, and reduction in translation and respiration rates [34].

Insulin/Insulin-Like Growth Factor (IGF-1)

This is the first and most well-studied pathway regarding its connection with ageing in animals, which, in addition, has been found to be evolutionary conserved [32]. Inhibiting insulin/IGF-1 signaling changes lifespan through changes (up- or downregulation) in gene expression of several transcription factors like the FOXO transcription factor, DAF-16, and the heat-shock transcription factor HSF-1 and SKN-1 [34]. In addition, the insulin/IGF-1 pathway senses nutrients and thus is a good candidate for mediating the longevity response to dietary restriction [33]. In worms [27], flies [11], and mice [3], dietary restriction extends lifespan through inhibition of the insulin/IGF-1 pathway, and in mice, a combination of mutations and dietary restriction can nearly double lifespan [5]. Completely knocking out the insulin/IGF-1 and PI3K pathways causes worms to live ten times longer than normal [4]. Furthermore, dietary restriction may inhibit cancer by downregulating insulin/IGF-1 signaling [29].

But can an insulin/IGF-1 activity perturbation increase lifespan in humans as well? Possibly yes. FOXO3A cohorts are located throughout the world, and variants of FOXO3A and AKT have been linked with longevity in several of them. Furthermore, in the German cohort, FOXO3A variants are found to be more frequent in centenarians than in 90-year-olds [40]. FOXO1 gene variants, as well, have been linked to longevity in American and Chinese cohorts [35]. In mammals, insulin levels rise in response to glucose, and this rise might shorten lifespan. In humans, conditions that inhibit insulin receptor signaling could actually promote longevity if the dietary glycaemic index was reduced [34]. Dietary restriction and nutrient sensors perturbation inhibit tumor formation as well, and mutations which increase lifespan during evolution probably also delay cancer, as cancer incidence correlates tightly with physiological ageing in different species [32].

Kinase Target of Rapamycin (TOR)

Inhibition of the TOR pathway increases lifespan in many species, and at least in *C. elegans*, it seems to activate a pathway which is distinct from the insulin/IGF-1 one, as it extends lifespan independently of DAF-16/FOXO [30]. TOR inhibition increases resistance to environmental stress consistent with a physiological shift toward tissue maintenance [34].

AMP Kinase

AMP kinase is an energy and nutrient sensor that represses anabolic and activates catabolic pathways when the cell's AMP/ATP ratio rises. In *Caenorhabditis elegans* again, AMP kinase overexpression has been shown to extend lifespan [2, 32]. In a way it mingles with the insulin/IGF-1 pathway since it can also extend lifespan in response to dietary restriction acting directly on DAF-16/FOXO [21].

Sitruins

Sitruins are NAD⁺-dependent protein deacetylases whose overexpression has been shown to extend lifespan in yeast, worms, and flies, but how exactly this is achieved is not clear yet [32]. In *C. elegans* though, sitruin overexpression seems to act by activating DAF-16/FOXO again.

Telomeres

Telomeres have been acknowledged as candidates for ageing determinants because they shorten with age. Their mode of action though is distinct from whatever is discussed above. Mice that are engineered to have longer telomeres live longer possibly because they are genetically modified to resist cancer. Telomere lengthening probably increases lifespan by preventing stem cell loss and certainly not by shifting the animal into a protective physiological state [48].

Telomere length (TL) is also associated with high cancer incidence. Recently, the results of a study where TL's differences between younger and older (≥ 70 years of age) colorectal cancer (CRC) patients were assessed and correlated with survival [14]. The relationship between telomere repeat copy number and single gene copy number (T/S ratio) of peripheral lymphocytes DNA evaluated with qPCR was used as a surrogate value for relative TL. A borderline significant difference in TL (mean TL 0.981 versus 0.925 respectively; $p=0.067$) was observed when patients under and over 70 years of age were compared. When the assessment was repeated using four age groups (50–60, 60–70, 70–80, >80), a statistically significant difference in TL between the youngest and the oldest age groups was demonstrated (mean TL 1.022 versus 0.874, respectively; $p=0.02$) with evidence of shorter TL with advanced age. A marginal relationship was detected between overall survival (OS) and age (p -value=0.066) with older patients exhibiting slightly poorer survival [hazard ratio (HR) of 1.03, 95 % confidence interval (CI) 0.998–1.065], and no correlation was noted between relative TL and OS in the univariate and multivariable analysis. The authors concluded that their results validate the ability of a qPCR-based assay to differentiate between younger and older CRC patients with the use of TL, and this methodology is being used with the scope to evaluate the relationship of TL to treatment tolerance in elderly CRC patients [14].

Prospects for Human Interventions

Until recently the idea of lifespan extension was not a science project. Now we know that longevity can occur without debilitating trade-offs, and in long-lived mutants, many age-related diseases are delayed. The US Federal Drug Administration does not recognize ageing as a condition to be treated, as an indication; thus, for the time being, drugs affecting ageing will be approved only if at the same time they

affect disease. Rapamycin, a TOR inhibitor, which is approved for human use for immune suppression has shown to extend the lifespan of mice even when administered late in life [23]. Drugs that are being developed to target age-related diseases, such as IGF-1 pathway inhibitors for cancer, may achieve extension of youth and life as well, but we do not know yet their potential or their side effects. It seems reasonable that drugs mimicking the effects of genetic mutations which extend lifespan might extend lifespan as well.

The Postponement of Human Senescence and Mortality

Senescence results from a cumulative imbalance between damage and repair. Progress in increasing repair (via medical intervention) and reducing damage (via public health preventing disease's strategies) are the two fundamental causes for health improvement [50].

Human senescence itself, as it was first documented back in 1994, has been delayed by a decade. This observation, as expected, has profound implications not only for individuals but also for society and economy. Mortality at advanced ages is being postponed because people are reaching old age in better health, not as a result of revolutionary advances in slowing the ageing process but as a result of ongoing and successful measures for improving health [50]. In countries with high life expectancies, the majority of children born since 2000 will arrive and celebrate their 100th birthday in the twenty-second century [10]. Although genetic factors have a modest role in determining the life longevity of individuals, nevertheless, the progress in postponing senescence is entirely due to medical revolution and public-health efforts, due to better education, rising living standards, healthier nutrition, and lifestyles. Since 1840 life expectancy has been increasing by more than 2 years per decade, and no imminent limit to further increases exist [39]. In addition it seems that weakness and frailness is being postponed as well. Prosperity and medicine are the two major factors contributing to postponement of senescence and debility. We cannot actively distinguish which is the most important because in many ways they interact with each other. Healthier populations are more productive and prosperous; prosperity allows access to better treatment, higher education, and more research [50].

In 1994, from a Swedish mortality data analysis, the first conclusive documentation that death is being delayed emerged. In the same year, two subsequent studies confirmed this finding in other countries as well. Since then, research is showing that postponement is continuing, and as a result of that, a remarkable increase in the numbers of centenarians is produced. From Aristotle's distinction between premature and senescent death, the widely accepted view was that the only cause of death at an advanced age is indeed old age and that nothing can be done about it. Thus, each species was thought to have a characteristic maximum upper limit of lifespan, which could never be overcome [50]. These notions, though, were recently contradicted [8, 12]. Mortality for humans seems to level off after the age of 110. Exceptionally long-lived people reach advanced age because they have a better state of health.

The search to discover genes related to major longevity has had little success, summarized to the modest effect of the two variants of the apolipoprotein E gene (APOE) [16, 20]. The theory of evolution as far as ageing is concerned supports that senescence is inevitable for all multicellular species [22]. Biodemography, though, has shown that this theory should be expanded in order to permit greater variations. Research in the laboratory and in the field confirms that for certain species and for certain periods of adult life mortality can decline with age. Furthermore, genetic, environmental, and dietary changes can substantially alter survival [22, 50].

In contrast with death, health is a difficult parameter to measure, and it is often unreliably documented. The prevalence of disease and morbid disorders among the elderly has increased over time, and part of this rise is due to earlier diagnosis of disease, like cancer and heart conditions [10, 50]. Most kinds of morbidity and disability, such as heart disease and dementia, lead to higher death rates. To achieve life expectancies of more than 100 years of age, novel knowledge will be needed. Genetic research will contribute to a deeper understanding of the mechanisms underlying senescence. Advances in research will potentially lead to prevention and more successful treatment of cardiovascular diseases and cancer [45]. Dietary restriction and other nongenetic interventions might also lead to strategies for delaying human ageing [38]. Although death reduction from any disease will not immediately and radically increase life expectancy, advances against many diseases acting synergistically will, especially because comorbidity is so common among the elderly. In this sense, geriatrics is becoming an attractive and important specialty, and research on ageing is now an engaging, proactive science with considerable funding from the authorities. Nothing in evolution can be understood except under the light of demography (and vice versa) because evolution is driven (and drives) by the dynamics of fertility, mortality, and migration of nonhuman species and humans as well [50]. Although the policy makers recognize that the world's population is ageing, they do not seem to realize that reform and change in the social, economic, and health-care system should be implemented in a faster pace. The twentieth century was the century of the redistribution of wealth, but the twenty-first will most likely be a century of the redistribution of work toward greater ages [51].

Mutational Profile of the CRC Genes in Relation to Age

CRC is typically detected in older people and has a median age at onset which reaches 70 years of age. Approximately 5 % of all CRC cases are diagnosed in patients younger than 50 years of age, and this early onset usually indicates an increased likelihood for genetic predisposition [6]. Nevertheless, the vast majority of these cases are ultimately regarded as sporadic, since no known genetic predisposition is found [37, 54].

The RAS-RAF-MEK-ERK-MAP kinase pathway mediates cellular responses to growth signals constituting an essential component of intracellular signaling from activated cell-surface receptors to transcription factors in the nucleus [41]. Some of

the above-mentioned genes are critical molecular markers in CRC carcinogenesis and have already been incorporated in the treatment of CRC patients. Indeed, the knowledge of a primary tumor's *KRAS* mutational status is mandatory for the treatment of metastatic disease, since it is a predictor of resistance to monoclonal antibodies of the epidermal growth factor receptor (anti-EGFR mAbs) [7, 15, 24, 47, 49]. In addition, *BRAF* V600E mutation identifies a subgroup (less than 10 %) of patients with an exceptionally unfavorable prognosis [13, 46]; conversely, the presence of a defective tumoral DNA mismatch repair (dMMR) system seems to be a favorable prognostic factor, although these patients seem to fair worse with standard adjuvant chemotherapy [18, 25, 42, 43]. Furthermore, *PTEN* (phosphatase and tensin homolog) protein expression, and specifically its loss, seems to be associated in a number of studies with resistance to anti-EGFR MoAbs treatment [44].

In a study by Berg et al. [6], 181 CRC patients were included and divided into three age groups, younger than 50, 51–70, and older than 70 years old. Among the CRC patients, stratified by microsatellite instability status, DNA sequence changes were identified in *KRAS* (32 %), *BRAF* (16 %), *PIK3CA* (4 %), *PTEN* (14 %), and *TP53* (51 %). In the oldest patient group, MSI and *BRAF* mutations were statistically significantly correlated ($p < 0.001$), but no such correlation was found in the <50 age group. *KRAS* and *BRAF* mutation frequencies increased with patient age, both when comparing age groups and when age was considered as a continuous variable. In patients younger than 50 years old, *PIK3CA* mutations were not observed, and *TP53* mutations were more frequent than in the older age groups, implying that *PIK3CA* mutations are important for tumorigenesis among the elderly. No difference between the age groups was observed regarding *PTEN* mutations and aberrations.

Genome complexity, assessed as copy number aberrations, was highest in tumors from the youngest patients (<50 years old) group than from the >70 years old group. Contrary, the tumors from elderly patients had the highest gene mutation index, even though this group included fewer advanced stages. One could speculate that among the young patients, there are carriers with genetic predisposition.

A comparable number of tumors from young (<50 years) and old patients (>70 years) were quadruple negative for the four predictive gene markers (*KRAS-BRAF-PIK3CA-PTEN*); however, 16 % of young versus only 1 % of the old patients had tumor mutations in *PTEN/PIK3CA* exclusively. This implies that mutation testing for prediction of anti-EGFR treatment response may be restricted to *KRAS* and *BRAF* in elderly (>70 years) patients. Finally, *KRAS* mutant patients among the young age group were found to have significantly shorter survival than *KRAS* wt ones ($p = 0.02$).

In conclusion, in the study by Berg et al. [6], it was documented that the mutation status of the above-mentioned critical gene set varies depending on age at diagnosis and provides evidence of differences in the somatic development of CRC tumors in young and elderly patients. Nonhereditary CRC tumors in young patients have less gene mutations but more copy number aberrations across the genome, suggesting that some young patients may have an increase risk for cancer caused by alterations in genes involved in maintaining correct chromosome segregation. Distinct genetic

differences found in tumors from young and elderly patients, whose clinical and pathological variables are comparable, indicate that young patients have a different genetic risk profile for CRC development than older patients.

Conclusion

The genetic alterations and subsequent molecular modification responsible for the initiation and progression of neoplasia in the colonic epithelium are the same between younger and older patients. The limited available data in the field support that colon cancer in elderly patients is associated with higher gene mutation index but less copy number aberration in comparison with tumors from younger patients. In addition, the incidence of *BRAF* mutations is higher in older patients.

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