



Ageing and Cancer Research & Treatment

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Abstract

Increasing life expectancy globally results in predictions that one in six people will be > 65 years of age by 2050. Because the occurrence of most cancers is strongly associated with older age, a significant increase in the number of older adults with cancer is to be expected. It is likely that increased cancer in older adults can be explained both by the greater duration of exposure to external factors such as ultraviolet radiation, alcohol, smoking and pollution (hence modifiable by non-medical means) as well as intrinsic factors (such as metabolic stress and reactive oxygen species). These insults contribute to DNA damage and mutation that can lead to carcinogenesis if not counteracted by the appropriate repair mechanisms, or other protective strategies. Tissues from cancer-free individuals frequently contain mutations commonly observed in cancer, but these cells remain dormant until some endogenous or exogenous events promote carcinogenesis. In ageing individuals, less efficient surveillance and immune responses against cancer may represent one such event, as well as the chronic low level inflammation commonly accompanying ageing. Additionally, because of comorbidities, older patients are less robust and it is more likely that polypharmacy interferes with cancer treatment. Despite all this awareness of the impact of ageing, most cancer research, both clinical and preclinical, fails to fully consider age-associated differences in cancer occurrence and treatment, and there are very few journals specifically dedicated to publishing explorations of these issues in either the basic research or clinical context. Hence, the time has come to establish a new journal dedicated to taking a holistic approach to all aspects of cancer in older individuals. We are therefore now welcoming papers that may shed light on these increasingly important issues.

Keywords: Ageing, cancer, inflammageing, comorbidities, treatment, geriatric oncology, immunosenescence

1. Introduction

The projection for 2050 is that one in six people in the world will be > 65 years of age and the number of people aged > 85 years in the European region is expected to double (from 19 million in 2020 to 40 million). This increase in life expectancy reflects improvements in public health and medical treatments^[1]. However, a corresponding increase in age-related diseases and disabilities is also to be expected albeit at even more advanced age but with consequent reduction in health span. Centenarians may be less affected by chronic conditions such as diabetes and dementia, as well as cancer, but eventually succumb to a similar range of pathologies with a lower frequency of cancer, presumably due to population selection pressure^[2]. Because cancer occurrence is strongly associated with ageing, a significant impact of the increasing numbers of older adults with cancer is also expected to be felt by the public health system^[3]. According to US statistics (2015–2016), cancer is the second leading cause of death exceeded only by cardiovascular disease^[4], but with the increase in the number of older adults cancer may become the main cause of death in the next decades. This raises the important question of how global health systems will manage cancer care of their increasingly elderly populations. Thus, although cancer mortality in age-standardised analysis is declining because of improved prevention, earlier diagnoses and more effective treatments, total diagnoses and death rates continue to rise due to population ageing^[3]. As noted above, the probability of cancer development and subsequent progression to invasive disease increases with age (1 in 16 at 50 to 59 years, but 1 in 8 at 60 to 69 years, and 1 in 3 for people older than 70 years) with the commonest cancers being prostate, breast, lung and colorectal^[4]. Hence, unless advances in cancer care specifically for the over-70's are forthcoming, the increasing number of patients may rapidly outrun the capacity of health care systems to cope. Therefore, a focus on age-related differences in carcinogenesis, cancer progression and treatment tailored specifically to the older population is a current imperative. Moreover, it is clear that assessing the impact of “age”



on cancer development and progression, and responses to treatment, merely in terms of chronological age, rather than biological age, offers only a very crude estimate of ageing processes. Currently, there is much discussion on relationships between biological age, geriatric assessment and frailty scores, and how best to translate these concepts to the clinic^[5,6]. Assessments of individual biological age at the subcellular, cellular, organismal and societal levels are beginning to play an increasingly important role in the field of ageing research and this will certainly impact on cancer research and treatment.

2. Extrinsic and Intrinsic Factors Contributing to Cancer Development and Progression

The increased susceptibility to cancer in older adults can be explained, at least in part, by more years of exposure to factors such as ultraviolet radiation, alcohol, smoking and pollution, as well as to intrinsic factors (including metabolic stress, reactive oxygen species, enzymatic errors) which all contribute to the accumulation of DNA damage if not properly repaired. These processes are not exclusive to overt carcinogenesis in that non-cancerous tissues commonly exhibit age-associated increases in such abnormalities. Thus, for example, sequencing data from normal tissues identified mutations commonly present in cancer and quantify cells with cancer-associated mutations present in individuals who nonetheless remained cancer-free. Increasing percentages of mutated cells with increasing age are found, of a type which can lead to various disruptions in tissue function and diseases as recorded in the Cancer Gene Census, with mutations that alter protein function. These findings suggest that mutated clones of cells remain dormant in tissues that are cancer-free until some additional events (endogenous or exogenous) promote overt carcinogenesis^[7]. Thus, it has been well-established that normal human epithelium from different tissues harbours cells with cancer-driver gene mutations (i.e. esophagus, skin, endometrium, lung, bladder, colon). Rather surprisingly, such cells can be more numerous than in actual tumor lesions^[8,9]. Therefore, normal adult tissues are composed of a mosaic of mutant clones that compete for space and survival, suggesting that less competitive clones are eliminated^[9]. However, it is still unknown how this competition could impact early tumor development and what might be more likely to cause loss of control in aged hosts. The process of how mutant clones in normal tissues can acquire malignant potential is being dissected using modern techniques such as whole genome sequencing (single nucleotide variants, SNVs) and mitochondrial DNA mutation (mtDNA), RNAseq and in situ single cell RNAseq. For example, Buhigas *et al.*^[10] reported a high number of SNVs and indels in addition to clonal expansion under selective pressure in morphologically normal tissues of patients with prostate cancer. In patients without prostate cancer the number of mutations was significantly lower and lacked clonal expansions under selective pressure. Cancer stem cells have been considered the likely miscreants in cancer development and progression, and have been most unequivocally investigated in the hematopoietic system. Thus, hematopoietic stem cells (HSC) harbouring mutations conveying an advantage over other mutated cells expand competitively and generate clones of specific mutated HSCs (clonal hematopoiesis) which accumulate during ageing. Pre-malignant clonal hematopoiesis may precede acute myeloid leukemia^[11] and chronic lymphocytic leukemia^[12]. A recently described important age-related event in hematopoietic tissue is clonal hematopoiesis of indeterminate potential (CHIP) that occurs in 10 to 30% of individuals older than 70 years. CHIP present cancer-associated somatic mutations in hematopoietic cells in the absence of overt hematologic carcinogenesis or other clonal disorder^[13,14]. In the context of solid tumours, Cereser *et al.*^[15] were interested in identifying stem cells within the mammary epithelium using a lineage tracing technique for mtDNA mutations as a marker of clonal expansion. Areas with clones containing mtDNA mutations were observed in the normal adult human mammary epithelium, whereas ductal carcinoma in situ presented large areas of mtDNA mutation implying that in premalignant lesions there was a change in the rate of clonal expansion^[15]. In all, it had been estimated over a decade ago that mutations in as many as ~140 cancer driver genes are needed to confer a competitive advantage contributing to tumor development^[16]. Hence, regarding competition between normal cells and mutant cells, there is much for selection to work on, and whether and how these process are influenced by age is not clear. What is known is that gene interactions can be neutral, tumor suppressive or tumor promoting, making age-associated differences crucial. In addition, it has been shown that the same mutation can lead to either tumor suppression or tumor promotion, at least in animal models^[17], probably depending on the type of tissue, mutant cell numbers in the tissue, microenvironmental changes, other mutations co-occurring, and treatment. It can be hypothesized that cancer development and progression in older adults exposed long-term to factors leading to DNA damage and accumulated mutations is due to: 1) at some point acquiring mutations in ~140 cancer driver genes; 2) having highly competitive mutated cells; 3) increased clonal expansion under selective pressure; 4) microenvironmental changes to tissues surrounding mutated cells. Other factors contributing to disequilibrium of the multiple positive and negative influences maintaining dormancy then come into play in determining whether or not overt cancer develops. These factors include a role for potentially less efficient surveillance and immune responses against cancer, exacerbating effects of age-associated low grade systemic chronic inflammation (“inflammageing”), and comorbidities.

3. DNA Damage and Cancer

For mammalian cells it is estimated that around 10^5 lesions/day/cell occur, most of which are efficiently repaired^[18]. External exposures such as UV light, ionising radiation, or chemical mutagens induce DNA damage. In addition, DNA damage occurs endogenously via reactive oxygen species (produced because of mitochondrial dysfunction and metabolic stress), enzymatic action and errors in replication leading to mutations. An excess of oxidative stress has been linked to DNA damage, ageing, and cancer. During the ageing process, lesions can escape detection, or are not possible to repair, are repaired too late or repaired erroneously. The consequences associated with DNA damage are genome instability, telomere dysfunction, alterations in epigenetics, proteostatic

stress and changes in the function of mitochondria^[19]. The accumulation of mutations over time is clearly, but as already reported a decade ago, not linearly, related to an increased risk of cancer^[20]. To overcome this problem, it is essential that the cell detects DNA damage, promotes cell cycle checkpoint arrest (via phosphorylation and ATR/ataxia-telangiectasia mutated (ATM) kinases) and repairs the damaged DNA, processes involving expression of p53 and p21. The net resulting cell fate if repair is not correct is senescence, apoptosis or quiescence, hypothesized to dictate whether the organism preserves mutated cells or exhibits a phenotype of accelerated ageing^[21].

Many studies illustrate the intersections of ageing and carcinogenesis pathways. In a recent example, Hadar *et al.*^[22] investigated B lymphocytes of healthy donors and found that a gene associated with longevity ATM and linked to DNA damage repair had a higher expression in centenarian women than in older women aged 56–88 years. These findings strongly suggest that effective DNA repair leads to maintenance of DNA stability, reduces cancer risk and plays a role in longevity. Age-related reduction of gene repair has been shown, for example, in the decreased expression of DNA polymerase β which is essential for replication and repair of DNA^[23]. Aparicio *et al.*^[24] evaluated the deficient DNA mismatch repair phenotype (dMMR) in older adults (75–100 years) with colorectal adenocarcinoma and reported a high level of dMMR, reaching 36% after 85 years of age. Probably as a consequence of defective DNA repair, in an evaluation of 100,000 cancer cases, Chalmers *et al.*^[25] found that tumor mutation burden is significantly increased with ageing (2.4-fold difference between 10 and 90 years).

Taken together, these examples and many other data suggest that hallmarks of ageing are already a part of the cancer cell phenotype. The accumulation of somatic mutations has been associated with the ageing process and thus it is, at least in part, the reason for ageing to be considered the major risk for cancer. Moreover, the chronic low-grade of inflammation, characteristic of the human ageing process, may influence the clonal selection and expansion alluded to above. Interventions targeted to lowering mutations and/or repair of DNA damage could therefore both slow ageing and delay cancer. Clearly a better understanding of these phenomena in the context of tumor occurrence and treatment in older patients, not only by chemotherapy, is of paramount importance for future progress towards improved cancer therapies.

4. Immune Surveillance and Immune Responses against Cancer

Replicatively senescent cells accumulate in older individuals due to different forms of stress (eg. DNA damage, telomere shortening), a phenomenon viewed as protective against carcinogenesis. Thus, cellular senescence via cell-cycle arrest is associated with the prevention of premalignant or damaged cell proliferation. However, cellular senescence, resulting in stable cell-cycle arrest, may also be related to excessive inflammation and imbalance in homeostasis due to secretion of pro-inflammatory cytokines (the senescence-associated secretory phenotype, SASP^[26]). These factors also attract NK cells, macrophages and T cells which eliminate the senescent cells in multiple tissues; hence, clearance of senescent cells relies, at least in part, on immune surveillance. In this way, the increased accumulation of senescent cells with age may be due to a combination of impaired immune elimination and the higher generation of these cells in late life^[27,28]. The ageing process is linked to alterations to the innate and adaptive branches of immune function (immunosenescence) which may contribute to incomplete elimination of senescent cells^[29]. However age-associated differences may not only reflect chronic dysfunction, but may be essential for prolonged survival/longevity, such that distinguishing between beneficial adaptive changes and pathology can be a challenge^[30]. This is made more complicated by the lack of specific senescence markers^[31]. However, there are many candidates which may be useful separately or clustered together for informing on the presence of senescent cells and their interactions with their microenvironment, depending on the tissue examined and the functional tests employed. For example, recently, a marker of senescent cells has been proposed based on the observation of an increased expression of HLA-E on senescent skin cells from older adults. This marker is induced by the SASP and has been linked to inhibition of the immune response against senescent cells by action on NK and CD8⁺ T cells (via the NKG2A receptor). Correspondingly, blockade of HLA-E-NKG2A interactions was associated with an increased immune response against senescent cells *in vitro*^[32]. In another *in vitro* model, senescent fibroblasts from a cell line showed an increased expression of PD-L1 after nutlin3a- and DNA damage-induced senescence, suggesting immune surveillance escape via ligation of the negative signalling receptor PD-1 on effector cells and consequent accumulation of uncleared senescent cells^[33].

As first proposed by Schreiber *et al.*^[34], tumor immune surveillance is a complex process including nascent cancer cell elimination, a balance between malignant cells escaping immunity and the induction of immunity by mutated cells in an equilibrium phase, followed by tumor antigenic evolution and consequent escape from immune control (evasion). Age affects all these processes and thus renders responses in younger and older individuals different in many respects. Immune cells infiltrating tumors have been evaluated with the aim of identifying the best approach for cancer therapy bearing in mind the impact of age. Based on the combination of characteristics such as nature, density, function and distribution of immune cells infiltrating tumors, for example, an “immunoscore” was proposed for colorectal cancer (CRC). This included establishing whether the tumor was T-cell infiltrated, inflamed but non-infiltrated, or non-inflamed, which was associated with survival (10%, 50% and 80% risk of relapse after 2 years, respectively), as well as predicting response to treatment^[35,36] with a terminology referring to these profiles as “hot” (infiltrated), “altered” (inflamed but non-infiltrated) and “cold” (non-inflamed) tumors within primary CRC^[37]. This classification also applies to melanoma and other types of cancer, and provides a set of standardized parameters that can be assessed for age-associated

divergences. The effects of patient age on all these parameters requires clarification. Associated with the presence and nature of tumor-infiltrating T cells, the products of these cells such as IFN- γ that can act as an anti-tumor or pro-tumor agent depending on the cellular microenvironment and/or molecular context, in addition to anti-tumor cytotoxicity, is also important and known to exhibit age-related differences. Also, immunosuppressive mechanisms in the tumor microenvironment (TME), both tumor-intrinsic and a local adaptive response, may differ with age as well. Tumor-intrinsic mechanisms may be related to activation of oncogenic pathways that interfere with cytokine and chemokine expression and lead to the exclusion of T cells. Local adaptive immunosuppression has been linked to hot or immunosuppressed tumors depending on the driving mechanisms^[37].

Based on our increasing understanding of the immune system, new approaches (precision immuno-oncology) to treat cancer have been developed. For example, Salih *et al.*^[38] found that in patients with metastatic melanoma, after one cycle of immunotherapy, there was an increase of diversity of the T cell receptor repertoire in peripheral blood in patients who were responding to immune checkpoint blockade (ICB). An expanding subset of CD8⁺ T cells with effector memory phenotype that was associated with response to ICB and an increase in overall survival was seen in these patients. Moreover, this subset of CD8⁺ effector cells was increased with age in these treated patients, suggesting a mechanistic basis for the emerging notion that older patients may counter-intuitively respond better to ICB than younger patients^[39]. Thus, Kugel *et al.*^[40] found that melanoma patients > 60 years of age exhibited an age-related increased response to anti-PD1 ICB. Older patients possessed intra-tumoral immune cells with lower levels of FOXP3 and higher levels of CD8⁺ effector T cells when compared with younger patients, suggesting that there were fewer suppressive T cells in the TME. Another example is provided by the report of Giunco *et al.*^[41] who evaluated 81 patients with CRC (mean age 76 years) and observed a correlation between peripheral blood CD8⁺ potentially senescent T cells (CD8⁺CD28⁻CD57⁺) and higher risk of disease relapse. These few examples serve to illustrate the importance of addressing “immunosenescence” in the context of ageing and cancer research and treatment, which should be a fruitful area for much future research.

5. Inflammageing

Briefly, inflammageing is characterized by slightly increased serum levels of pro-inflammatory cytokines such as IL-6, IL-8 and IL-15, among other factors, that could be a result of increased SASP in older adults, as well as reflecting the immune history of antigen exposures over the lifetime of the person. Considering that these exposures could be very different in quantity and quality for each individual and be under genetic influence, it is expected to find a great heterogeneity in older adults. The low level of chronic inflammation (inflammageing) is a common phenomenon observed in aged individuals and it has been associated with age-related conditions such as cancer^[42]. Thus, for example, inflammatory biomarkers in serum (eg. C-reactive protein, IL-6, serum amyloid A) and the TME (tumor associated macrophages, matrix metalloproteinases, sphingosine 1-phosphate, C-reactive protein, etc.) have been associated with tumor relapse and breast cancer progression/metastasis^[43]. Inflammatory cytokines have been shown to exert pro-tumor effects in vitro by enhancing cell proliferation, migration/invasion, and driving stem cell emergence. On the other hand, cytokines can recruit immune cells to the TME which eliminate senescent cells and cancer cells^[44]. To demonstrate that systemic factors present in older patients can interfere with cancer development and, most importantly, that these soluble factors have distinct actions in different individuals, Barajas-Gómez *et al.*^[45] incubated human breast cancer cells from the MCF-7 cell line with high proliferative but low metastatic potential with serum of older patients (60-83 years old) and compared the capacity of WI-38 senescent cells (secreting inflammatory cytokines) to induce proliferation of MCF-7. It was observed that some sera caused an increase in MCF-7 proliferation whereas others decreased it. Incubation of MCF-7 cells with cytokines from WI-38 senescent cells caused a significant increase in proliferation. It was concluded that the inflammatory microenvironment plays an important role for the high incidence of cancer in older adults, but with marked inter-individual variability. Thus, both pro-inflammatory and anti-inflammatory profiles in the circulation and the TME co-exist in the same individual and an imbalance between them, as seen in ageing, could contribute to tumor development and progression. This is one of the current themes that deserve much more rigorous investigation in the context of ageing and cancer research and treatment.

6. Comorbidities and Cancer

As discussed above, the accumulation of senescent cells in tissues and the consequent chronic inflammation profile due to the SASP has been linked to the decrease in tissue integrity and function which plays an important role in age-related diseases^[46]. This may set up a vicious feedback circle, between, for example, inflammation, cancer and cardiovascular disease. Thus, Akonde *et al.*^[47] analysed data from the 2017 US National Health Interview Survey and found that individuals with cancer presented hypertension as the prevalent disease (52% of cancer patients). In addition, a significantly higher incidence of the most common comorbidities was seen in patients with cancer than in those without cancer. This paper also raises the specter of health disparities in ageing and cancer due to different frequencies of comorbidities in disadvantaged populations. Because of comorbidities, polypharmacy is common in older patients, which also needs to be considered for anti-cancer therapy, different from younger patients. In an early study, van Erning *et al.*^[48] evaluated a large number of patients with CRC (> 70 years of age) and found that half of them used as many as 7 different drugs and only 10% did not take any drug. The coexistence of cancer and other chronic diseases with consequent polypharmacy can alter the toxicity and side effects of anti-cancer therapy, leading to a less effective treatment, often excluding patients from optimal treatments. Unsurprisingly, it has been clear for many years that comorbidity has a negative impact on the survival of patients with

cancer that correlates with the severity of the comorbidity^[49]. A vicious circle can also be established here, where the risk of developing comorbidities is increased due to cancer therapies^[50].

In addition to the most common comorbidities observed in older adults, another important public health concern in many countries is obesity, with excessive adiposity being associated with increased inflammation, insulin resistance, p53 activation and telomere shortening^[51]. Renehan *et al.*^[52] performed a systematic review and meta-analysis to identify the risk of cancer related to a 5 kg/m² increase in body mass index (BMI). In 282,137 cases it was found that this increase in BMI had a strong association with esophageal, thyroid, colon and renal cancers in men. In women, a strong correlation was observed with endometrial, gallbladder, esophageal and renal cancers. That study also clearly highlighted crucial differences between the sexes which must always be taken into account. Further data on the impact of adiposity derive from a study by Kim *et al.*^[53] using positron emission tomography/computed tomography to measure glucose standardized uptake values (SUV) of visceral adipose tissue (VAT) in 148 breast cancer patients. It was found that high SUVmean-VAT was strongly correlated with tumor recurrence, suggesting that a new target for breast cancer therapy could be activated visceral fat metabolism (control of dysmetabolism and systemic inflammation). In a different cancer, Del Cornò *et al.*^[54] performed RNA sequencing in human visceral adipocytes from subjects (lean, obese) with or without CRC. It was found that genes with altered expression in obese patients were related to fatty acid, glucose and pyruvate metabolism. CRC was associated with deregulated expression of genes involved in cell adhesion/migration and extracellular matrix remodelling (collagen). It was concluded that changes observed in visceral adipocytes of obese subjects may play a role in tumor promotion via inflammation, metabolism (lipid and glucose), fibrosis, cell-cell communication, secretion of circulating factors signalling to other tissue and coordinating energy metabolism. The same investigators observed that adipocytes from obese subjects with CRC presented higher complexity in terms of the number of genes, long non-coding RNAs, microRNAs, in addition to changes in biological pathways, suggesting that transcriptional and post-transcriptional processes of adipocytes were significantly affected by obesity^[55]. A final example in the context of adiposity is provided by the work of Frasca *et al.*^[56] who observed that cells from obese young and older adults exhibited impaired B cell function in vitro with increased secretion of pro-inflammatory cytokines and decreased secretion of anti-inflammatory cytokines relative to lean subjects. In addition, B cells from obese subjects supported the production of pro-inflammatory IL-17 and IFN- γ by T cells. Considering that VAT increases with age and that this is negatively associated with 5-year overall survival (in women), as shown many years ago by Folsom *et al.*^[57], obesity could be related to cancer development both via impairment of the immune system and by promoting an inflammatory profile.

7. Physical Exercise

Worldwide increased sedentary behavior seems to parallel increasing income^[58] which may become particularly relevant as the world population ages and becomes more affluent, because “insufficient exercise” is associated with an increased risk for many different cancers^[59]. One simple possible mechanism is by reducing the low-grade inflammation often present in older adults^[60], although many subtle mechanisms may be involved^[61]. Obesity, at least partly associated with decreased activity, is also related to an increased prevalence of different types of cancer^[62]. The effect of aerobic physical activity on immune system cells such as neutrophils, natural killer cells, cytotoxic T cells and immature B cells may lead to improved immunosurveillance^[63] and thus benefit older adults and those with obesity. In addition, there are some reports linking physical activity to changes in gut microbiota composition which could be extrapolated to beneficial effects in cancer prevention and/or development^[64,65] as discussed in the following section.

8. Gut Microbiota

Changes in the composition and function of microbes in the gut have recently been shown to influence the development and progression of several different diseases; the composition of this gut microbiota differs in younger and older individuals^[66]. For example, Odamaki *et al.*^[67] reported an age-related increase in *Bacteroidetes* and *Proteobacteria* with decreases in Firmicutes. A study in Chinese found that the presence of Firmicutes had a negative correlation with IgM levels whereas *Bacteroidetes* positively correlated with IgG and CD8⁺ T Cells. Adults older than 60 years presented decreases in *Bacteroidetes* and increased *Verrucomicrobia* which had a positive correlation with IgA and CD8⁺ T cells^[68]. In a short nutritional intervention study (2 weeks) adults from 40 to 65 years of age consuming whole grains (WG) or refined grains were compared. The WG group showed an increase in the short-chain fatty acid producer *Lachnospira* whereas the pro-inflammatory *Enterobacteriaceae* decreased. In addition, the WG group had a higher percentage of terminally differentiated effector memory cells in the blood and greater ex vivo production of TNF after LPS stimulation^[69]. In a longer (10-week) dietary intervention with high-fiber or highly fermented foods, healthy adults (mean age 51 years) were evaluated for microbiota in stool (composition, function, metabolic output) and for immune markers in blood (cell frequency, cytokine levels). In high-fiber diet recipients, the expected increase in the diversity of microbes was not seen, whereas in highly fermented food consumers there was an increased microbiota diversity correlated with a decrease in markers of inflammation^[70]. These findings link diet to age-associated changes in microbiota composition and function which modulate numerous physiological parameters, including immunity.

A correlation between commensal bacteria and cancer progression/response to therapy is also very likely. Sivan *et al.*^[71] observed that mice with different commensal microbiota presented dissimilar immunity against melanoma and that *Bifidobacterium* was associated with spontaneous antitumor responses. The use of ICB with anti-PD-L1 combined with oral administration of

Bifidobacterium yielded better results than either alone. The positive antitumor response was associated with increases in dendritic cells and CD8⁺ T cells in the tumor. Moreover, Vétizou *et al.*^[72] showed that mice kept in regular specific pathogen-free (SPF) conditions versus mice in germ-free (GF) conditions, exhibited very different responses to anti-CTLA-4 ICB treatment of MCA205 sarcomas in that neither GF nor antibiotic-treated mice were cured, whereas SPF mice could be. The positive effect of anti-CTLA-4 was associated with the presence of *Bacteroides*. The authors went on to show that melanoma patients treated with the anti-CTLA-4 antibody Ipilimumab presented changes in their microbiota with predominance of *Prevotella* and *Bacteroides*. Since these two seminal papers, many reports have confirmed that cancer immunotherapy (and other cancer treatments) is markedly affected by the gut microbiota, explaining why the administration of antibiotics is associated with reduction in the response to immune checkpoint inhibitors^[73]. Heshiki *et al.*^[74] found that fecal samples from patients with different cancers evaluated at various time points (baseline/post-treatment) presented *Bacteroidetes* and *Firmicutes* as the most abundant phyla. Baseline findings predicted the outcome for cancer therapy and intestinal microbial compositions were correlated with responder or non responder status. *C. symbiosum* and *R. gnavus* present at high abundance in non-responders suggested dominance of *Firmicutes* and inhibition of *Bacteroidetes* whereas in responders the microbiota appeared similar to healthy individuals. A final example of the accumulating evidence for the crucial influence of the gut microbiota comes from an evaluation of patients 37 to 92 years of age with metastatic melanoma receiving ICB, showing that the presence of *Firmicutes* was associated with the clinical efficacy of anti-CTLA-4 plus anti-PD1 antibody treatment. Increased *Faecalibacterium* was linked to a high density of infiltrating CD8⁺ T cells^[75].

Cross talk between the gut microbiota and the immune system may occur at least in part via short chain fatty acids which are microbial metabolites having modulatory effects on immunity^[76]. The long-term consumption of a Western diet (high animal protein, choline, saturated fat) has been linked to high abundance of *Bacteroides* and low abundance of *Prevotella*. However, the enterotype of low *Bacteroides* and high *Prevotella* is seen when consuming a plant-based diet rich in fiber, simple sugars, and plant-derived compounds. In addition, an enterotype with *Ruminococcus* (*Firmicutes*) at a high frequency has been associated with irritable bowel syndrome possibly because *R. gnavus* produces L-rhamnose oligosaccharide that induces pro-inflammatory TNF^[77]. In contrast, a Mediterranean diet with complex carbohydrates (cereals, legumes, vegetables, fruits), polyunsaturated fatty acids with antiatherogenic and anti-inflammatory actions (olive oil and nuts), antioxidant bioactive products (flavonoids, phytosterols, terpenes and polyphenols), and micronutrients (vitamins, minerals) correlates with eubiosis (high *Bacteroidetes* and certain beneficial Clostridium groups, low Proteobacteria and Bacillaceae)^[78]. Considering the importance of the nutritional components present in the Mediterranean diet, its use has been proposed for the clinical management of non-communicable diseases, including cancer, but these would then need to be tailored to the age of the patient. Many findings raise the possibility of including some identified dietary components as pharmacological interventions in cancer therapies, rather than adjusting entire diets. One early example of this is represented by a study of patients with oral cancer (46–75 years old) receiving oral APG-157 (polyphenols). Saliva microbiota were evaluated in addition to blood immune cells. A decrease of *Bacteroides* species and increased inflammatory markers (IL-1 β and IL-8) was observed in saliva whereas in the tumor tissue T cells, PD-1 and PD-L1 expression was increased. It was therefore suggested that APG-157 could be used as an adjuvant or neoadjuvant therapy for head and neck cancer^[79].

9. Tumor Microenvironment and the Microbiota

In addition to the influence on cancer outcome of the gut microbiota, which varies with age, microbial dysbiosis actually in the tumor tissue itself also influences occurrence, progression, and/or treatment outcomes, but the impact of age in this context is less clear. Data are only just beginning to accumulate in this area too. For example, in 94 patients (45.7 to 76.6 years old) with prostate cancer (Pca), dysbiosis of the prostate microenvironment and the presence of *Shewanella* genera was linked to malignant transformation^[80]. It is likely that local microbes and host immune system interactions modulate cancer growth and metastasis^[81]. A comparison of prostate tumor mutational burden showed that the total bacterial burden and *Eubacterium* abundance in tumor biopsies was associated with host tumor hypermutation^[82]. In fact, the evaluation of 1,500 tumors representing seven cancer types showed that microbes are distinct between tumor types and that microbial metabolic pathways correlate with clinical features^[83]. This is an area where the impact of ageing remains more or less completely unknown.

10. Conclusions

The Comprehensive Geriatric Assessment is an important tool to optimize therapy effects and to include older patients in tailored anti-cancer treatments to maximise benefit. This assessment or something equivalent is sometimes carried out, especially for chemotherapy, because patients are very heterogeneous regarding the increasing divergence between chronological and biological age^[84]. However, it is not yet clear in how far the many different ways of assessing biological age impact on cancer treatments. This will be a fruitful area for future research. What is clear is that most of our understanding of tumor biology in animal models is derived from studies that do not include old individuals, while clinical data from trials of new therapeutics still commonly exclude older patients. Even when scrutinising data on real-world treatments it is challenging to ascertain the impact of chronological age on outcome, and more or less impossible to determine the effect of biological age, and all the multifarious factors discussed above in this Editorial. Hence the need for studies focussed on any aspects of basic, preclinical, translational and clinical cancer research in ageing hosts to fill this yawning knowledge gap.

Declarations

Conflicts of interest

Valquiria Bueno is an Editorial Board member of *Ageing and Cancer Research & Treatment*. Pawelec G is the Editor-in-Chief of the journal.

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