Clinical & Experimental Immunology
The Journal of Translational Immunology
doi:10.1111/cei.12875 REVIEW SERIES: AGEING AND THE IMMUNE SYSTEM, EFFECTS OF IMMUNOSENESCENCE AND CLINICAL IMPLICATIONS
Clinical and Experimental Immunology REVIEW ARTICLE Series Editors: Birgit Weinberger and Arne Akbar

Considerations for successful cancer immunotherapy in aged hosts

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Accepted for publication 13 September 2016
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Summary

Immunotherapy is now experiencing unprecedented successes in treating various cancers based on new understandings of cancer immunopathogenesis. Nonetheless, although ageing is the biggest risk factor for cancer, the majority of cancer immunotherapy preclinical studies are conducted in young hosts. This review will explore age-related changes in immunity as they relate to cancer immune surveillance, immunopathogenesis and responses to immunotherapy. Although it is recognized that declining T cell function with age poses a great challenge to developing effective age-related cancer immunotherapies, examples of successful approaches to overcome this hurdle have been developed. Further, it is now recognized that immune functions do not simply decline with age, but rather change in ways than can be detrimental. For example, with age, specific immune cell populations with detrimental functions can become predominant (such as cells producing proinflammatory cytokines), suppressive cells can become more numerous or more suppressive (such as myeloid-derived suppressor cells), drugs can affect aged immune cells distinctly and the aged microenvironment is becoming recognized as a significant barrier to address. Key developments in these and other areas will be surveyed as they relate to cancer immunotherapy in aged hosts, and areas in need of more study will be assessed with some speculations for the future. We propose the term 'age-related immune dysfunction' (ARID) as best representative of age-associated changes in immunity.

Keywords: aging, cancer, immunity, immunotherapy

Introduction

The immune system is exquisitely able to identify specific antigens and eliminate cells expressing them. Tumours are quintessentially antigenic tissues as the result of their many genetic mutations. This antigenicity (expression of antigens), however, does not usually translate into clinically meaningful immunogenicity (the ability of these antigens to elicit useful immunity), as spontaneous rejection of clinically apparent tumours occurs rarely. Tumour-specific and tumour-associated antigens were identified more than 60 years ago, prompting strategies to attempt to boost anti-tumour immunity paralleling successful approaches to boost anti-pathogen immunity. It is now clear that the inability of endogenous immunity to eradicate clinically evident cancers derives from various factors, including tumour-driven immune dysfunction, co-evolution of anti-tumour immunity as tumours mutate to escape immune elimination (termed 'immunoediting', discussed below) and because anti-tumour immunity is autoimmunity [1,2]. Recent discoveries have helped thinking advance to develop more effective anti-cancer immunotherapies. With age, some of these impediments are compounded, and new barriers to successful cancer immunotherapy emerge [3–6].

Tumour immune surveillance is part of a more comprehensive process termed 'immunoediting' [7], associated

with the 'three Es' [8]. The first E stands for elimination of nascent cancer cells. The second E is equilibrium, in which growth of malignant cells escaping immunity is balanced by immunity that induces immune elimination. This selective pressure results in antigenic evolution of tumours that leads ultimately to immune escape, the third E is where the tumour has evaded the immune defences and becomes clinically evident in mouse models [9–11] and humans [12,13].

Characterization of cancer properties led to the original six fundamental cancer hallmarks, but these did not include immunity [14]. The updated eight fundamental hallmarks include lack of immune rejection [15]. Chronic generalized inflammation is another newly appreciated cancer hallmark [16,17], suggested as another fundamental hallmark [18], along with genomic instability [19], abnormal vasculature [20] and stem cell features [21].

As we will discuss, these cancer hallmarks (especially immune rejection and chronic inflammation) bear directly upon the challenges in developing age-specific immunotherapy. Age effects on immunity extend far beyond simple declines in functions or reductions in cell numbers. We propose the term 'age-related immune dysfunction' (ARID) to encompass the full range of age-related alterations in immunity with advancing age. The following sections address major topics relating to age effects on cancer immunotherapy.

Tumour-specific T cells

With ageing, a general reduction in T cell immunity results from various processes affecting T cell numbers, diversity, phenotype and function [22]. For example, phenotypically naive T cells ($CD45RA^+CD62L^+CD27^+CD28^+$) are produced throughout life in the thymus but thymic production wanes with age [23–25], reducing global T cell repertoire diversity even in healthy individuals, as overall peripheral T cell numbers remain relatively constant [26]. Reduced haematopoietic stem cell production of T cell precursors [27] also contributes. Even as naive T cell numbers decrease, T cells with a memory phenotype, including cytokine-producing cytotoxic $CD8^+$ T cells, increase with age. Dysfunctional, terminally differentiated effector cells also increase, especially virus-reactive cells, with highly reduced T cell receptor repertoire diversity and with limited proliferative ability [28]. Thus, most T cells are memory/effector cells and low-level chronic inflammation is characteristic of an aged immune system. In addition, T cell signalling declines with age [29].

Therapeutic strategies have been developed to lessen these age-related defects and help to elicit effective T cell immunity. For example, $CD4^+$ T cell functions decline with age, but function loss is mitigated by giving cytokines, including tumour necrosis factor (TNF)-α or interleukin (IL)-6 [30]. Defective age-related T cell priming can be rescued using agonist αCD137 antibodies [31]. Tumour-specific immunity can also be enhanced. For example, OX40-enhanced tumour rejection and effector T cell differentiation decreases with age [32,33], but aged mice developed protective anti-tumour immunity to a lymphoid tumour with an agonist αCD40 antibody [34]. We showed that aged mice develop significant anti-tumour immunity to aggressive and poorly immunogenic B16 melanoma, comparable to young mice, with similar clinical effect by simultaneous depletion of suppressive myeloid and T cells [5], discussed in detail below.

Regulatory T cells (T_{regs})

As T_{regs} are key mediators of tumour immune dysfunction, reducing T_{reg} function or numbers is a rational cancer immunotherapy strategy [35–38]. Reports of T_{reg} contributions to age-related decline in immune responses are contradictory, with some studies showing increases in T_{reg} prevalence and/or function with age in humans and mice [39–42], whereas others show no changes or reduced T_{reg} contributions [43,44].

Increased T_{reg} prevalence in lymphoid organs but not blood or thymus have been shown in aged mice [5,45,46]. The effect of age on T_{reg} functional properties is complex, depending on the experimental setting and the function assessed. Some functions appear to be reduced [47], such as suppression of delayed-type hypersensitivity responses *in vivo* [41] or inhibition of T helper type 17 (Th17) function [45]. In other studies, T_{regs} from aged mice appear to have similar or greater suppressive function *versus* young mice [5,48]. Few studies have assessed the changes in T_{reg} prevalence in elderly humans [49], but they could increase in circulation with age [50]. T_{regs} from young and elderly individuals similarly inhibited the proliferation of responder cells, whereas the production of the anti-inflammatory cytokine IL-10 was reduced in cells from aged subjects [51].

Although T_{reg} depletion is an effective approach to improving anti-tumour immunity and responses to immunotherapy [36,38], conflicting studies report the effect of T_{reg} depletion as cancer immunotherapy in aged hosts [52,53]. One early study correlated defective tumour clearance to increased T_{reg} prevalence and used αCD25 to deplete T_{regs} and improve anti-cancer immunity [53]. We used denileukin diftitox to deplete T_{regs} in mice bearing B16 melanoma [5]. While denileukin diftitox depleted T_{regs} similarly in young and aged hosts, slowed tumour growth and improved tumour-specific immunity was observed only in young mice. Denileukin diftitox-mediated T_{reg} depletion affected interferon (IFN)-γ- and IL-17 producing T cells differentially in young *versus* aged mice. Tumour-bearing aged mice had

more CD11b^{+}Gr-1^{hi} myeloid-derived suppressor cells (MDSC) that were more suppressive. T_{reg} depletion resulted in a further increase in MDSC numbers. When MDSC depletion using anti-Gr-1 antibody was added to T_{reg} depletion, anti-tumour immunity was restored in the aged mice resulting in slowed tumour growth similar to young hosts. This strategy did not improve treatment further in young mice as their MDSC did not increase with

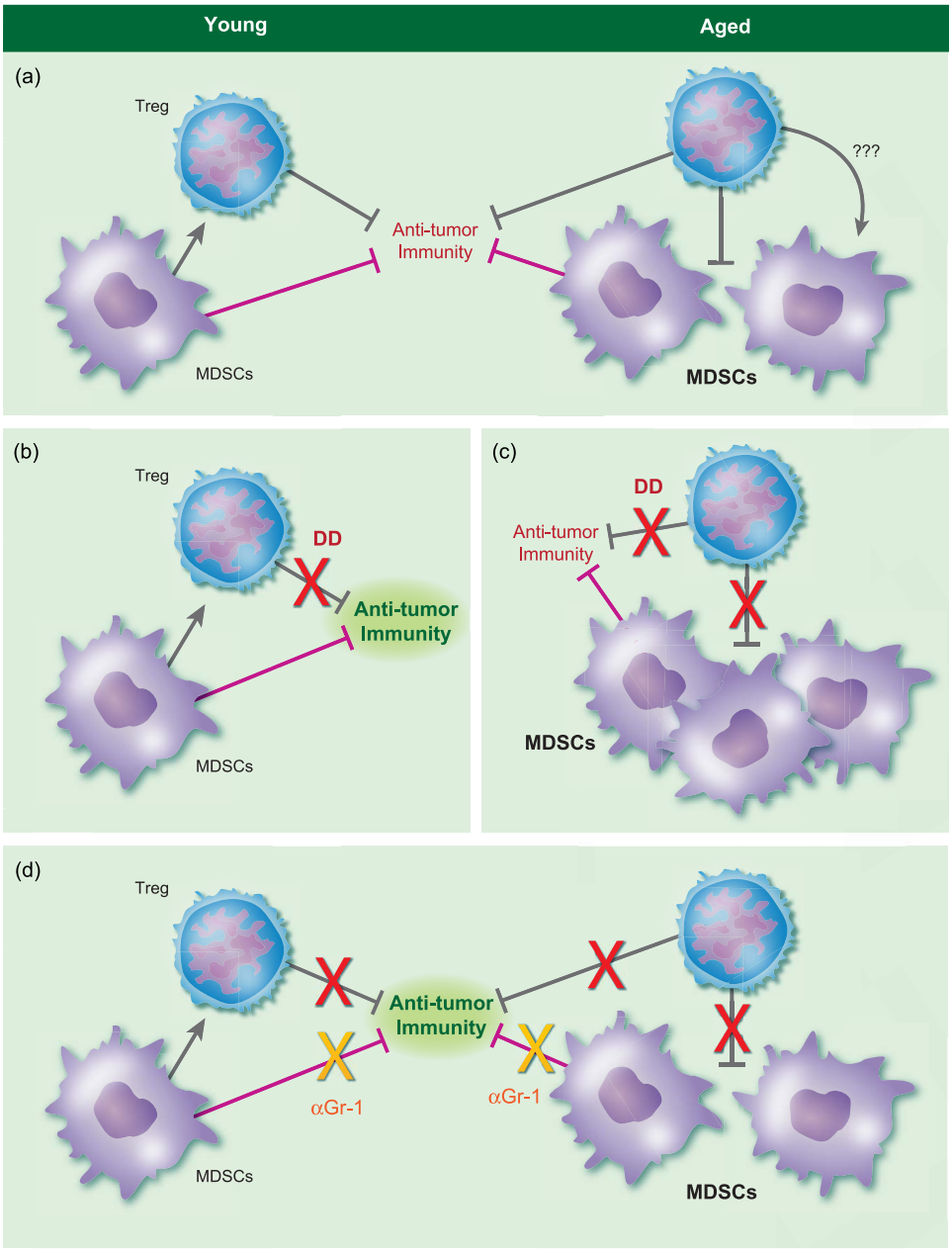

Fig. 1. Example of an age-specific immune effect that can be ameliorated to allow effective anti-meanoma immunity. (a) Young mice challenged with B16 melanoma experience increased regulatory T cells (T_{regs}), but not myeloid derived suppressor cells (MDSC), whereas aged mice experience increased T_{regs} and MDSC. In the aged, the increased MDSC could be due to poor T_{reg} control of them directly, or through indirect mechanisms (denoted by question marks). (b) In young mice, denileukin diftitox (DD) reduces T_{regs} with little MDSC effect, improving anti-tumour immunity [increased interferon (IFN)-γ^{+} T cells]. By contrast, in aged mice (c), DD-mediated T_{reg} reduction reduces T_{regs} but without significant increase in IFN-γ^{+} T cells. Interleukin (IL)-17^{+}, potentially detrimental T cells, increase, as do deleterious MDSC, thereby inhibiting beneficial anti-tumour immunity. Green anti-tumour immunity means good immunity, whereas red means less effective immunity. (d) By adding anti-granulocyte-differentiation antigen-1 (αGr-1) antibody to DD in aged mice, the MDSC increase is blunted and aged mice now mount anti-tumour immunity comparable to young hosts receiving DD alone, with comparable clinical efficacy. Adding αGr-1 to DD in young hosts does not improve immune or clinical effects further, as MDSC were not increased further by DD. The red 'X' denotes DD effects to reduce T_{reg} inhibition.

denileukin diftitox, representing the first cancer immunotherapy to work in aged but, to our knowledge, not young hosts [5]. An illustration to represent events is shown in Fig. 1. Thus, mitigation of aged-specific immune suppressive mechanisms allows successful cancer immunotherapy even in aged hosts.

Innate immunity

Declines in T cell function and chronic low-level inflammation with age can promote expansion of suppressive myeloid cells. Thus, as anti-tumour T cells may not be optimally functional in elderly cancer patients, targeting innate cells could represent a better strategy [54].

Dendritic cells (DCs)

DCs are antigen-presenting cells that play a key role in mediating T cell immunity [55]. The tumour environment promotes expansion of dysfunctional DC subsets that hamper effective anti-tumour immune responses and immunotherapy [56,57].

Circulating DC precursors and skin Langerhans cells decrease with age. Age effects on DC function depend on the function assessed and are reported variably as decreased or unchanged [58]. As DC function declines, any related impaired T cell function or increased inflammation could contribute to age-related cancer risk. Augmenting DC antigen-presenting abilities, which is reported inconsistently to decline with age, induces strong tumour-specific cytotoxic T cell immunity. For example, CD40L or agonist anti-CD40 antibodies can boost DC activation in animal and human studies [59]. In older cancer patients, a vaccine using CD40L linked to specific antigens has potential [60].

Macrophages

In contrast to reduced lymphopoiesis in age, myelopoeisis increases [61], increasing myeloid cell numbers. Macrophages are an important component of tumour stroma and tumour-associated immune dysfunction [62]. Tumour-resident macrophages are characterized as proinflammatory M1 or anti-inflammatory M2 macrophages and can switch phenotypes. M1 macrophages secrete proinflammatory cytokines, such as TNF-α and IL-12, that boost anti-tumour immunity. M2 macrophages produce anti-inflammatory cytokines (e.g. IL-10, TGF-β) that promote tumorigenesis [62].

Age effects on macrophage differentiation and function are complex. Macrophage prevalence in lymphoid organs increases in aged mice [63]. M1 macrophage function could increase through production of age-related reactive oxygen species (ROS), but other studies show reduced function with age in M1 macrophages [64], which could be from increased IL-10-producing M2 macrophages [62]. Thus, macrophages from ageing hosts could promote tumour growth.

Tumour-associated macrophages from elderly, but not young, mice produce high levels of immune-suppressive TGF-β, consistent with an M2-type phenotype [63]. Detrimental M2 macrophages can be converted to beneficial M1 using IL-12 or poly-(cysteine 5′ to guanine) (CpG) plus an αIL-10 receptor [65]. Thus, targeting tumour-associated age-related M2 macrophages could be useful to treat cancers in aged hosts.

MDSC

MDSC are immature, immunosuppressive, myeloid cells that increase in inflammatory diseases, particularly tumours [66–69], and suppress anti-tumour immunity [70]. MDSCs produce inhibitory factors (e.g. IL-10, arginase) that inhibit T cells and promote T_{regs} and detrimental M2 macrophages [71]. MDSCs increase during ageing in human blood [72] and in lymphoid organs in mice [5,63]. MDSC contribute to immunopathology in aged hosts, including in cancer [73,74]. T_{reg} depletion with denileukin diftitox increased MDSCs in aged mice, suggesting T_{reg} control over MDSC [5], which could include indirect effects of T_{reg}-controlled cytokines that alter MDSC mobilization, proliferation or differentiation. In a CT26 colon cancer model, a *Lentinula edodes* mycelia extract reduced MDSC infiltration with a whole tumour cell vaccine in aged mice by suppressing the inflammatory MDSC-promoting cytokines IL-6 and TNF-α [75]. This extract also improved vaccine-induced *in-vivo* priming of tumour-specific cytotoxic T cells. Targeting MDSC is another potentially effective approach to reverse cancer-associated immune dysfunction in aged hosts.

Immune check-point inhibitors

Immune check-point receptor blockade has become one of the most successful immunotherapy strategies for various cancers [76,77]. None the less, the impact of those novel approaches in treating elderly patients has been little reported.

Immune check-point molecules are those that control the degree of immune responses either positively (activating immunity) or negatively (dampening immunity), which is often the case in cancers. Immune check-point inhibitor antibodies block these negative signals to improve anti-cancer immunity [76,77]. The expression of regulatory immune check-points on T cells increases with age in humans and mice [5,78,79], consistent with accumulation of hyporesponsive memory-like T cells that express these molecules. The immune check-point molecules identifying exhausted (poorly functional) T cells, such as programmed death 1 (PD-1), lymphocyte activation gene 3 (Lag-3) and T-cell immunoglobulin and mucin-domain containing 3

(Tim-3) also increase with age. These and other related molecules on T cells are targets for immune check-point blockade anti-cancer immunotherapies. Other immune check-point receptors, such as PD-L1, are more prominent on myeloid cells or B cells in young hosts, but can be expressed at high levels on tumour cells and on $CD8^+$ T cells in aged mice [80]. Defining age-specific strategies to reduce those inhibitory signals and reverse the hyporesponsiveness or exhaustion of aged T cells while reducing potential cytotoxic effects is important in developing these promising immunotherapies.

PD-1

PD-1 is immunopathogenic in cancers by impeding anti-tumour $PD\text{-}1^+$ T cells. Monoclonal αPD-1 antibodies (αPD-1) have demonstrated remarkable clinical efficacy against a variety of cancers and two distinct αPD-1 antibodies are US Food and Drug Administration (FDA)-approved to treat melanoma, renal cell carcinoma, non-small-cell lung cancer, lymphoma and head and neck cancer.

PD-1 is expressed preferentially on the surface of effector-memory ($CD44^{hi}CD62L^{lo}$) T cells that increase with ageing. $CD4^+PD\text{-}1^+$ T cells from old mice exhibit proliferative hyporesponsiveness, suggesting that the up-regulation of surface-expressed PD-1 could contribute to the age-dependent functional decline in effector-memory T cells [81]. PD-1 increases on T cells with age [82]. αPD-1 improves T cell functions in aged mice [83], although this strategy has not been reported in aged hosts with cancer to our knowledge. We showed that rapamycin reduces age-related T cell PD-1 expression, and $PD\text{-}1^+$ cells in rapamycin-treated mice were more functional *versus* $PD\text{-}1^+$ T cells in untreated, aged mice [82], suggesting that rapamycin or another mammalian target of rapamycin (mTOR) inhibitor could improve anti-tumour immunity in aged hosts, as was shown for the ability of the related molecule, everolimus, to improve B cell immunity to influenza vaccine in aged humans [84].

PD-ligand 1 (PD-L1)

PD-L1 is an immune co-signalling molecule that signals through PD-1. Like αPD-1, αPD-L1 is thought to work as cancer immunotherapy by protecting $PD\text{-}1^+$ anti-tumour T cells from inhibition by tumour PD-L1 expression [77,85–88].

Most old naive $CD8^+$ T cells in mice are reportedly $PD\text{-}L1^+$ *versus* 25% in young mice. Aged $CD8^+$ T cells showed reduced proliferation, but αPD-L1 improved their proliferation to a level similar to young $CD8^+$ T cells *in vitro*. αPD-L1 improved anti-tumour immunity in aged hosts to young host levels in a mouse lymphoma model [80].

We showed that αPD-L1 treats B16 melanoma in young but not aged mice, but that treatment efficacy was partially restored by combining αPD-L1 with anti-cytotoxic T lymphocyte antigen 4 (αCTLA-4) [89]. The above study [80] tested αPD-L1 in a lymphoma model in BALB/c mice, whereas we studied a carcinoma in BL6 mice. Thus, either lymphoma *versus* carcinoma or host genetic background, among other considerations, could help to explain different results with αPD-L1.

CTLA-4

The anti-CTLA-4 antibody ipilimumab was the first immune check-point inhibitor agent that clearly benefited human cancer by improving overall and disease-free survival in metastatic melanoma [90]. There are no reports, to our knowledge, of published studies of age effects of anti-CTLA-4 in human cancer. We showed that αCTLA-4 was the only single-agent immunotherapy effective in aged mice in the B16 melanoma model [89].

Immune check-point agonists

OX40 agonists and CD137 agonists are discussed above under T cells [31,34].

Adoptive cell transfers

Older adoptive cell strategies (passive vaccination) using DC or tumour-infiltrating lymphocytes to treat cancer were generally poorly effective. Chimeric antigen receptor (CAR) cell transfers have shown great promise more recently in haematological malignancies. To make a CAR-expressing cell, an artificial antigen recognition receptor (the CAR) is engineered into a lymphocyte that is then transfused into the patient [91]. To our knowledge, there are no published reports on the effects of aged T cells on generating CAR T cells, aside from the recognition that *in-vitro* culture of T cells from older patients generally yields fewer CAR T cells *versus* younger patients. To the extent that aged T cells have reduced cytolytic or homing potential, they could generate less effective CAR T cells for cancer immunotherapy. Means to boost aged T cell functions discussed above could potentially be used to increase efficacy of CAR T cells made from aged cells. As natural killer (NK) cells and γδ T cells do not require major histocompatibility matching to kill their targets, CAR engineered into such cells could potentially be useful to treat aged cancer patients with CAR NK or CAR γδ T cells, as these strategies are under investigation in younger hosts. Similarly, to the extent that aged DC have reduced T cell-activating or antigen-presenting functions, their utility in DC adoptive cell transfers could be limited, although means to improve aged DC functions discussed above could be tested in this regard.

mTOR inhibitors

mTOR inhibitors at doses lower than used usually for immunosuppression can improve antigen-specific immunity, including against cancers [92]. We showed that rapamycin can reduce T cell PD-1 expression and improves PD-1$^+$ T cell function in aged mice [47] and improves γδ T cell-mediated anti-cancer immunity [93]. Rapamycin prolongs life in mice even when given late in life [94]. Thus, mTOR inhibitors could be used as adjuncts to various cancer immunotherapy agents to improve aged immune function, as we showed is possible [82], with potentially additional life or health extension effects.

mTOR signals are critical to T cell differentiation, and it is well known that mTOR suppression can promote T_{reg} cell function differentiation [82,95]. Thus, there is some concern that small molecule inhibitors could reduce anti-tumour immunity by promoting T_{regs}, as these can be detrimental to anti-tumour immunity [36]. However, in appropriate settings and at sufficiently low doses, small molecule mTOR inhibitors produce net benefits to anti-tumour immunity [47,82,92,93] and do not appear to promote increased T_{reg} numbers or function [82]. We showed recently that low-dose rapamycin could be beneficial to, whereas typical therapeutic rapamycin doses could impair, anti-cancer immunity (Yang *et al.*, in revision). More work on this important issue is needed.

Caloric restriction

Caloric restriction suppresses mTOR similar to rapamycin. When used during 6–8 months, caloric restriction improved αCD40 treatment responses in models of sarcoma and breast cancer when mice were aged 12 months. Tumour antigen-specific CD4$^+$ but not CD8$^+$ T cell priming was similar to young controls [96]. Certain types of caloric restriction are tolerable in aged patients, and in young subjects can improve anti-tumour immunity [97]. However, mTOR suppression can reduce immunity in the aged [24] and caloric restriction at too late an age or at too great a caloric reduction can harm aged hosts. This interesting intervention merits additional studies in aged hosts to mitigate cancer treatment symptoms, or prevent or treat cancer.

Tumour microenvironment

The tumour microenvironment consists of tumour, immune and stromal cells. Until recently, most studies of ageing and cancer have focused upon the tumour and the immune system, but tumour microenvironmental/stromal effects are now also recognized as important drug discovery areas. The aged tumour microenvironment could be more immunosuppressive than in young hosts. Factors include increased M2 macrophages and MDSC that result from chronic, low-grade age-related inflammation. This aged, protumorigenic tissue microenvironment could be compromised further by tumour cells that can attract detrimental MDSC, T_{regs} or neutrophils that not only inhibit anti-tumour immunity but also produce protumorigenic factors [63,98]. Primary prostate stromal fibroblasts from older *versus* younger patients produce more proinflammatory factors [99].

A transgenic murine model of prostate cancer and benign prostate hyperplasia found an age-related increase in TGF-β1 that resulted in altered tissue architecture consistent with local inflammation [100], a result corroborated in prostates of aged normal mice [101]. Aged primary fibroblasts attract CD4$^+$ T cells that promote prostate epithelial cell proliferation. Macrophages, neutrophils and CD8$^+$ T cells promote prostate cancer cell proliferation [90].

Fibroblasts in the aged melanoma microenvironment can contribute to melanoma growth and progression. Aged fibroblasts undergo senescence and can drive increased tumour metastases and angiogenesis through production of secreted frizzled-related protein 2. Older fibroblasts also produced fewer ROS scavengers that can promote DNA damage [6]. Finally, in studies of an agonist αCD40 antibody, aged mice failed to respond to cancer treatment from defective CD40 signalling in tumour microenvironmental CD40 signals, not to T cell-intrinsic effects [33]. Thus, therapeutically modifying stromal elements, in particular myeloid cells or their products, could be relevant for elderly cancer patients.

Toll-like receptor (TLR) agonists

Bacille Calmette–Guérin (BCG) is an attenuated *Mycobacterium bovis* that is FDA-approved to treat non-muscle invasive bladder cancer. It is a strong TLR agonist. Although its mechanism of anti-cancer action is incompletely understood, it is thought to promote anti-cancer immunity. Observational data suggest that age could influence response to BCG therapy in bladder cancer. In a trial of BCG plus IFN-α immunotherapy in bladder cancer, aged patients had increased relapse rates following BCG compared to younger patients [102]. Of the patients who were aged 61–70 years *versus* patients older than 80 years, cancer-free survival was 39 *versus* 61%, respectively, at a median follow-up of 24 months ($P = 0{\cdot}002$). In analyses of aged patients receiving BCG for non-muscle invasive bladder cancer, age was an independent risk for progression and the 2-year progression-free survival was 87% among patients aged less than 75 years compared to 65% among patients aged greater than 75 years [103]. In a large ($n = 805$) cohort of patients with bladder cancer age was found to have a small but measurable association with response to BCG therapy [104]. Nevertheless, the influence of competing morbidities and selective surgical management of elderly patients *versus* immune effects is not clear from these studies. Thus, although BCG is the sole agent to our knowledge for which age-specific immunotherapy

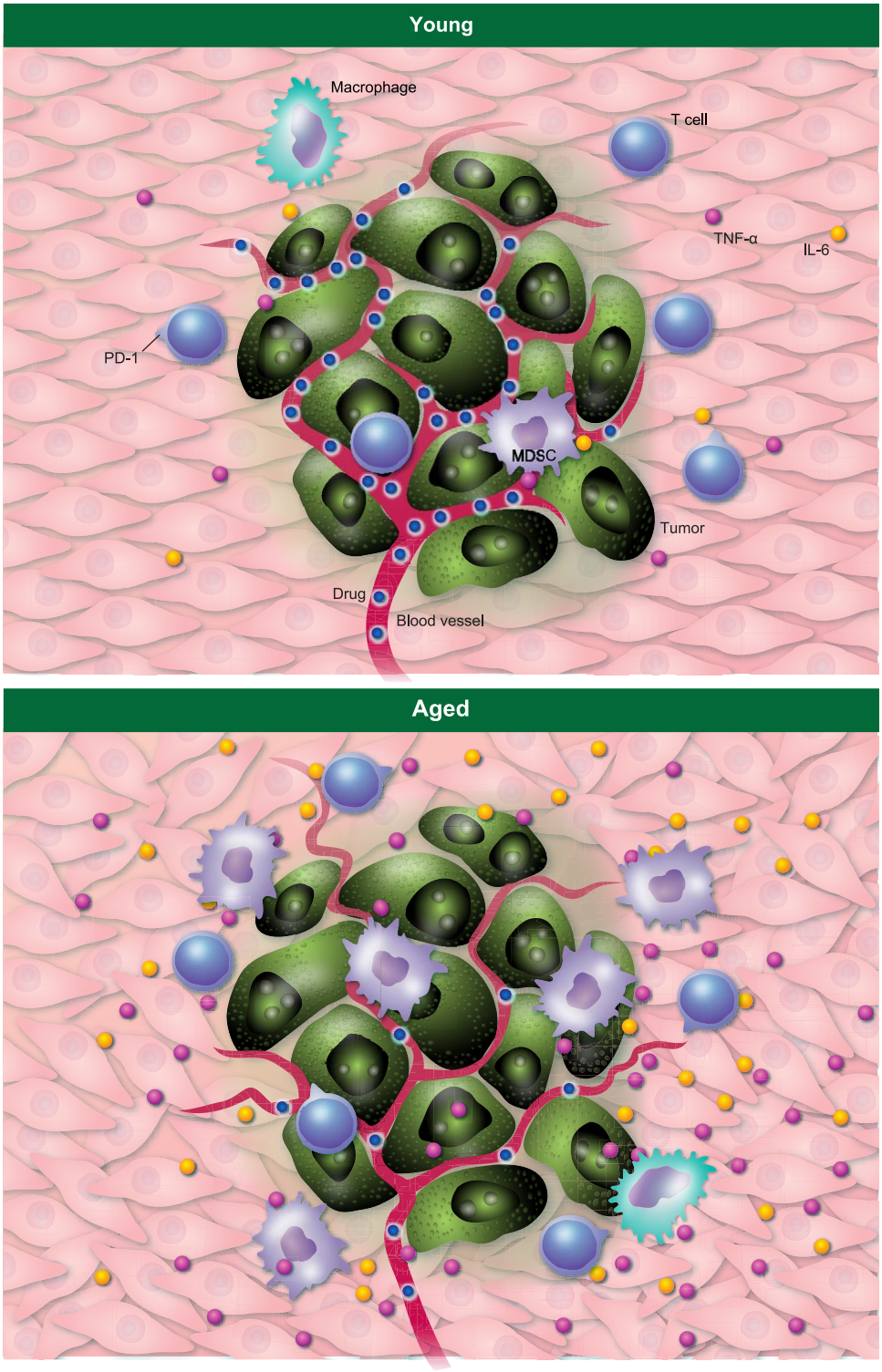

Fig. 2. Examples of age effects in the tumour microenvironment. The aged tumour microenvironment can have elevated levels of proinflammatory molecules that reduce anti-tumour immunity such as interleukin (IL)-6 (yellow dots) and tumour necrosis factor (TNF)-α (purple dots). Green cells = tumour. Myeloid cells, including myeloid-derived suppressor cells (MDSC) (light purple) and macrophages (light green) that inhibit anti-tumour immunity can also be increased in the aged tumour microenvironment. These cells can be a source of detrimental molecules. Local IL-6 and other factors can increase MDSC. T cells programmed death 1 (PD)-1 expression can be increased, suggesting reduced T cell functions. As the Wnt antagonist secreted frizzled-related protein 2 (sFRP2) can promote angiogenesis, we have taken the liberty of showing bigger and more numerous blood vessels in the aged microenvironment, although more work is needed in this area. Drug delivery could be reduced from abnormal vasculature.

effects in humans has been reported extensively, a clear conclusion on age-related immune effects cannot be made from these data. As BCG is standard-of-care immunotherapy and bladder cancer patients tend to be older than for many other cancer types, these data merit follow-up. There are no reports to our knowledge of age effects on efficacy of other approved or investigational TLR agonists for cancer treatment.

Immunotherapy toxicity mitigation

Cancer immunotherapy in aged mice can generate rapid and/or lethal toxicities in distinct organs due to proinflammatory cytokine production, both systemically and locally in affected tissues. Proinflammatory effects could be driven by macrophages rather than T or NK cells. Myeloid cell depletion during therapy mitigates these toxicities without significantly compromising treatment efficacy. Aged macrophages from mice and normal humans produce higher proinflammatory cytokines, including TNF-α and IL-6 *versus* young macrophages. Blocking TNF-α in aged mice also improves survival and reduces toxicities without loss of anti-tumour effects [3,4]. As αTNF-α, αIL-6 and αIL-6R antibodies are FDA-approved, this concept merits further investigation. However, as other studies have shown that IL-6 and TNF-α administration can improve aged T cell function [30], much additional work is required to understand how such approaches could be incorporated safely and effectively into cancer immunotherapy strategies.

Microbiome effects

The gut microbiome affects systemic immunity and is affected by age [105–107]. Two recent reports showed that gut microbes affected anti-cancer immunotherapy in human subjects receiving αPD-L1 [108] or αCTLA-4 [109]. There is currently much justified interest in understanding microbial effects on anti-cancer immunity although, to our knowledge, age effects are not yet reported in cancer immunotherapy. As the gut microbiome can affect anti-cancer treatments through immune effects [110], including modulation of tumour microenvironmental myeloid cells [111] which themselves are also affected by age [82], it is reasonable for there to be age-associated microbial effects on anti-cancer immunotherapy, an area deserving of additional studies.

Conclusions

Immune therapy for cancer, including in elderly people, has a strong scientific rationale. Recent breakthroughs in understanding the basis for cancer-driven immune dysfunction have led to the development of highly successful anti-cancer immunotherapies. Nonetheless, much of our understanding of tumour immunity derives from studies of younger hosts. There is now a growing, but still relatively small, body of literature demonstrating age effects on cancer immunity and responses to immunotherapies, which have led in some instances to demonstrations of novel approaches to improving anti-cancer immunotherapy in aged hosts most at risk for cancer.

'Immune decline' is an inaccurate term, and 'immunosenescence' and 'inflammageing' describe specific attributes of an aged immune system. We propose the term 'age related immune dysfunction' (ARID) to describe the totality of age-related immune changes to include increased or decreased numbers of certain immune cells, appearance of novel immune cell populations, increased proinflammatory or immune suppressive functions, restricted T cell receptor (TCR) repertoire and the myriad other changes that age brings to immunity. To the extent that underlying ARID can be reversed in aged cancer patients, clinically relevant anti-tumour immunity could potentially be achieved, as has now been demonstrated clearly.

Challenges in developing effective age-appropriate cancer immunotherapy

Improved understanding of tumour-specific immunopathology and related age-specific effects will help to guide more effective treatment approaches. Individual immunotherapy agents are unlikely to treat most cancers effectively, and thus optimal means to combine agents and approaches need to be defined, including specific agents, doses and scheduling. We need to identify biomarkers that differentiate aged patients with sufficiently responsive tumour-specific immunity from those in whom additional adjuncts will be needed. Adjuncts for those patients with impaired immunity could include adoptive transfer of rejuvenated or young CAR-expressing cells, novel antigen-presenting cells, thymic transplants, gene therapy [including with caspase 9/clustered regularly interspaced short palindromic repeats (CRISPR) approaches] or other approaches.

Toxicity mitigation strategies that do not compromise clinical efficacy are also needed, as is identification of rational combination therapies to reduce dosage of potentially harmful individual agents. Studies of the effect of age on the human microbiome are in their infancy, and could help understanding of the heterogeneity of responses to immunotherapy observed both in humans and in preclinical models. Tumour mutational burden clearly affects the efficacy of many types of cancer immunotherapies. Mutational burden will be dictated, among other considerations, by immune editing. We thus need a clearer understanding of age effects on immune editing and tumour mutational burden, which could produce related or individual contributions to cancer immunotherapy efficacy. Finally, we need to deepen understanding of age effects on tumour stroma, including vasculature effects that can alter immune cell trafficking and drug delivery. An illustration of some challenges is shown in Fig. 2.

As we use ever more powerful but costly and potentially harmful approaches in ever-older cancer patients, economic, feasibility and ethical issues will need to be addressed.

Acknowledgements

Financial support is acknowledged for T. C. (CA170491, CA54174, CDMRP, The Holly Beach Public Library, The

Owens Foundation, The Barker Foundation and the Skinner endowment).

Disclosure

None to declare.

Author contributions

V. H., R. S. S. and T. J. C. wrote the manuscript. V. H. and A. P. performed some experiments described.

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