Failing to adapt - The ageing immune system’s role in cancer pathogenesis
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Abstract
Cancer incidence rates rise exponentially with age, previously considered to be due to increased exposure to mutagenic agents. Refined statistical analysis has, however, highlighted a plateau in cancer incidence rates amongst the general population post eighty-five years of age. This, coupled with the peak of numerous malignant pathologies during early or middle life, indicates a crucial role for other factors in controlling the timing and nature of cancer development. Immune function is known to decrease with age, indicating that increased chronic infection amongst the elderly may, in part, give rise to increased cancer incidence. Further, the chronic low grade inflammatory environment created as one ages may also initiate malignant neoplastic progression. Pro-inflammatory cytokines, such as TNF-alpha, IL-6 and prostaglandins (increased through TNF-alpha induced COX increases) increase during ageing and cause malignant transformation through inducing cellular proliferation, angiogenesis and the inhibition of apoptosis. This article will discuss these changes in detail and show that centenarians possess key polymorphisms, responsible for decreased TNF-α and IL-6 production amongst other changes, that act as survival advantages; protecting them from age-induced malignant neoplastic transformation. The need to transition to reviewing cancer as a disorder at the tissue, rather than cellular, level will thus be highlighted.

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1.1 – Cancer, Ageing & Immunity – The missing link

From age thirty the population of the UK, and indeed the wider western world, experiences an exponential increase in the incidence of malignant neoplastic pathology1-6 (discussed herein as cancer). In contrast, immunity appears to decline with age7 and low level chronic inflammation becomes commonplace8. Interestingly however, cancer incidence begins to plateau at age eighty-five1 (see figure 1) and studies on centenarians have demonstrated a marked decrease in cancer incidence amongst these individuals when compared to a younger populace9.

It is confusing then perhaps, that cancer is frequently discussed as resulting from an ‘accumulation of genetic change’10 as a means of explaining the rise in incidence of this disease with increasing age. Whilst this article will not contest this long-established viewpoint, it will argue that the plateau of cancer incidence post ninety years of age, coupled with low cancer prevalence in centenarians, indicates that another factor - the immune system - must play a role in age-related cancer pathogenesis. It will further be argued that polymorphisms in genes controlling cytokine production within a set few population groups provide a crucial evolutionary advantage and evidence of adaptation to longer life that is significantly beyond that of the general population. Accordingly, the article will close by encouraging a new tissue-based approach to cancer research, in which the microenvironment of a cancerous tissue is regarded to be as important as the cancerous cell itself.

2.1 - The concept of ageing

Beyond the fascinating morphological changes accompanying the ageing of an individual there sits
a wealth of variation in a person’s functioning. The body systems develop, mature and fail from birth to death, with many potentially negative changes underlying these processes. If these changes are to be reviewed it is necessary to explore what is to be understood as the distinction between normal and pathological ageing, or whether indeed ageing is to be regarded as a fundamentally pathological process. Centenarians, for example, have outlived the majority of their contemporaries and can justifiably be argued to not offer a typical example of a normally ageing individual as a result. Similarly, whilst many accept decreasing mobility as a normal consequence of ageing bone and muscle, osteoporosis is commonly seen as pathological. Defining ageing and what is to be regarded as ‘pathological’ in this context is accordingly a difficult necessity.

This article will discuss any change that significantly reduces function or quality of life in a proportion of those who are ageing (i.e. that does not have complete penetrance through all aged individuals) as pathological (it may be noted that this is a highly contestable definition and cannot be widely applied, but will be beneficial when discussing the link between cancer and immune dysfunction), whilst centenarians will be exclusively used as an example of a ‘well-aged’ populace with an inherent survival advantage not present in the majority of the population, rather than as a typical example of the effects of ageing.

Further, this article will discuss successful ageing not as aiming to live to a greater age, but as striving to reduce the pathological complications that can accompany an increase in age. Additionally, ageing in itself can be a much confused and conflated term. It is described by the Oxford Medical Dictionary as ‘the accumulation of changes in an organism over time’12 and could encompass any period of an individual’s life. This article will focus on later ageing, analysing the changes in the immune system of humans between mid-adulthood (around thirty years of age) and later life (above sixty years of age), with a view to explaining the increase in cancer incidence from around thirty years of age.

2.2 - Malignant neoplastic change

Cancer is noted most predominately as a devastating condition of ageing, with increasing age allowing for further accumulation of genetic change12. In order for a cell to be regarded as cancerous it must commonly possess limitless replicative potential, a lack of response to growth inhibitory signals, an ability to evade apoptosis and a tendency to invade tissues and metastasise. Many cells adopt these changes, although it is important to note that only cancers arising in solid tissues demonstrate invasive potential. The haematological cancers, such as leukaemia and myeloma, will not be discussed during this work. Furthermore, cancer is regarded as a disease of increasing genetic instability, and is thus associated with a multi-step pathogenesis through which no one insult can induce the disease alone.12

Whilst cancer is associated with increasing age, the exponential increase in cancer incidence beginning at around thirty years old (see figure 1) is not without exception. Rates of diagnosis of testicular cancer, as an example, peak between the ages of twenty-five and thirty-five, falling thereafter1-4. Further, male bowel cancer incidence rates peak shortly before ninety years of age, falling over the following decade1,4. These exceptions to

1 ‘Incidence rates’ are a very different entity to ‘incidence’, in that a lower incidence would be reflected post ninety years of age purely because fewer individuals are alive. Incidence rates allow us to eliminate this source of bias and focus on whether
the rule, coupled with the low incidence rates of cancer in centenarians (as previously described) provide evidence that increased exposure to mutagenic agents does not reasonably explain cancer incidence rates in all cases.

Furthermore, epidemiological evidence indicates that the ageing immune system could explain these discrepancies through failing to protect from the pathogenic causative agents of some cancers\(^7,13\) and by aberrantly initiating inflammation and thus acting to induce malignant neoplastic change\(^14\). Inflammation, for example, is known to increase the risk of cancers of the bowel (particularly in patients with crohn’s colitis or ulcerative colitis, for example)\(^15\), bladder\(^16\), oesophagus\(^17\) and prostate\(^18\), amongst others\(^19\). Many organisms, such as the bacterium H. Pylori have also been indicated as causative agents of numerous cancers\(^19,20\), as demonstrated in figure two.

3.1 – New life for an ageing field

These findings, made through in-vitro and in-vivo study whilst also borrowing from epidemiological evidence, thus serve to illustrate that the genetic makeup of cancerous cells, and their precursors, is influenced by their immediate extracellular environment. Kuperwasser et al\(^21\), publishing in PNAS during 2004, very elegantly highlighted that seemingly normal epithelial cells from breast tissue could be altered to grow in a malignant fashion under variant extracellular conditions. This, and important work published by Bissell et al\(^22\) in 2003 (which discovered that it was possible to revert malignant breast epithelium back to non-malignant epithelium under differing tissue conditions) have reignited interest in the cancer cell’s susceptibility to change induced by its immediate environment.

In his eminent 2004 paper, Schwartzburd\(^23\) termed this environment the ‘cancer-supportive microenvironment’ (CM) or the ‘pro-cancer microenvironment’ (PCM), depending on the level of instability of the cells in question. One can thus hypothesise that the ageing immune system, in creating an environment of pervasive inflammatory stimulation, has a role in creating a PCM/CM. The importance of this microenvironment is emphasised further by evidence indicating that cancer cells will only continue to proliferate within a CM\(^24\), and that some cancer cells actively secrete factors to ensure that their extracellular environment is supportive to their growth\(^25\). It is consequently appropriate to hypothesise that, as part of the multistep pathogenesis model of cancer, mutagenic insults (whether germline or somatic) contribute to the onset of disease but that the age at which such cancers develop and their behaviour on presentation is ultimately likely to be related to their CM, which is directly under the control of the immune system. This, one theorises, is likely to explain why centenarians often escape cancer despite living longer and why incidence rates for neoplastic pathologies
fail to correlate completely with exposure time to potential mutagenic agents.

3.2 – Immunosenescence

Immune dysfunction with increasing age is commonly termed ‘immunosenescence’ and encompasses a perplexing array of changes in all aspects of the immune system. Many of these changes lead to an increased susceptibility to infection whilst several more lead to a state of chronic, low-grade inflammation. The impact on cancer of this state of continual inflammation (which carries the epithet of ‘inflammaging’) and the role of cytokines in its induction will be discussed at great length in the remaining sections of this essay. It is important however to briefly convey the significant impact of a declining immune system on pathogenic infection, tumour immunity and resultant cancer incidence in the elderly. It is also of interest to note that both forms of immune system change discussed above are inexorably linked.

There are many contradictory reports concerning the fate of various components of the immune system during ageing, although it is widely accepted that a general decline in function occurs. Much of this debate centres on the interplay between components of the innate and adaptive immune systems and how changes in the cellular components of the innate immune system in particular influence overall immune function. Dendritic cells (DCs), for example, are vital to the immune system’s ability to recognise and respond to antigen, but their ability to migrate to infective sites and phagocytose potential antigen is thought to be impaired in ageing. Research attempting to clarify this hypothesis has been relatively unproductive however; as it remains unclear as to whether this impairment is due to an inherent problem with the DC itself or with declining numbers of DCs in old age.

Ageing in general, and more specifically the ageing of the immune system, is thought in evolutionary terms to exist as a result, at least partly, of the advantages such a process provides to the preservation of life. For instance, decreased lymphopoiesis is a hallmark of the ageing immune system and may allow for energy conservation in an ageing biological organism. It has also been speculated that, as a more tentative example of this possibility, decreased production of B-cells may be initiated in infancy in order to reduce the likelihood of a fatal lymphoid malignancy developing in later life. However, reproduction ceases long before
many of the changes in the immune system occur and it is thus difficult to envisage evolutionary pressures initiating all of the age-related changes in the immune system. With this said, much detail concerning the ageing process has been successfully elucidated at the molecular level\(^1\)–\(^2\).

Footnote)

Lifelong metabolic activity can, for example, lead to the accumulation of damaging ‘free-radicals’. The oxidative stress induced by these unpaired electrons can lead to significant genetic damage\(^42\),\(^43\). Indeed, Blackburn\(^35\),\(^46\),\(^47\), Greider\(^45\),\(^46\) and Szostak’s\(^47\) 2009 Nobel Prize winning discovery of the role of telomeres and telomerases in chromosome protection, and knowledge of the shortening of these telomeres with age\(^48\), allows us to hypothesise that further damage is induced during ageing as a result of reduced DNA protection (figure 3). These changes are likely to induce growth arrest and apoptosis in the cells of the immune system, leading to the immunosenescence identified during ageing. Age-induced free radical accumulation is thought to be a further direct causative factor of rising cancer incidence in the elderly.

3.2.1 – The ageing innate immune system

It is likely, particularly in the light of the molecular change discussed previously, that all cells of the innate immune system are affected by ageing\(^48\). Although this is supported by substantial research, many findings thus far have been contradictory, particularly when in-vitro findings are compared to those made in-vivo. It is difficult to discuss immune-cell changes in exact detail as a result.

Various research groups have identified potentially raised in-vivo neutrophil infiltrate in aged individuals when compared to their younger counterparts (Nomellini\(^69\), Gomez\(^70\) and Swift\(^71\), amongst others). Yet, apoptosis in these cells during inflammation is reported to occur more readily with increasing age in-vitro\(^52\)--\(^54\), thought to be due to defects in bel-2\(^53\) and the JAK-STAT pathway\(^54\). This latter finding, coupled with evidence of poorer phagocytosis\(^55\) and respiratory burst action\(^55\),\(^56\), indicates declining neutrophil function with age partially compensated for by increased bone-marrow production.

Eosinophils, acid-staining granulocytes with similar polymorphic nuclei to neutrophils, are vital in the response to parasitic infection but also play a significant role in mediating type one hypersensitivity reactions. Asthma is one such reaction and whilst patients suffering with this condition are defined by a constant eosinophilia throughout life\(^57\), increased morbidity and mortality in later life\(^58\) indicates declining eosinophil function with increasing age. The eosinophil blood count of healthy individuals has, however, been shown to increase with age (and intriguingly in parallel with IL-6 concentration\(^59\), raising suggestions of a role for eosinophils in modulating age-related IL-6 levels), supporting the rise seen with neutrophils.

Basophils, and the mast cells these granulocytes give rise to, have failed thus far to demonstrate an overall increase or decrease with increased age\(^60\). It is important to note that the significant distribution of mast cells amongst many different tissue types is likely to be responsible for presenting this confusing picture. It is thought, however, that both the number and the effector function of mast cells increase with age, potentially underlying, at least in part, the process of inflammaging\(^23\).

Macrophages, mononuclear cells deriving from monocytes, typically secrete a raft of pro-inflammatory cytokines when activated. In-vitro evidence appears to indicate decreased cytokine production in some populations of older macrophages\(^60\)--\(^62\). This can be regarded as particularly surprising in the context of inflammaging, and in-vivo evidence points towards an overall increase, rather than decrease, in cytokine production\(^63\). Exciting new research has, on the other hand, demonstrated decreased TNF-α production by cutaneous macrophages in the elderly\(^62\), supporting the former assertion. The apparent decline in macrophage function with increasing age is supported by findings that indicate decreased phagocytic macrophages in the elderly\(^53\), in the face of a potentially increased progenitor number\(^64\). Macrophages, much like mast cells, reside in multiple different tissues and an examination of their changes with age is confounded as a result\(^65\). It is thus hypothesised that

\(^1\) Much of this detail stems from the initial work of Hayflick and Moorhead, and the crucial ‘Hayflick factors’ they defined as controlling the number of passages cells in culture may undergo\(^1\).
although their response to acute infection is poorer\textsuperscript{60-62}, macrophages in ageing individuals chronically secrete pathological low levels of cytokines\textsuperscript{61}.

More conclusive change is offered by NK and NKT cells however, with circulating numbers of both cellular populations increasing in older individuals\textsuperscript{63}. NK cell number changes are possibly, though a mechanism is yet to be elucidated; a compensatory response to the age-related decline in the cytotoxic-killing function of these cells\textsuperscript{48}. The obvious consequence of such a change is an apparent decrease in the body’s ability to fight off viral infection with increasing age but little research has been conducted with a view to identifying the contribution of NKT cells to immunosenescence.

3.2.2 – The ageing adaptive immune system

Many of the changes noted as occurring in the adaptive immune system with increasing age are likely to arise as a result of differences in the innate immune system, as will be discussed in section 3.2.3. Of crucial importance, however, is the process of thymic involution\textsuperscript{(3-Footnote)} that occurs with increasing age. Evidence from mouse-models and more recently in-vivo human-studies, has elucidated further details concerning this process\textsuperscript{66}. Fascinatingly, the thymus is still active in later life (though at a much decreased level to very early life) despite the process of involution potentially starting during early childhood\textsuperscript{67}. Unsurprisingly, this decreased activity significantly impacts on T-cell and B-cell lymphopoiesis.

The relative lymphopenia seen in ageing is accentuated by increasingly impaired lymphocyte function overall. One such change, the age-related expansion of antigen-specific CD8\textsuperscript{+} (and to a lesser extent CD4\textsuperscript{+}) T-cells\textsuperscript{68}, is exceptionally well characterised and exceedingly interesting (it may potentially also occur in B-cells, but this is less well characterised\textsuperscript{68}). It is thought that this expansion, of T-cells specific for previously encountered antigen, results in a T-cell population primed predominately for a set few antigenic determinants and unable to rapidly adapt and respond to newly exposed pathogens. Mature naïve T-cells also require ‘niche’ sites on which they may encounter antigen, but a large population of antigen-specific T-cells is likely to inhibit their ability to reside on these sites and respond to new antigen\textsuperscript{69}.

T-regulatory cells (T\textsubscript{reg}) have also been the subject of much attention from immunologists and gerontologists alike. Lages et al\textsuperscript{70}, publishing in The Journal of Immunology during 2008, beautifully illustrated the more suppressive nature of T\textsubscript{reg} in older individuals when compared to their younger counterparts, hypothesising (and supporting with in-vitro findings) that these cells stifle T-lymphocyte function in older individuals and thus allow for the reactivation of chronic infections. Other studies have supported these findings with evidence of age-related in-vivo increases in T\textsubscript{reg} cell number\textsuperscript{62}. The result of this

\textsuperscript{3} The process of thymic involution is thought to begin shortly after birth, although this remains a contested point, and involves continual regression of the thymic tissues – a process that is thought to underlie immunosenescence.\textsuperscript{66}
increase in pathogenic infection is discussed in section 4.1.

3.2.3 – Interlinked ageing

The changes discussed thus far have been noted in a very linear fashion but the very dynamic nature of the immune system, in which cells feedback on one another through secreted factors and direct contact, is likely to mean that no one change occurs without affecting another and that cells of the immune system age as a whole, rather than independently of one-another. It is also apparent that contrasting research findings present a confusing picture of the aged immune system. Whilst cancer is the subject of this article, ageing carries further significant consequences. The elderly suffer from increases in both the number and the severity of acute infection for example, and chronic-infections are known to be re-activated as we age70. A startling example of this is the varicella-zoster virus which re-activates, causing shingles in a significant number of elderly individuals.

Figure 4 presents an overview of the potential changes in the immune system’s response to danger signals in older individuals but it is important to note that the orchestration of this change is likely to occur through cytokine action8. This is particularly important when discussing inflammaging, and will be noted in subsequent sections of this article. It will also assist in reducing the confusion regarding the more contestable changes that may or may not be seen in the ageing immune system. Appendix 1 summarises the results of multiple studies, identifying how cell type specific cytokine production changes with age.

4.1 – Pathogen onslaught

The bacterium H. Pylori, and its counterparts Human Papilloma Virus (HPV), Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) amongst many others have been associated with evading the immune response and causing persistent infection as a result (see figure 5). The outcome of this continual pathogenic presence and the corresponding unrelenting infection is an uncontrolled and undesirable inflammatory response, thought to largely be responsible for the neoplastic transformation induced by these pathogens20,23. Whilst this change corresponds well with that induced through the immune system itself in inflammaging, it is exciting to identify how immunosenescence impacts on the immune system’s inability to clear harmful bacteria and viruses that may progress to cause malignant neoplastic disease.

It is important to note that a significant proportion of the elderly may have initially been exposed to a pathogen, (that has since unrelentingly infected them) in the early stages of their life. Although the ageing immune system is thus not at fault in terms of the ease at which they are infected, its changing characteristics with age, such as the increase in specific CD4+ and CD8+ T-cells, will affect the potential for carcinogenesis. Oligoclonal expansion of a T-lymphocyte population specific for the pathogen with increasing age will lead to a greater inflammatory response against it, for example. Furthermore, pathogen reawakening, occurring as a result of immunosenescence, is likely to cause further damage.

The immune response to H. Pylori offers an excellent anecdote on which to discuss these points. Figure 2 indicates the usual immune response to H. Pylori infection. In an aged individual, it is unlikely that DCs would initiate the cascade of immune cell events as effectively as in a younger individual, allowing the bacterium to infect the host. Macrophages in the skin, as has been discussed, would also be limited in their antimicrobial response and research has demonstrated a weakening of their NO (Nitric Oxide) production37. NO release, one of the most effective anti-H. Pylori responses, is often, but not always, down regulated by H. Pylori19,20, allowing the bacterium to survive within the host. The reduction in NO production with age is, therefore, likely to uniformly eradicate this effective anti-microbial response. T-reg activity also increases with age70, and the resultant inhibition of Th1 activity, for the few (if, indeed, any at all) lymphocytes that may have escaped thymic involution with adequate specificity for epitopes on the surface of H. Pylori, is likely to
result in a dampened immune response against this pathogen\textsuperscript{70}.

A coordinate and effective immune response is also vital for the body to effectively eliminate cells recognised to be undergoing malignant change\textsuperscript{71}. This ‘tumour surveillance’ and ‘tumour immunity’ is likely to be severely dampened in the elderly, not least if the antigen receptor pool is diminished in overall specificity as a result of oligoclonal expansion. New techniques to use the immune system to target cancer cells, as part of the ‘tumour immunotherapy’ field, are thus likely to need refining and rethinking in the elderly as a result of the decline in the immune system’s function. It is important to note, however, that little direct evidence has supported epidemiological evidence that indicates a role for the immune system in targeting its own cancer cells. This is correspondingly a very small part of this article.

The consequences of immunosenescence are severe in terms of allowing pathogenic microorganisms capable of triggering an inflammatory response to take hold in the body. The decline in NK cells, though no example is illustrated, is also beneficial to viral agents. Yet this is a paradoxical situation. If the responses of immune cells are dampened with age, how then would such pathogens trigger potentially carcinogenic inflammation? The answer to this question potentially lies in the smouldering and ineffective cytokine orchestrated inflammatory state of inflammaging.

4.2 - Inflaming cancer – Deadly cytokines

A chronic low-level state of inflammation has been identified in the elderly and is associated with the induction of a PCM/CM\textsuperscript{33}. This chronic inflammation is thought to stem from low-level persistent infection, chronic exposure to toxic agents or aberrant responses against the body’s own antigenic determinants\textsuperscript{35,72}. Although inflammation is thus thought to be deleterious in the state that characterises inflammaging, when acute it is essentially a protective process, usually occurring in response to pathogenic insult\textsuperscript{4}\footnote{Polly Ratzinger has developed self-non-self (SNS) model to accommodate for abnormal responses against the body’s own tissues. Instead of SNS, her model discusses the immune system’s responses against ‘danger signals’, whether endogenous or exogenous.}. Various clinical signs characterise this inflammation, including rubor (redness), calor (raised temperature), tumor (swelling) and dolor (pain) and yet chronic low-grade inflammation (not the higher-grade inflammation associated with rheumatological conditions, for example) is generally associated only with functio laesa (a loss of function)\textsuperscript{9,73}. Specific cell types are responsible for creating this clinical picture, both in acute inflammation (when the offending source of danger signals is removed and the inflammation resolves) and in chronic inflammation (where the immune system continues to respond to apparent danger signals). The principal aim of inflammation is thus to remove the source of danger signals and this is essentially coordinated by a cascade of cytokine-cellular interactions.

4.2.1 – TNF-\(\alpha\) & COX

Foremost in the cytokine hierarchy is TNF-\(\alpha\) (Tumour Necrosis Factor – \(\alpha\)), which is associated predominately with the induction of inflammation and neoplastic modulation\textsuperscript{74}. This cytokine is typically produced by macrophages, though more recent evidence has highlighted a role for T-lymphocytes in its production\textsuperscript{75}, and is thought to act to encourage malignancy through triggering DNA damage and angiogenesis\textsuperscript{74} (angiogenesis is
growth of the endothelium, typically under the stimulus of VEGF [Vascular Endothelial Growth Factor]. Increased vascularisation as a result of this process allows tumours to grow beyond 2-3 mm in size [i.e. through delivering nutrients and removing cytotoxic waste products] and, crucially, provides greater potential for metastatic spread), and is also thought to act through inducing the anti-apoptotic NF-κB transcription pathway76,77. TNF-α’s effects are, however, notably pleiotropic and very high concentrations of this cytokine are associated with an anti-neoplastic response78.

TNF-α is significantly upregulated during ageing79,80, although tissue-specific contradictions are present in the literature. One such discrepancy is the skin where, as previously stated62, cutaneous macrophages have been noted to synthesise and release reducing quantities of TNF-α as an individual ages. This would imply a direct role for TNF-α in inducing skin cancer (as it would no longer be found in protective high concentrations) but may also indirectly influence carcinogenesis. This, one theorises, would occur through reduced cutaneous Th2 (T-lymphocyte helper type 2) recruitment and a resulting decrease in immunosurveillance; thus allowing pathogens to colonise the skin and cause chronic infection. It is also known that the susceptibility of macrophages to age-related oxidative stress is reduced amongst centenarians79, potentially leading to protectively increased TNF-α production amongst this populace.

A study by Bruunsgaard et al81 assisted in simplifying the controversy surrounding TNF-α levels present in elderly individuals by inducing infection and identifying the cytokine response. Figure six depicts the results this study attained and it is evident that, with increasing age, acute TNF-α production is likely to be reduced but more chronic release is increased when compared to younger individuals. Chronic low-level TNF-α production in the elderly will not only directly increase malignancy but will, intriguingly, interact with COX to indirectly increase malignant potential23. These interactions commonly involve chronically raised TNF-α stimulating the oxidative cytotoxic cascade, thus forming NO (nitric oxide)82. This NO then interacts with cytotoxic ONOO⁻ (perinitrite) and activates COX-283 (cyclooxygenase type 2)

COX-2 produces inflammatory mediator prostaglandins and is thus thought to promote cell proliferation, stimulate angiogenesis and inhibit apoptosis as a result84. Interesting epidemiological studies support this hypothesis by indicating that bowel cancer, the development of which is closely linked with pervasive inflammation, is decreased in incidence amongst patients prescribed NSAIDs85 (non-steroidal anti-inflammatory drugs; these inhibit the COX enzymes irreversibly or reversibly, depending on the particular formulation).

Of intrigue, therefore, is evidence from the centenarian population that indicates adaptation to lower inflammatory cytokine levels, thus reducing the likelihood of cancer development. COX alleles known to be pro-inflammatory are at much lower incidence amongst this population86, for example, whilst the -308A TNF-α SNP (single-nucleotide polymorphism), associated with decreased longevity and increased inflammation when compared to the -308G variant87, is at remarkably low incidence amongst both those who live to a greater age and those in low-cancer incidence populations86,87.

4.2.2 – Highs and lows: IL-6 & IL-10

Adaptation to a reduced likelihood of developing cancer through single base changes in the genetic code is thus evident and appears to be consistent through most cytokines involved in creating the chronic, low-grade inflammation seen during ageing. IL-6, for example, acts both to induce cellular growth88 and inhibit apoptosis89, with

![Figure 7: IL-6 & IL-10 SNP localisation schematics](Reference: Figure 7 (Caruso C et al. Ann. N. Y. Acad. Sci. (2004) 1028:1-15)
several studies even indicating its potential use as a general prognostic factor in cancer. This cytokine has for some time also been associated with the induction of metastases through up-regulated endothelial adhesion molecules and increased VEGF production.

The polymorphic -174CG base pair of IL-6 is an example of beneficial adaptation in a select few, for example. If homozygous for the G allele, subjects are known to produce dramatically increased quantities of IL-6 with ageing, reducing cancer incidence amongst these individuals. Centenarians and several population groups with low cancer incidence have, however, been found to feature this allele in exceptionally low incidence whilst polymorphisms providing high quantities of the anti-inflammatory cytokine IL-10 are far more prevalent than in the general population. It is also important to note that polymorphic changes controlling eosinophil production are important in this context, since rising eosinophil number is associated with increased IL-6 concentration in old age.

Interleukin-6 is also known to increase the production of C-reactive protein (CRP), concentrations of which rise during ageing. Intriguingly CRP is used as a surrogate marker of inflammatory activity, providing evidence of inflammaging, but raised levels have also been associated with the development of bowel cancer, further supporting the link between ageing, inflammation and cancer.

4.2.3 – TLRs

Whilst TNF-α, COX, IL-6 and IL-10 are the principal cytokines to have been strictly associated with ageing; the TLR (Toll-Like Receptor) family of proteins also appears to be important in age-related cancer pathogenesis. This is likely to be due to their role in ‘detecting’ the danger signals that fuel the pro-inflammatory cytokine pool discussed as a feature of ageing and cancer pathogenesis during the essay. There are many polymorphisms in the TLR genetic code and numerous examples of these are associated with a longer lifespan and, conversely, the development of specific cancers, potentially through creating less specific TLRs. This raises the intriguing possibility of individuals less well adapted to fighting off infection, being conversely better adapted to longer life.

4.2.4 – IL-2: Paradoxical change?

Concentrations of IL-2 are thought to decrease during ageing, which may assist in reducing metastatic spread through limiting angiogenesis (IL-2 is a potent stimulator of VEGF production, which causes angiogenesis to occur). The decrease in production of this cytokine occurs predominantly as a result of changes in CD4+ T-cells (figure eight highlights this point by illustrating potential age-related changes in both the CD4+ and the CD8+ T-cell compartments) and it is important to note that IL-2 is crucial for foxp3+ Treg peripheral expansion. This appears paradoxical in the light of the age-related increase in Treg activity and presents a research conundrum that is yet to be fully mapped out.

4.3 – Immunosenescence in the young?

The focus of this work has been immune dysfunction with increasing age as a cause for increased cancer development in the elderly, but very interesting research published recently in PNAS has raised the possibility of immune dysfunction in the very young – an apparent immunojuvenescence – allowing for the development of malignant neoplastic disease. In the study, Isoda et al not only provided evidence of cancer transmission from a mother to her foetus but also highlighted a genetic change in the cancer cell’s MHC molecules that enabled it to evade the infant’s immune response (and the placenta’s immunological barrier). This phenomenon is likely to be rare, with limited likely cases even in the last 100 years, but highlights that the immune system’s role in cancer pathogenesis must not be undermined.
5.1 – Conclusion – New approaches are necessary

Allowing one to successfully age is, and will remain for some time, medical science’s ultimate challenge. The immune system is complex and dynamic, ageing as a whole to unleash a raft of pathological changes in older individuals. Cancer, a disease of vehemently negative consequence, arises principally as a result of an accumulation of genetic mutations; but the role of the changing immune system in both the progression, and regression, of cancers is not to be ignored.

Elegant experiments have demonstrated the ability of the immune system to modulate a cell’s malignancy through modifying its immediate environment. Indeed, whilst the declining ability of the body to fight off infection with increasing age is likely to assist in the seating of oncogenic microorganisms within the body, the inflammatory cytokine soup created as a result demonstrates the body’s own ability to create a pro-cancer microenvironment. Indeed, so poor does the immune system’s function become with increasing age that tumour surveillance is also severely compromised.

This role for the immune system in cancer pathogenesis is reflected not just in those cancers which peak in incidence in middle age, but by the plateau and fall of cancer incidence rates in the very latest stages life, by the exceptionally low incidence rates of cancer in the oldest old – the centenarians – and through the many cancers associated with pathogenic infection and chronic inflammation. It may be argued that centenarians escape cancer through better repairing genetic damage, but little evidence exists for this in the midst of the wealth of evidence supporting polymorphic changes in cytokine production and immune cell action, for example.

It is thus imperative that the view of cancer transitions from simply being a ‘genetic disorder at the cellular level’, to instead take account of the significant role the microenvironment of the entire tissue in which the cell resides plays in cancer pathogenesis. Only then will we begin to attenuate the painful consequences of this all too prevalent disease.

Suggested further reading


5733 Words
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Figure 2: Ref 19: Wilson KT, Crabtree JE. Immunology of Helicobacter pylori: Insights Into the Failure of the Immune Response and Perspectives on Vaccine Studies. Reviews in Basic and Clinical Gastroenterology (2007) 33;288-308

Figure 3: Satyanarayana A, Rudolph KL. P16 and ARF: activation of teenage proteins in old age. Journal of Clinical Investigation (2004) 114(9); 1237-1240

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Figure 8: Maue AC, Yager EL, Swain SL, Woodland DL, Blackman, MA, Haynes L. T-cell immunosenescence: lessons learned from mouse models of aging. Trends in Immunology (2009) 30(7);301-305
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Stimulation</th>
<th>Cell type</th>
<th>Time</th>
<th>Cytokine production in ageing</th>
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<tbody>
<tr>
<td>Goh et al. (1995)</td>
<td>10 &gt; 80-year-olds</td>
<td>LPS</td>
<td>Monocytes</td>
<td>24 h culture</td>
<td>Decreased TNF-α and IL-1β</td>
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<tr>
<td></td>
<td>10 &lt; 39-year-olds</td>
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<td>Mclachlan et al. (1995)</td>
<td>25 &gt; 65-year-olds</td>
<td>LPS</td>
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<td>16 h culture</td>
<td>Decreased IL-1β</td>
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<td>25 young controls</td>
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<td>Rudd and Barerjee (1989)</td>
<td>33 &gt; 70-year-olds</td>
<td>LPS</td>
<td>Monocytes</td>
<td>24 h culture</td>
<td>No difference in IL-1β</td>
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<td>40 elderly with infections</td>
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<td>40 &lt; 45-year-olds</td>
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<td>Roubenoff et al. (1998)</td>
<td>742 elderly (mean 79 yr)</td>
<td>(a) LPS and S.</td>
<td>PMNC</td>
<td>22 h culture</td>
<td>(a) No difference in TNF-α and IL-1β</td>
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<td>21 young (mean 30 yr)</td>
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<td>(b) No difference in IL-6</td>
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<td>Riancho et al. (1994)</td>
<td>15 elderly &gt; 55 yr</td>
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<td>24 h culture</td>
<td>Increased IL-1β, No difference in TNF-α</td>
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<td>18 young &lt; 55 yr</td>
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<td>Bom et al. (1995)</td>
<td>16 elderly (mean 80 yr)</td>
<td>LPS</td>
<td>Undiluted whole blood</td>
<td>48 h culture</td>
<td>Increased TNF-α and IL-1β</td>
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<td>Gabriel et al. (2002)</td>
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<td>LPS</td>
<td>(a) Whole blood diluted 1:9</td>
<td>(a) 24 and 72 h culture</td>
<td>(a) Increased IL-1β and IL-6 after 24 h, No difference in TNF-α</td>
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<td>16 young (mean 28 yr)</td>
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<td>(b) PMNC</td>
<td>(b) 24 h culture</td>
<td>(b) Decreased IL-1β and IL-6</td>
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<td>Bruunsgaard et al. (1999)</td>
<td>168 &gt; 80-year-olds</td>
<td>LPS</td>
<td>Whole blood diluted 1:4</td>
<td>24 h culture</td>
<td>Decreased production of IL-1β and TNF-α compared to young men but not compared to young women. No difference in IL-6.</td>
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<td>Fagiolo et al. (1993)</td>
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<td>PMA + PHA</td>
<td>PMNC</td>
<td>24, 48 and 72 h culture</td>
<td>Increased production of TNF-α, IL-1β and IL-6</td>
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<td>24, 48 and 72 h culture</td>
<td>Increased TNF-α production</td>
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<td>29 &lt; 35-year-olds</td>
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<td>O'Mahony et al. (1991)</td>
<td>9 &gt; 62-year-olds</td>
<td>PMA</td>
<td>PMNC</td>
<td>24, 48 and 72 h culture</td>
<td>Increased percentage of TNF + CD3 + cells and IL-6 + CD3 + cells. No significant difference in TNF, IL-1β and IL-6 producing monocytes. No difference in TNF-α, IL-1β or IL-6 or culture supernatants (72 h)</td>
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<td>(mean 73 yr)</td>
<td>10 young (mean 29 yr)</td>
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<td>McNerthney et al. (2002)</td>
<td>13 elderly (mean 92 yr)</td>
<td>PMA + ionomycin</td>
<td>Whole blood diluted 1:1</td>
<td>4 h culture</td>
<td>Increased percentage of TNF + CD3 + cells</td>
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<td>Sandlund et al. (2003)</td>
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<td>PMNC</td>
<td>4 h culture</td>
<td>Increased percentage of TNF + CD3 + cells</td>
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<td>14 ≥ 80-years-old</td>
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<td>28 young (mean 22 yr)</td>
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<td>Beharka et al. (2001)</td>
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<td>PMNC</td>
<td>48 h culture</td>
<td>(a) No difference in IL-6</td>
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<td>21 young (20–30 yr)</td>
<td>(b) Coc-A</td>
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<td>(b) Decreased IL-6 production</td>
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