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Review

Cytokine signaling in the modulation of post-acute and chronic systemic inflammation: a review of the influence of exercise and certain drugs

Stephen C Allen[1,2,*]

[1] The Royal Bournemouth Hospital, Castle Lane East, Bournemouth, Dorset BH7 7DW, UK
[2] Centre for Postgraduate Medical Education and Research, Bournemouth University, Bournemouth, Dorset BH12 5BB, UK

* **Correspondence:** Email: drscallen@aol.com; Tel: +441202303626; Fax: +441202704542.

Abstract: Acute inflammation in response to stimuli such as infection can be of deleterious amplitude and/or duration in some individuals and often tends towards chronicity in older adults. This inflammatory pattern appears to be causally linked to higher all-cause mortality and other adverse outcomes such as frailty, sarcopenia, mood disorders and impaired cognitive function. Patients in this clinical state have a persistent pro-inflammatory cytokine profile. Exercise has been shown to shift baseline levels of tumor necrosis factor (TNF), interleukin-1 (IL-1) and other cytokines to a less inflamed setting, with interleukin-6 (IL-6) playing a key modulating role. Drugs can also modulate innate immune cells and their biochemical networks with a shift to a surveillance pattern. Theophylline and chloroquine are examples of drugs that could have clinical value as immune modulators. For example, theophylline induces a 20 percent fall in TNF and around 200 percent increase in IL-10 production by blood-harvested mononuclear cells, and a fall of about 50 percent in interferon-gamma (IF-γ) release. Pharmacological activity in that domain could be exploited in clinical practice, with the aim of establishing a less pro-inflammatory innate immune milieu after provocations such as infection, trauma or major surgery.

Keywords: infection; inflammation; innate immunity; cytokines; exercise; anti-inflammatory drugs; immune modulation

1. Introduction

Physicians in a range of specialties recognize the need to improve collective knowledge of the role of persisting inflammation as an adverse prognostic factor in the context of acute illness. It is also increasingly understood that sustained and slowly resolving systemic inflammation is a contributing mechanism to chronic clinical states such as the frailty syndrome, physical deconditioning, sarcopenia, impaired cognition, low mood, poor functional performance and higher all-cause mortality. To some extent this pertains to people of all ages, though the brunt tends to fall mainly on elderly patients in whom inflammation can cause multiple clinical and functional difficulties. This review will consider the operation of sustained pro-inflammatory states in the causation of various disease phenotypes, using frailty and sarcopenia as the main examples. The role of physical exercise in the prevention and treatment of inflamed states will be considered, drawing on information selected from the large body of extant literature published in these areas of research. Further, the emerging potential for using a number of drugs to modulate inflammation will be examined, with particular attention to those that influence the balance of cytokines involved in the pro-inflammatory and anti-inflammatory signaling networks.

2. Clinical considerations

Physical deconditioning and frailty are now widely recognized as deleterious clinical states seen mainly but not exclusively in older people and those with chronic, usually inflammatory, conditions such as chronic obstructive pulmonary disease (COPD). It predisposes sufferers to a variety of problems with normal activities of daily living, particularly once the diminished physical reserves associated with ageing and chronic disease are further compromised by superimposed acute illnesses. Definitions of frailty vary, and though there is none that is universally accepted, a broad consensus is emerging that focuses on diminished strength, poor stamina, low mood and vulnerability to disease and injury [1]. Importantly in the context of this paper some features of the frailty syndrome are reversible, most importantly in the early stages and in the wake of acute events such as significant infections. Therefore, examples of the treatments that might ameliorate or reverse frailty will be a focus in this paper, with special reference to the probable mechanistic function of cytokines in that regard.

3. Systemic inflammation, frailty and sarcopenia

A number of studies have shown that systemic inflammation is likely to be causally associated with characteristic features of frailty, including loss of muscle mass and strength (sarcopenia) and poor appetite with weight loss (cachexia) [2–4]. The relationships between ageing, inflammation, exercise and muscle structure and performance are being progressively delineated and have been the subject of considerable recent attention in the scientific literature [2,5]. The molecular biology and chemical mechanisms of this pathogenic link are proving to be intricate and it has not been possible to date to propose a verifiable and unifying set of molecular mechanisms that can consistently describe all of the empirically recorded effects. The most likely explanation is that elements of the between-cell communication array controlling immune activity, such as cytokine signaling, the action of catecholamines, cortiso-steroids and other hormones, as well as more peripheral influences

such as complement activation, and interferon release influence one another in a way that can be best conceived as a multi-directional net with a web-like function and not as a collection of near-linear chemical reactions. Therefore, perturbation due to a noxious stimulus, or treatment intervention, in one part of the notional web causes alterations elsewhere in the network that are dependent upon variables with a large number of permutations, and consequently results in the appearance of inconsistency and unpredictability when studies are performed on subsets of the innate immune system or a very restricted suite of molecules. Therefore, it is reasonable to argue that it is likely to be impossible to discover generic pathways that describe and predict the precise immune-modulating effects of drug treatments or other interventions in all cases and circumstances. Effective treatments could therefore be the ones that result in wide corrective changes to the overall tension of the innate immune system, a phenomenon that is often called immune modulation, and through that mechanism lighten the inflammatory load that predisposes to frailty and other adverse clinical phenotypes.

4. Persistent inflammation in later life

At this stage, it is illustrative to take account of the operational condition of innate immune function in older age. Empirical research has shown that the baseline settings of chemical markers of inflammation, such as interleukin-1 (IL-1), tumor necrosis factor (TNF) and C-reactive protein (CRP) tend to be around 2 to 4 times higher in the plasma of elderly people, mainly but not exclusively in those over 80 years of age, in comparison with the plasma concentrations found in healthy younger volunteers [6,7]. In a study of adults with no overt illnesses the mean baseline peripheral plasma TNF level was 0.6 pg/mL in those age 29 years or less and 1.5 pg/mL in those age 69 years or more [6]. Further, a community study established the higher 95th centile for CRP to be age/50 and age/50 + 0.6 for white men and women respectively. Similarly, the CRP distribution metrics for people of African heritage were age/30 and age/30 + 1.0 [8]. CRP can be conceived as a broad non-specific indicator of pro-inflammatory activity and the rise with age has been termed "inflammaging" by some researchers [7]. In many people the higher background inflammation can be explained by clinically obvious chronic inflammatory conditions such as chronic obstructive pulmonary disease (COPD) or rheumatoid arthritis (RA) [9]. Also, similarly elevated biochemical indices of inflammation have been described in older adults with various pathological states that appear to pull the innate immune setting from normal baseline in a pro-inflammatory direction. Important examples are central and visceral obesity, atheromatous arteritis, or diabetes type 2 [10–12]. Also pertinent to this review is the elevated pro-inflammatory state that often persists or resolves slowly after an acute inflammatory event, such as infection or trauma [13,14]. Elevated markers indicative of inflammation have been found with a high prevalence in Alzheimer's disease (AD), chronic renal disease, osteoarthritis and physical inactivity [10,15–17]. Apparently well elderly people are sometimes found to have biochemical evidence of persistent low-level systemic inflammation with no apparent clinical cause, so old age therefore appears to be independently associated with a low-amplitude chronic inflammatory state in some individuals [7,18–20]. A large study of healthy volunteers living in the community found the mean plasma CRP to be 0.9 mcg/mL in young adults compared to 3.0 mcg/mL in people aged 65 years or more [18]. Baseline IL-6 and IL-1 also appear to correlate with age [20] though in some studies of healthy volunteers statistically significant correlation was not reached; some of the discrepancy might be due to participant selection criteria [21,22]. Persisting low-level inflammation appears to be linked with higher overall mortality [23,24], muscle weakness [25,26],

reduced daily living capability [24] and lower subjective perception of health [27]. The corresponding indicators of inflammation, such as CRP, IL-1, IL-6 and TNF tend to be found in varying proportions in different studies, depending to some extent on the exact laboratory methods deployed, but overall the detrimental effects outlined in earlier paragraphs were generally found in those with 1.5 to 3-fold elevation above the levels detected in well people of similar age. Comparative studies of the same type are lacking for young patients.

From the pathogenic viewpoint it is important to take into consideration the evidence that chronic disease progression appears to be in part driven by a chronic inflammatory state and is not merely an indication of it [28], suggesting a complex mutually augmenting relationship between cause and consequence. Inflammation of the arterial endothelium, as observed in atherosclerotic disease is arguably the most well-defined example, and can be viewed as a template to understand the relationship between inflammation, ageing and pathology [29]. Further, it is apparent that a substantial proportion of older people have inflammatory biochemical responses to acute conditions, for example infection or trauma, that resolves more slowly than it does in younger adults [13,14]. The elevated blood levels of IL-1, IL-6 and TNF tend to be elevated longer and the corresponding increase in the anti-inflammatory cytokine interleukin-10 (IL-10) occurs later, is slower to rise and of lower amplitude. The empirical data that support this phenomenon have been consistently and unequivocally confirmed for pneumococcal and Gram-negative endotoxin antigens [30,31], in which cases the time taken to return to baseline in older people is approximately double that of young adults, despite comparable peak levels at the beginning of the episode. This suggests that in older subjects there is impaired anti-inflammatory regulation manifesting as a slower process to re-set the innate immune network to its surveillance baseline. That is likely to be a component mechanism leading to the more gradual physical and functional recovery often seen in old age, and might contribute to the tendency towards a chronically inflamed state.

There are alternative explanations for chronic age-associated inflammation. For example, lower anti-oxidant capacity with a consequently higher vulnerability to oxidative stress [32]. Such a mechanism might contribute to a pro-inflammatory shift through inducing a higher density of toll-like receptors on a range of immunologically competent cells [33]. A case can consequently be constructed that teleologically links the elevated baseline inflammatory biochemistry in older age to appropriately increased anti-tumor immune vigilance or to unrecognized or asymptomatic auto-immune conditions. Similarly, there is not a proper understanding of the observation that cortisol and catecholamine concentrations tend to be elevated higher and with an extended duration after acute infection or trauma in older patients [34]. Whether that is solely in response to higher pro-inflammatory cytokine production or in part generated through other mechanisms determined by pituitary and adrenal activity is not known. Despite these uncertainties, the case for cytokines having a key regulatory role in the inflammatory phenotype associated with ageing is now in no doubt.

5. Inflammation as a driver of pathology

The perturbation of the inflammatory baseline setting and modulation described in the previous paragraph appears to play an important part in the pathogenesis of a number of several clinically important conditions in old age, including cardiovascular and cerebrovascular disease, metabolic syndrome, sarcopenia, neuronal dysfunction and some malignancies [9]. The effect on neuronal function tends to be insidious and is not fully understood, but the evidence that the tendency toward a

pro-inflammatory state and delayed or partial anti-inflammatory counter-regulation are contributory to acute and long-term cognitive impairment, depressed affect, illness behavior and autonomic dysfunction is persuasive. However, the recorded contribution of inflammation on the pattern of these clinical phenomena varies substantially depending upon sampling, assessment methods and clinical-pathological context [9].

Persisting low-amplitude elevation of CRP, mainly manufactured and secreted by hepatocytes in response to elevated IL-1, IL-6 and TNF, has been linked to an increased risk of vascular disease [29,35]. In that pathogenic setting CRP is probably best viewed as a marker for the elevated levels of the pro-inflammatory cytokines that are more directly implicated in the pathogenesis of vascular disease via their promotion of insulin resistance, dyslipidemia and inflammatory macrophage activity. Moreover, IL-1, IL-6 and TNF have been found to be reproducibly associated with such metabolic vectors of vascular pathology [36]. In later studies the pro-inflammatory cytokines interleukin-15 (IL-15), interleukin-18 (IL-18) and interleukin-8 (IL-8) were shown to be more specific risk factors for coronary artery disease, type 2 diabetes and some malignancies [37–39].

The neuro-pathological role of inflammatory cytokines is worthy of particular mention because of the burden of delirium and dementia to sufferers and those caring for them. Receptors for cytokines that augment inflammation are located on the cell membranes of most neurons [40] and supportive data are accumulating for the involvement of several chemokines, and other biochemicals with key roles in inflammatory responses, such as cortisol and adrenalin, in the regulation and control of nerve cell function. Receptors for a number of inflammatory chemokines are located not only on brain nerve cells but also on glial cells, including receptors for TNF, IL-1, IL-6 and interleukin-1 receptor antagonist (IL-1ra). Further, transport mechanisms located at the blood-brain barrier (BBB) have been found to facilitate the entry of certain cytokines into the cerebro-spinal fluid (CSF) and brain interstitium, including IL-1, TNF, IL-6 and IL-1ra, partly by transport of formed cytokines from plasma and partly by de novo synthesis and secretion on the CSF side of the BBB. In animal studies, it was found that quantifiable and consistent alteration in behavior patterns, such as appetite loss, hiding and drowsiness, can be caused by injecting physiological doses of IL-1 and TNF [40–42]. These high-level neurological effects provide a pathway to a better appreciation of the cyto-chemical and structural mechanisms through which inflammation can alter high-level nerve function, including a mechanistic framework from which it might be possible to gain further insights into lethargy and delirium. A considerable volume of cognitive research has been focused on the dementias, particularly Alzheimer's disease (AD) and related neurodegenerative conditions such as Parkinson's Disease, and it has clearly been shown that the inflammatory state of individuals, including the modulation of cytokines, is altered in such patients but can be downregulated by regular exercise [15,43,44]. On the other hand, the part played by cytokines in the initiation and promulgation of the processes resulting in AD, or its rate and pattern of progression, is not so clear. The question still remains as to whether the raised CSF and plasma cytokine levels found in AD are a secondary consequence of a separate pathological process or a key factor in the pathogenesis of the disease. The observed protective properties of regular moderate-to-vigorous exercise on objective measures of cognitive performance indicate a real effect [43,44]. Inflammation also has an impact on other aspects of neurological function. For instance, there is evidence that the autonomic down-regulation, such as reduced vagal tone, consequent upon acute episodes of inflammation caused by illnesses such as lower respiratory tract infections or pyelonephritis, is partly mediated by cytokines, though other deconditioning mechanisms are probably involved [40]. The

down-regulation of cardiovascular sympathetic and parasympathetic reflexes is of particular interest in medical practice because that is an important factor in the causation of the postural hypotension, which can result in syncope and falls especially in older patients after acute illnesses, and is likely to a substantial degree to be a result of cytokine-induced sympathetic dysfunction [45]. Similar mechanisms are likely to contribute to the long-term autonomic dysfunction found in people with diseases characterized by chronic inflammation. The mechanisms whereby abnormalities of inflammation chemistry lead to dysfunction in sensory, motor and extrapyramidal systems are less well defined and likely to be a rewarding field for targeted research.

6. IL-6 as an inflammation-modulating myokine

IL-6 has tended to be regarded as a pro-inflammatory cytokine with a broad range of influences on the immune network that includes promoting the action of IL-1 and TNF, and as one of the key inducers of the insulin-resistant state often found in physically inactive people. Supporting this interpretation is the finding that plasma IL-6 concentrations become progressively elevated during the early phase of the response to acute pro-inflammatory stimuli, such as infection, and are frequently found to be raised above the normative level in patients with chronic inflammation, such as those with rheumatoid disease between acute episodes [46]. However, more recently it has become apparent that the function of IL-6 within the intricate web of influences that control innate immunity is considerably more subtle than its function as an acute phase chemokine. Under most physiological conditions the principal origin of IL-6 is active striated muscle and it is consequently referred to as a myokine in some classifications [47], though IL-6 is also synthesized and released by many other somatic cell types. Under exercise conditions, during and immediately after repetitive muscle action, IL-6 has been found to possess autocrine, paracrine and endocrine functional roles that mediate other metabolic effects, particularly insulin sensitization, on the contracting myocytes and other cells. Subtly, under those metabolic conditions IL-6 appears to stimulate the production and secretion of anti-inflammatory cytokines, particularly but not exclusively IL-10 [48]. Though the entire suite of actions of IL-6 on metabolic processes remains to be defined it clearly has an influence on the biochemistry of inflammation that is variable and conditionally dependent upon fluctuating metabolic settings with pleiotropic flexibility [47,48]. For example, under septic conditions IL-1 promulgates IL-6 and TNF though after exercise in a non-septic state IL-6 facilitates the release of the anti-inflammatory cytokines IL-10 and IL-1ra. This putative coordinating property of IL-6, a cytokine synthesized and secreted by actively contracting striated muscle, positions it as a key factor when considering the modulating influence of physical activity on inflammation and intermediate metabolism, and possibly posits the idea that IL-6 might be understood not simply as an regulatory chemokine but also in a hormone-like role with paracrine and autocrine functions [49]. A number of myokines with at least partially defined functions have been described but most have narrower biochemical roles than IL-6 and little or no controlling influence on setting the timing and amplitude of inflammatory chemical and cellular responses. The context-dependent and apparently broad-spectrum effects of IL-6 also signals the likelihood that one or more, as yet unrecognized, substances act as more proximal controllers, with the most likely site being intra-cellular or intra-nuclear and the most probable domain being epigenetic. Nevertheless, for the purposes of this paper IL-6 can be viewed as a cytokine that has an increasingly well-documented pleiotropic modulating role in immune system activity, with key functions in the re-setting of innate immune

baselines in response to physical activity.

IL-6 rises in response to exercise at all ages [29,43,44,50,51]. In humans, this has been most thoroughly shown during concentric reciprocating exercise against a moderate resistance, such as running, though IL-6 is also produced by myocytes in response to eccentric muscle use and isometric contraction [52]. During normal movement the pattern of muscle contraction tends to be a changeable mixture of all these forms of muscle activity. The most definitive research has been conducted on young adult participants performing strenuous exercise regimens. In such studies, IL-6 concentrations in plasma can rise by a factor of 100 or more above baseline levels, especially in response to moderate-severe exercise of long duration, for example distance running at the elite level, and similar responses have been demonstrated in animal studies conducted on mice [51,53]. A dose-response relationship between peak IL-6 amplitude and work rate, and duration, has been consistently demonstrated, particularly the latter. Measurable rises in blood IL-6 also occur in response to less strenuous forms of exercise, such as level-ground cycling or fast walking for 10–20 minutes [54]. However, there have been no studies of the IL-6 response to very low work rates, for example slow walking for short distances, that is representative of the amount of physical work that can be achieved by many frail people. Interpreting the IL-6 response to muscle activity is rendered more complex by the baseline concentration fall that has been observed between repeated sessions of exercise separated by several hours [55]. In participants who take regular exercise it is reasonable to posit that the lower between-session baseline IL-6 levels are likely to be the critical anti-inflammatory outcome of muscle action, whereas the brief rise after exercise increases insulin sensitivity via a separate mechanism [56]. Further, the hormone-like influence of IL-6 on muscle cells also appears to be dependent on the physiological context and temporal profile of IL-6 secretion so that the steep rises after vigorous exercise seem to have a role in increasing muscle volume, contractility strength and stamina, therefore an anti-sarcopenic effect, while in contrast chronically raised baseline IL-6 concentrations probably contribute pathogenically to the degenerative changes that lead to muscle cell apoptosis and sarcopenia [50,57]. It might therefore be reasonable to hypothesize that the benefits of physical activity that appear to be mediated by IL-6 are the result of 2 describable mechanisms. First, a broad-spectrum effect that dampens inflammation by stimulating the release of IL-10 and other anti-inflammatory cytokines that have a positive ameliorating influence on, for example, endothelial metabolism, insulin receptor function and liver protein synthesis. Second, more narrowly defined mechanisms through which the high but transient IL-6 levels after exercise maintain muscle architecture and function and low between-exercise baseline concentrations reduce the drift to a sarcopenic phenotype, probably via complex gene-switching mechanisms that are currently not fully understood but have a profound influence on muscle cell metabolism and apoptosis [58–61].

7. The use of drugs to alter cytokine responses

Under some clinical conditions it is not possible to utilize natural processes, such as spontaneous immune correction and exercise, to suppress inappropriately intense systemic inflammation, such as after severe trauma or during certain orthopedic treatments, when resistive exercises and regimens based on walking are not practical or are ruled out for clinical reasons. Similarly, for the majority of very sick or frail patients, including those with impairments for whom exercise-based treatment programs cannot be applied, it is impossible to achieve the work rates

required to obtain and sustain an immune-modulating effect. The same restrictions are also a factor for a large proportion of older patients as they recover from acute inflammation due to, for example, infection and trauma. Further, clinicians, particularly geriatricians, encounter many frail patients recovering from sepsis who are neither able nor willing to take part in attempts to regain basic mobility and feel unable to participate in a graduated exercise program. For such patients there is an imperative to consider deploying other methods to facilitate the re-setting of a normative baseline innate immune cytokine profile to try to mitigate the deleterious consequences of prolonged inflammation. Once aspects of nutrition, such as vitamin D status have been corrected as much as possible and the primary cause of the inflammation, for example pneumonia, has been adequately treated, and an exercise regimen is not possible, the next suite of interventions is pharmacological. However, it is important to emphasize that drugs must not be regarded as a substitute for the non-pharmacological interventions mentioned above, and a logical argument can be posited for the addition of immune-modulating drugs to treatments, such as physical activity and nutritional support, when that is a practical possibility. Drugs of many classes have been found to influence innate immune cell function and chemistry by shifting it to a less pro-inflammatory state. There is a substantial evidence base for benefit in chronic inflammatory states, though few studies of benefit in post-acute inflammation.

8. Rationale for the therapeutic use of immune-modulating drugs

From a practical perspective there is clearly a substantial tranche of patients who are unable to participate in exercise-based treatments to ameliorate inflammation, decrease the transition to sarcopenia or delay a lapse into an overtly frail condition in acute and chronic disease contexts. This review now proceeds with a discussion of the potential for drugs of several pharmacological classes to be used to shift patients' innate immune state from a physiologically damaging inflammatory phenotype to a less detrimental surveillance setting. Because the immune modulatory effect of many drugs is not their primary therapeutic indication, most have not been studied to the extent that the precise anti-inflammatory mechanisms are thoroughly understood. Considering the complex net-like interactions between the cells, chemokines and other bio-chemicals involved in immune systems it is arguably inappropriate to try to depict such a system with the conventional model of linear reactions. Instead it is probably more informative to look at how some drugs seem to tug the immune web toward a more anti-inflammatory mode; a property that potentially could have usable therapeutic utility. In general, the evidence for a clinically beneficial effect is predicated on observational clinical studies, animal and cell culture experiments and clinical trials on a pilot scale. Full scale prospective clinical trials of good design are very few with the purpose of testing the efficacy of drugs in dampening the chronic inflammatory states leading to, for example, frailty and sarcopenia. Nevertheless, in some categories there is sufficiently strong evidence to advocate the careful use of some drugs outside their usual licensed indications for that purpose. To illustrate this potential this review will now consider in some detail the evidence for using methyl-xanthine drugs for their anti-inflammatory action, as an example, then briefly scan other drugs that may be utilized for similar purposes.

9. Immune modulation by methyl-xanthines

Theophylline, for many years primarily prescribed for treating airflow obstruction in patients with asthma and COPD, is now known to have several other pharmacological properties including an anti-inflammatory influence on innate immune responses. Its function as a bronchodilator is constrained by requirements to take account of a narrow therapeutic range (trough plasma level 10–15 mg/L) that is close to the levels associated with significant symptoms of toxicity (>20 mg/L) so its therapeutic usefulness has been largely displaced by the better efficacy and less troublesome toxicity of beta-2 agonist and anti-muscarinic bronchodilators. However, some improved functional outcomes, for example timed mobility, took place in COPD sufferers receiving theophylline despite no measurable change in their lung function tests or arterial blood gas indices. More importantly, the apparent benefit remained present at low, usually non-toxic, (<10 mg/L) plasma concentrations [62]. Follow-up studies showed a local anti-inflammatory effect of theophylline on bronchial epithelium and sub-epithelial structures, at systemic level in vivo and on immune cells in vitro [62,63]. This appears to be a class effect as other methyl-xanthines, for example pentoxifylline, have a comparable effect [64] though the extant literature on this topic is more extensive for theophylline. A full biochemical understanding of the inflammation modulating characteristics of theophylline has yet to be elucidated, and it is likely to vary between individuals according to the prevailing pathological and physiological conditions. In an in vitro experiment it was found that a theophylline concentration of 15 mg/L lowered mean TNF production from 0.26 to 0.21 pg/mL ($p < 0.05$) by harvested monocytes and raised mean supernatant IL-10 from 0.35 to 0.98 pg/mL ($p < 0.01$). There was simultaneous reduction of the mean interferon-gamma (IFγ) level from 24.5 to 13.4 pg/mL ($p < 0.05$) [65]. In a similar manner, in vivo application of approximately equivalent levels of pentoxifylline over 4 days resulted in progressive decline in the production of pro-inflammatory cytokines (IL-6, IL-1, IL-8 and TNF) of the order of between 20 and 80 percent by harvested immune competent cells [64]. This phenomenon appears to act via epigenetic mechanisms involving induction of histone deacetylase-dependent gene switches that alter immune settings in the direction of a more anti-inflammatory phenotypic profile for immune cell activity, a mechanism that is independent of phosphodiesterase inhibition that is responsible for the bronchodilator action of methyl-xanthines such as theophylline [63,66]. Further, it has been found that theophylline also reduces baseline IL-6 concentrations in peripheral blood in humans [67], but IL-6 appears to have a malleable function that depends on prevailing physiological and inflammatory conditions, as has been described in an earlier paragraph, so the therapeutic significance of this property is uncertain. Further, no empirical research has been conducted on the influence of theophylline or other methyl-xanthines on IL-6 production during and after exercise. However, from the existing evidence, taking into account the current state of understanding of epigenetic mechanisms, it is probable that theophylline induces a shift in the direction of an anti-inflammatory state through gene activation and deactivation in immune competent cells which are known to possess several gene switches that regulate the rate of synthesis of a number of cytokines [66,68,69]. Interestingly, a consistent finding has been that patients with COPD receiving theophylline in addition to their standard regimen have lower between-exacerbation baseline CRP levels, improved mobility and better scores on functional scales when compared with COPD control patients [70]. These apparently broad-spectrum effects of theophylline are a credible example of immune "modulation", and it is particularly germane that theophylline given at standard bronchodilator doses also appears to suppress inflammation without lowering the essential protection

of timely and rapid innate immune responses to infection. Encouragingly, a well-designed study showed a lower mortality rate in patients with serious systemic infection given theophylline in an intensive care context [71,72]. From the patient safety perspective, it is important to note that the potentially beneficial anti-inflammatory effect has been found to occur at in vitro theophylline concentrations much lower than the plasma concentrations required for an optimal broncho-dilatator effect. A key study has shown that fibroblast IL-6 and IL-8 release was lowered by 25–30 percent at in vitro theophylline concentrations of 5 mg/L [73]. At such levels (5–10 mg/L) in vivo significant side effects or signs of theophylline toxicity are not usually encountered in clinical practice. Therefore, it is reasonable to advocate the short-term use of theophylline at low doses in an attempt to modulate inflammatory responses when they are extended beyond the beneficial phase after acute pro-inflammatory, typically after episodes of infection, particularly frail and physiologically vulnerable patients, when there are clinical and laboratory indicators of inappropriately prolonged inflammation and if they are not able to participate sufficiently in physical activity. By the same argument, there could be benefit conveyed by the extended use of theophylline to reduce chronic low-amplitude inflammation in an attempt to delay the onset and reduce the severity of long-term complications such as sarcopenia. To improve the evidence base in this therapeutic area there is clearly a need for well-designed research, including clinical trials, to ascertain the possible benefit of theophylline on certain key outcomes, such as mortality, muscle strength and cognition in patients with systemic inflammation of various patterns. In particular, properly conducted studies should be considered that explore the utility of low plasma concentration (5–10 mg/L) oral theophylline, as an adjunctive drug intervention for patients in the aftermath of septic illnesses or trauma to determine whether low-amplitude extended inflammation can be beneficially suppressed in such clinical settings.

10. Examples of other immune-modulating drugs

Though methyl-xanthines have been considered in detail above, drugs in other categories also alter innate inflammation chemistry. However, in many cases the side effects that occur at effective doses reduce their potential to be used as immune modulating agents. Some examples are briefly summarized below but the list is by no means exhaustive.

Monoclonal antibodies (MCAs) now have an established position in the management of inflammatory disorders, with anti-TNF drugs, for example infliximab, being among the most widely applied examples. However, when deployed in an anti-inflammatory role MCAs are usually targeted to specific chemokines or their receptors [74] and thereby have a profound but narrow influence on certain immune functions. At normative doses MCAs also tend excessively to suppress some components of immune surveillance and consequently render patients vulnerable to unusual infections and some malignant neoplasms, particularly after long-term exposure to the drug. MCAs are costly, have to be administered parenterally and must be monitored closely for serious side effects, all of which limit their utility as subtle immune modulators.

Corticosteroids have been used therapeutically for many years as drugs with generalized anti-inflammatory properties that can be exploited in a wide range of clinical conditions. They down-regulate pro-inflammatory immune cell synthetic and migratory activity, including cytokine release, but have a poorly defined influence on the re-establishment of the baseline equilibrium of a surveillance phenotype [75]. The broad immune dampening properties of corticosteroids is likely to

be the mechanism through which they convey, for example, benefit in severe forms of Covid-19 pneumonia [76]. When used systemically, corticosteroids are limited by their mineralocorticoid effects (sodium and water retention), glucocorticoid effects (enhanced protein catabolism and glucose intolerance), tendency to disturb sleep and precipitate delirium, and increase the risk of some infections by lowering cell-mediated immune activity.

Thalidomide and its analogues have been in use for many years as anti-inflammatory drugs for the treatment of mycobacterial diseases, particularly leprosy, and for the reduction of inflammation during chemotherapy for malignant neoplasms. Thalidomide appears to possess complex immune modifying activities including the lowering of pro-inflammatory cell activity and reducing IL-1, IL-6 and TNF release [77,78]. This multi-point traction of the biochemical inflammatory milieu is comparable to that caused by methyl-xanthines. However, thalidomide is constrained by several important adverse effects at the doses normally prescribed, though diamino-diphenyl sulfone, an analogue of thalidomide, is better tolerated and was found to reduce indicators of sarcopenia, a frequent consequence of sustained systemic inflammation, in patients receiving it for the treatment of leprosy [79]. Further research targeted at that drug in a range of inflammatory states is clearly needed.

Chloroquine and analogous 4-aminoquinoline drugs (4AQs) such as hydroxychloroquine and amodiaquine suppress the release of IL-1, IL-6, TNF and IFγ and promote the proliferation of immunologically active cells that produce IL-10 and IL-4 [80]. 4AQs have an established record as anti-inflammatory agents, particularly for the treatment of diseases with an auto-immune etiology, for example rheumatoid disease and systemic lupus erythematosus. The influence of 4AQs at low concentrations on cell behavior and cytokine chemistry has not been systematically researched and at normative treatment doses for inflammatory disorders, which are generally lower than the anti-malarial doses, many recipients experience significant adverse effects. However, 4AQs certainly warrant targeted research to define their potential role in the management of systemic post-infective inflammation [81].

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the clinical manifestations and biochemical indicators of localized and systemic inflammation and there are compelling data from a large credible study indicating that they have a preservative effect on muscle function in older age. The latter is most probably due to reduction of the pro-sarcopenic effect of pro-inflammatory cytokines [82]. NSAIDs are restricted, though not contraindicated, for prolonged courses of treatment by their clinically significant nephrotoxicity, interference with gastric mucosal protection and tendency to increase the risk of thrombosis.

Beta-adrenergic receptor blockers (BBs) modify innate immune biochemical profiles, with a shift toward the anti-inflammatory phenotype. Propranolol has been studied most extensively in this regard but the effect is thought to be a class property of BBs [80]. This effect has largely been found with regard to the biochemical pattern of inflammation characteristic of chronic heart failure and arterial atherosclerosis [80,82]. The mode of action of BBs as anti-inflammatory drugs has not been fully delineated but is probably due to beta adreno-receptor blockade and the consequent fall in catecholamine-induced release of inflammatory chemokines by mononuclear cells. It can be argued that the lower overall mortality observed in patients receiving BBs for cardiac indications could be a consequence, at least in part, to suppression of systemic inflammation.

Statins are now known to reduce systemic inflammation by a mechanism that is apparently independent of, and not dependent upon, the lowering effect on plasma lipids. The observed

reduction in the cellular and chemical manifestations of endothelial inflammation appears to be a result of suppression of a TNF-induced increase in reactive oxygen species in the vascular endothelium, but a non-specific systemic anti-inflammatory effect is also a contributary factor [83]. However, targeted research is lacking on the influence of statins on acute-phase or immediate post-acute inflammation due to stimuli such as sepsis and trauma.

Metformin, and other biguanide drugs, have been shown to have anti-inflammatory properties, probably mediated as a result of a switch toward an anti-inflammatory phenotype by macrophages. No properly conducted intervention clinical trials have been carried out and the main key evidence derives from in vitro studies of endothelial function. However, it can be contended that the apparent improvement in cardiovascular outcomes observed in diabetic patients prescribed metformin are likely to be at least partly due to its anti-inflammatory properties [84,85]. There has been no research on the effect of metformin on acute inflammation or non-diabetic chronic inflammatory states.

11. Conclusions

There is a steadily rising degree of understanding of the relationship between systemic inflammation and the pathogenic pathways leading to of a range of acute and chronic illnesses, particularly when immune cells and cytokines express an inappropriately prolonged or intense pro-inflammatory phenotype. Regular moderate exercise improves a number of adverse consequences associated with inflammation. The most likely reason for this effect is the exercise-induced shift of the immune cellular and biochemical network to a less pro-inflammatory setting. IL-6 appears to have a key function in the modulation of innate immune chemistry toward a less deleterious baseline. Through this mechanism, and probably others, exercise is an important factor in preserving health during recovery from illnesses such as infections and trauma. Because some people are not able to achieve or sustain the work rates or keep up the exercise programs that lead to those benefits there is a need to look for alternative means of dampening dys-immune pro-inflammatory states. For that purpose, there is theoretical, laboratory, observational and some empirical clinical evidence that drugs with immune modulating properties, such as theophylline, could be used to reset innate immune cytokine dynamics, with potential health benefits. Logically, such drugs should also be considered as adjunctive treatments for patients who are able to participate in a therapeutic exercise regimen. Few of the candidate drugs are licensed for use as anti-inflammatory agents so there is a need for properly conducted trials to explore their therapeutic possible therapeutic utility. On reviewing these topics, it is apparent that we currently have an incomplete understanding of the control mechanisms that operate in the innate and adaptive immune systems, and even less knowledge of the interactions between the immune network, exercise and a wide variety of drugs. This is fertile ground for research which should be focused on illuminating the complex molecular biological chemistry of immune system control as well as the potential beneficial use of drugs to reset disordered immune cellular and chemical networks in a clinical context.

Conflict of interest

The author declares no conflict of interest.

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