Does Exercise Attenuate Age- and Disease-Associated Dysfunction in Unconventional T Cells? Shining a Light on Overlooked Cells in Exercise Immunology

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Key Words: exercise training, MAIT cells, NKT cells, gamma delta T cells

Abstract

Unconventional T Cells (UTCs) are a unique population of immune cells that links innate and adaptive immunity. Following activation, UTCs contribute to a host of immunological activities, rapidly responding to microbial and viral infections and playing key roles in tumor suppression. Aging and chronic disease both have been shown to adversely affect UTC numbers and function, with increased inflammation, change in body composition, and physical inactivity potentially contributing to the decline. One possibility to augment circulating UTCs is through increased physical activity. Acute exercise is a potent stimulus leading to the mobilization of immune cells while the benefits of exercise training may include anti-inflammatory effects, reductions in fat mass, and improved fitness. We provide an overview of age-related changes in UTCs, along with chronic diseases that are associated with altered UTC number and function. We summarize how UTCs respond to acute exercise and exercise training and discuss potential mechanisms that may lead to improved frequency and function.

Abbreviations

αGalCer Alpha-galactosylceramide

CD	Crohn's Disease
d	day
γδ T cell	Gamma Delta T cell
GI	gastrointestinal
h	hour
IBD	Inflammatory Bowel Disease
IFNγ	interferon gamma
IL	interleukin
MAIT cell	Mucosal associated invariant T cell
MHC	Major histocompatibility complex
MR1	Major histocompatibility complex class I-related gene protein
NK cell	Natural Killer cell
NKT cell	Natural Killer T cell
OT	Overtrained
PBMC	Peripheral Blood Mononuclear cell
TCR	T cell Receptor
TNFα	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis
UTCs	Unconventional T cells
wk	week

1. Overview of UTCs within Innate and Adaptive Immunity

Unconventional T Cells (UTCs) are a collection of immune cells that bridge innate and adaptive immunity and include Mucosal-Associated Invariant T (MAIT) cells, Natural Killer T (NKT) cells, and Gamma Delta (γδ) T cells. UTCs are multi-functional and recognize antigens and cancerous cells, regulate inflammatory responses, and play a role in allergy and autoimmunity with their development function recently reviewed elsewhere (Pellicci et al. 2020). These cells play key roles in barrier immunology and reside in the mucosa of the lungs and gastrointestinal (GI) tracts (Godfrey et al. 2000; Voillet et al. 2018; Zhao et al. 2018a). Like many cells of the immune system, aging and chronic disease adversely affect UTCs (Godfrey et al. 2015). Systemic inflammation, a hallmark characteristic of many chronic diseases such as diabetes, obesity and cancer, appears to be a modulating factor that decreases UTC frequency and functional capacity (Fay et al., 2016; Kumar & Ahmad, 2018; Marrero et al., 2015). Additionally, chronic inflammation promotes immune cellular infiltration and creates a pro-tumor environment that increases the risk for several different types of cancer (Tan and Coussens 2007). UTCs are unique, with a rapid response relative to conventional T cells while possessing both innate and adaptive immune qualities. UTCs are found in high frequencies within selective tissues and novel applications to utilize these cells within age or diseased populations are emerging (Godfrey et al. 2015).

From an exercise immunology perspective, UTCs are understudied. In contrast, modulation of conventional T cells with acute exercise has been well-established (see Section 3.1). Increased hemodynamic shear stress and catecholamine levels initiate endothelial detachment that leads to cellular mobilization due to adhesion molecules (e.g. CD62L and CD11b) alterations (Shephard 2003). Following exercise, there is a redeployment of T cells with greater effector function migrating to both lymphoid and non-lymphoid tissues (Krüger et al. 2008), potentially leading to a transient lymphopenia that returns to baseline levels within hours unless the bout was particularly long or intense (Peake et al. 2017). Given the paucity of evidence in UTCs, a key objective of this review is to assess the evidence of the effects of acute and regular exercise on these cells, the possible therapeutic role of physical activity of during aging and disease, and to outline future directions for the field.

This review is divided into five sections. First, **i)** an overview of UTCs and their function is provided, followed by **ii)** a summary of the effects of aging and disease. **iii)** As we hypothesize that increasing physical activity may help offset age- and disease-related deficits in UTCs, the effects of acute exercise and exercise training is presented. **iv)** Exercise-induced alterations in pro- and anti-inflammatory cytokines are discussed as possible

mechanisms contributing to improved UTC frequency and function via 1) myokines released with skeletal muscle contraction, 2) reductions in total fat mass and sedentary behavior, or 3) via changes in metabolites and hormones with acute exercise. Finally, **v)** future directions are identified to facilitate further investigation of the role of exercise to improve the UTC profile for aged and diseased populations.

1.1 MAIT Cells

MAIT cells were first described in 1999 (Tilloy et al. 1999) and make up ~1-8% of all T cells in healthy adults (Le Bourhis et al. 2010). In humans, MAIT cells are characterized the invariant T cell antigen receptor (TCR) alpha-chain Vα7.2-Jα33/12/20 (Wakao et al. 2017), high levels of CD161 expression (Howson et al. 2015), and restriction by the major histocompatibility complex class I related (MR1) protein (Tilloy et al. 1999; Le Bourhis et al. 2010). $CD8^+$ MAIT cells are the major (80-90%) subpopulation (Dias et al. 2018), followed by $CD4^-CD8^-$ cell with limited expression of $CD4^+$ (Walker et al. 2012; Reantragoon et al. 2013). MAIT cells are located in the blood and barrier mucosal tissues (Voillet et al. 2018) that includes the lungs (Hinks, 2016), liver (Dusseaux et al., 2011), and GI tract (Treiner et al. 2003). These innate-like lymphocytes combat a wide range of microbial infections via interactions between the invariant TCR and MR1 (Gold et al. 2010; Le Bourhis et al. 2010, 2011). Additionally, MAIT cells can be activated independent of MR-1 via cytokines (Suliman et al. 2019) and viral infections (Hinks et al., 2018; Ussher et al., 2018).

The ability to detect and control bacterial infections is the most well-established MAIT cell function (Le Bourhis et al. 2013; Meierovics et al. 2013; Ussher et al. 2014). However, MAIT cell activation occurs during viral infections suggesting a possible functional role in immunopathology (Cosgrove et al. 2013; van Wilgenburg et al. 2016). Following activation via either TCR-dependent or independent mechanisms (Figure 1), MAIT cells secrete TNFα, IFNγ, IL-17, granzyme B, and perforin (Kurioka et al. 2015; Howson et al. 2015; Bennett et al. 2017). MAIT cells are also stimulated by innate cytokines such as interleukin (IL) 12, 15, 18 and type-I interferon (Hinks and Zhang 2020), leading to the release of pro-inflammatory cytokines and cytotoxic proteins (Ussher et al. 2014). MAIT cells express multiple chemokine receptors (Hanson et al., 2019) that when bound to their ligands direct migration to inflammatory sites of inflammation (Vangelista and Vento 2018) and to accumulate in the mucosal lamina propria and the liver (Hinks, 2016). Certain diseases may cause MAIT cell hyperactivation, which may impede their cytotoxicity and ability to elicit an inflammatory response (Rudak et al. 2018). Current evidence suggests that MAIT

cells recruit other immune cells, exert cytotoxic responses against bacteria and possibly viruses, and secrete pro-inflammatory cytokines that may contribute to systemic inflammation.

1.2 NKT Cells

In the early 1990s, murine NKT cells were first described as T cells in the thymus with low CD3 expression and were positive for the NK cell marker NK1.1, also known as CD161 in humans (Sykes 1990; Arase et al. 1993). NKT cells reside mainly in the liver and can also be found in the lung but make up only ~0.01-0.5% of blood T-cells (Berzins et al. 2005, 2011; Godfrey et al. 2015). Of the different types of NKT cells, human type I invariant NKT cells (iNKT) express the Vα24-Jα18 and Vβ11 semi-invariant TCR and are restricted to only lipid antigens presented by the non-classical MHC-I-like protein CD1d. Because the TCR is restricted to a handful of lipid antigens, CD1d tetramers loaded with αGalCer or an anti-Vα24-Jα18 CDR3 loop clonotypic monoclonal antibody are the gold standard tool for iNKT identification (Berzins et al. 2011; Krovi and Gapin 2018). iNKT cells can be $CD4^-CD8^-$ but typically express CD4, with a small population of $CD8^+$ iNKT cells found only in humans (Montoya et al. 2007). Type II NKT cells (non-classical NKT cells) are more abundant than iNKT cells in humans (Blood: 1% vs. 0.1%), and have a more diverse (but not polyclonal) CD1d restricted TCR repertoire with broader lipid specificities (Rhost et al. 2012). Human Type II NKT cells are mostly $CD4^+$, but can also be $CD8^+$ or double negative (Godfrey et al. 2004). A third population are $CD161^+$ NKT-like cells that are classical MHC restricted rather than CD1d restricted (Godfrey et al. 2004, 2015). Like Type II NKT cells, these cells have diverse TCR α- and β-chains, and are either $CD4^+$, $CD8^+$ or double negative (Godfrey and Berzins 2007). These NKT cells are often defined as $CD3^+CD161^+CD56^+$ (Kronenberg and Gapin 2002). Co-expression of CD3 and CD56 alone to identify NKT cells has also been used (Campbell et al., 2001; Chan et al., 2013; Krijgsman et al., 2019). However, it is clear not all $CD3^+CD56^+$, $CD3^+CD161^+$, or $CD3^+CD161^+CD56^+$ cells are CD1d restricted so these populations are referred to as "NKT-like" cells (Berzins et al. 2011).

A primary role of NKT cells is to modulate the immune response by influencing the functional properties and activation of other cell types against allergens, infectious agents, and tumors (Wu and Van Kaer 2011). A hallmark function of NKT cells is rapid production of Th1 pro-inflammatory and Th2 immune modulatory cytokines upon lipid-CD1d recognition (Arase et al., 1993). Major Th1 cytokines include IFNγ that activate dendritic cells, $CD8^+$ T cells, and NK cells (Terabe and Berzofsky 2008) and is one example of how NKT cells link adaptive and innate immunity. With IFNγ secretion and tumor recognition via CD1d, NKT cells demonstrate direct *in vivo* effects that makes them

strong anti-cancer candidates (Brutkiewicz and Sriram 2002; Krijgsman et al. 2018; Bae et al. 2019). Alpha-galactosylceramide (αGalCer) is the most studied and widely used lipid antigen for activating iNKT cells (Kronenberg and Gapin 2002). When administered therapeutically (e.g. soluble or αGalCer pulsed APCs), iNKT number and function is increased (Nair and Dhodapkar 2017). αGalCer stimulates potent NKT cell actions that are being extensively tested as an immunotherapeutic agent in diseases like cancer (Nair and Dhodapkar 2017), with activated iNKT cells directly killing tumor cells by CD1d-dependent and –independent (e.g. perforin and granzymes) mechanisms (Wolf et al. 2018). When NKT cells are not present, multiple chronic conditions are worsened (Balato et al. 2009), including increased risk of infections, asthma, allergies, atherosclerosis, cancer and graft-versus-host disease (Ambrosino et al. 2007; Berzins et al. 2011).

1.3 γδ T Cells

While most TCR molecules express α and β chains, γδ T cells contain disulfate-linked or nonlinked gamma and delta chains (Kabelitz 1992). First discovered in 1987 (Born et al., 1987), γδ T Cells account for 1–10% of adult human peripheral blood T lymphocytes (Beetz et al. 2008) and are found in two different types. γδ T cells in human peripheral blood mainly express the Vγ9JγPCγ1 chain paired with a Vδ2 chain within the TCR (Lefranc and Rabbitts 1990). Vδ1 (Type-1) cells are found in the thymus and peripheral tissues such as the intestine and lungs and recognize various stress-related antigens (Vantourout and Hayday 2013; Lawand et al. 2017). In general, γδ T cells are ~70% of $CD4^-CD8^-$, with the remaining ~30% being $CD8^+CD4^-$ and very few are $CD4^+CD8^-$ (Garcillan et al. 2015). Similar to MAIT and NKT cells, γδ T cells have both innate and adaptive immune qualities. From an innate perspective, γδ T cells rapidly respond following activation but also possess the TCR and pleiotropic effector functions associated with longer-term immunity (Vantourout and Hayday 2013). With broad antigen recognition and cytotoxic function, γδ T cells contribute to the body's defense against a wide array of pathogens (Lawand et al. 2017).

γδ T cells are a unique subset of T lymphocytes because of their ability to detect lipid antigens, even without the presence of MHC molecules (Heng and Heng 2013; Lawand et al. 2017). This allows them to attack target cells directly via cytotoxic activity, or indirectly via activating other immune cells. γδ T cells have a protective role against both viral and bacterial infections (Latha et al. 2014; Lawand et al. 2017; Zhao et al. 2018a). The functional responses initiates with antigen recognition, which then drives cytokine production and regulates the clearance of pathogens, inflammation, and promotes tissue homeostasis in response to stress (Lawand et al. 2017). When activated (Figure 1), γδ T cells express high levels of IFN*γ,* TNF*α,* and IL-17 and collectively these effector functions allow for participation

in the efferent phase of immune responses (Vantourout and Hayday 2013). The ability of γδ T cells to produce IFN*γ,* TNF*α,* and IL-17 suggests a regulatory role (Beetz et al. 2008) but are also involved in tumor management (Galluzzo et al. 2007). Additionally, activated γδ T cells may regulate the organization of B cells by producing large amount of CXC-chemokine ligand 13 within the lymphoid tissues (Vantourout and Hayday 2013). In humans, γδ T cells contribute to immunity through both their cytotoxic potential and inflammatory phenotype (Lawand et al. 2017), which is consistent with MAIT and NKT cells.

2. UTCs during Aging and Chronic Disease

2.1 Aging

The aging process has a profound impact on the immune system, which in turn has implications for health later in life, typically manifesting as sustained low-grade inflammation, a decreased ability to fight infection, higher incidences of cancer and autoimmunity, and decreased vaccination responsivity (Akha 2018). Overall, UTCs demonstrate consistent age-related declines. Compared to younger individuals, older adults have lower absolute γδ T cells counts in circulation (Argentati et al. 2002; Pistillo et al. 2013). Moreover, the proportion of blood γδ T cells expressing the senescence marker CD57 is increased in individuals greater than 60 years (Bruni et al. 2019). MAIT cell prevalence in peripheral blood peaks between age 30-40 and then declines such that absolute counts and percentages are 10 times lower by age 80 (Novak et al. 2014). Most studies also indicate age-related declines in NKT cells (Mocchegiani and Malavolta 2004; Molling et al. 2005; Chen and Liao 2007) although reports of increased cell number and functions do exist (Faunce et al. 2005). However, some aspects of functional capacity of UTCs may be preserved in older adults. In response to *in vitro* isopentenyl pyrophosphate (IPP) and IL-2 stimulation, γδ T cell cytokine production and cytotoxicity against tumor cells is maintained across the lifespan (Argentati et al. 2002), while MAIT cells from elderly individuals displayed similar upregulation of inflammatory cytokines and cytotoxic proteins following *E. coli* simulation (Loh et al. 2020). Similarly, in very old adults, NKT cytotoxicity and IFNγ production are preserved with IL-12 stimulation (Mocchegiani and Malavolta 2004). While absolute numbers decline with age, the preservation of functional capability in the remaining UTCs suggests they retain importance in the immune response of older adults, with potential benefits being most likely with interventions that boost cell numbers.

2.2. Inflammatory bowel diseases

Crohn's disease (CD) and ulcerative colitis (UC) are the two inflammatory bowel diseases (IBD) that demonstrate alterations in UTCs. CD is characterized as a systemic inflammatory disease that largely effects the GI

tract and is associated with immune disorders (Baumgart and Sandborn 2012). UC is also associated with chronic inflammation but involves only the innermost mucosa of the colon and rectum (Head and Jurenka 2003). There is growing evidence that UTCs are implicated in the pathogenesis of IBD (Catalan-Serra et al., 2018; Giuffrida et al., 2018; Hinks & Zhang, 2020). Blood MAIT cell frequency was reduced several-fold during IBD; however, MAIT cell proliferation was higher in CD and there was greater accumulation of cells within the inflamed ileum (Serriari et al. 2014). Moreover, CD exhibited decreased IFNγ production while UC showed elevated IL-22 production with greater IL-17 levels in both CD and UC. Similarly, γδ T cells localize to areas of inflammation in IBD patients and are a source of IFNγ production in the effected tissue (McVay et al. 1997). Furthermore, declines in blood γδ T cells are associated with negative clinical implications in CD (Catalan-Serra et al. 2018). NKT cells may have dual roles in UC, as iNKT cells demonstrate protective contributions via enhanced cytokine production but type II NKT cells may promote inflammation in the intestines (Giuffrida et al. 2018; Lai et al. 2019). In summary, UTCs appear to migrate towards inflamed tissue, thus reducing circulating levels in IBD patients with greater disease progression, with further research needed to fully understand the implications of UTCs and IBD.

2.3 ***Obesity***

Increased adiposity shifts the immune system toward a pro-inflammatory phenotype (Saltiel and Olefsky 2017). Blood UTCs are reduced with obesity and negatively correlate with the severity of adiposity (Apostolopoulos et al., 2016; Carolan et al., 2015; Costanzo et al., 2015; Magalhaes, Pingris, et al., 2015; Touch et al., 2017). Obese individuals have more differentiated γδ T cells with a reduced ability to produce IFNγ and IL-2 that lowers anti-viral capacity (Costanzo et al. 2015). Obesity also attenuates NKT and MAIT cell cytokine production, especially IFNγ (Lynch et al. 2012; Carolan et al. 2015; Magalhaes et al. 2015b; Apostolopoulos et al. 2016). Weight loss (through diet or bariatric surgery) partially rescues both cell counts and cytokine productions (Magalhaes et al. 2015b). As exercise training also influences body composition, increased physical activity either alone or in conjunction with dietary changes is another avenue by which UTCs may be targeted to potentially improve cell number and function.

2.4 Diabetes

Type I and type II diabetes are involved in autoimmunity and inflammation, respectively, especially the relationship between the gut microbiota, intestinal epithelial cells, and the mucosal immune system (Moffa et al. 2019). Similar to obesity, both types of diabetes are associated with decreased iNKT and MAIT cell frequency and function (Magalhaes et al., 2015b) but it is unclear if this is due to nutritional variation or from disease progression (Touch et

al. 2017). UTCs may play a regulatory role in metabolism (Magalhaes et al. 2015a; Touch et al. 2017), suggesting that MAIT and NKT cells may have protective roles against type II diabetes but the potential mechanism is unclear (Magalhaes et al. 2015b; Xia et al. 2017). γδ T cell proportions and counts are elevated in the peripheral blood of individuals at high risk for type I diabetes (elevated islet cell antibody titers) and may be predictive of disease progression (Lang et al. 1993). Additionally, low absolute γδ T cell counts were associated with a diminished insulin response to an intravenous glucose tolerance test. As Type II diabetes and obesity are often intertwined, it is presently unclear which factor(s) are driving the relationships within UTCs.

2.5 Asthma

Asthma is characterized as a chronic inflammatory disease affecting the airway (Lambrecht et al. 2019). A recent review on NKT cells, MAIT cells, and asthma highlighted many mechanistic questions, such as age (NKT and MAIT cells are not fully mature in children when asthma first develops) and the pathophysiology of UTCs and asthma remain unclear (Lezmi and Leite-de-Moraes 2018). Blood iNKT cell frequency appears similar between individuals with asthma and healthy controls (Koh and Shim 2010) and there is no relationship between asthma and IL-4 or IFNγ production (Chandra et al. 2018). iNKT cell frequency from bronchial tissues or bronchoalveolar-lavage fluid (BALF) produced inconsistent results (Iwamura and Nakayama 2018). In contrast, both circulating and sputum MAIT cells and circulating γδ T cell frequency are reduced in adults with asthma compared to controls (Hinks et al., 2015; Krejsek et al., 1998), with the MAIT cell reductions being associated with disease severity (Lezmi and Leite-de-Moraes 2018). However, the clinical significance of γδ T cell changes has been questioned recently given the complex role these cells may play in asthma and further research is needed to substantiate any association with aging (Victor et al., 2020). Because asthma is typically diagnosed during childhood when the functional capabilities of UTCs are likely still developing, evidence from individuals across the lifespan is needed to better understand if detriments in UTC function and number are linked to disease implications or from age of the population studied.

2.6 Cancer

Anti-cancer therapies such as chemotherapy and radiation elicit profound damage to the immune system, including the depletion of lymphocyte populations (Kaur and Asea 2012; Bracci et al. 2014). UTCs have been proposed as promising targets for immunotherapy (Godfrey et al. 2018), with NKT cells inhibiting tumor growth in murine models (McEwen-Smith et al. 2015; Nair and Dhodapkar 2017). Peripheral blood NKT cell numbers are reduced in human cancers, including breast (Molling et al. 2005) and lung cancer (Motohashi et al. 2002). NKT cell

functions, such as stimulated IFNγ production, is unaffected by tumor load (Molling et al. 2005) while increased tumor infiltrating NKT cells offers favorable prognosis (Tachibana et al. 2005; Bricard et al. 2009). Because MAIT cells share many qualities (e.g. cytotoxicity, cytokine production) with NKT cells, this raises the possibility of an anti-tumor role (Peterfalvi et al. 2008). Indeed, circulating MAIT cells are reduced in mucosal associated cancers that includes lung, colon, gastric tumors but cytokine producing abilities were preserved with an elevated presence within cancerous tissue (Ling et al. 2016; Won et al. 2016). Interestingly, UTCs may exhibit a differential response to chemotherapy, with MAIT cells proportions remaining constant during breast cancer (Dusseaux et al., 2011) while γδ T cells counts decrease with advanced colorectal cancer (Bruni et al. 2019). γδ T cells have been linked to cancer due to an ability to produce IFNγ early on in tumor immunosurveillance, with γδ T cell deficient mice demonstrating higher tumor loads (Gao et al., 2003). Recent reviews on UTCs and immunotherapy for cancer report that γδ T cells promote tumor rejection via IFN-γ and TNFα secretion, direct cytotoxic effects, and activation of additional components of the immune system (Godfrey et al., 2018; Zhao et al., 2018), making them good candidates for clinical trials. Furthermore, many UTCs reside in non-lymphoid tissue that allows tumors in these specific areas to be targeted by potential immunotherapies (Godfrey et al. 2018). However, subsets of γδ T cells contribute to progression in certain cancer types via greater angiogenesis, metastasis, and immune escape (Zhao et al., 2018). While UTCs have clear potential to assist with cancer management, further investigations are needed to understand their full potential for use in immunotherapy and to further explore how tumors and treatments affect cytotoxic function.

2.7 Summary

Considering the impact of aging and chronic disease, decreased blood UTC cell count emerges as a common thread. Additionally, obesity, low-grade inflammation and inactivity present as key components in disease-related detriments on UTC function (Figure 2). Consequently, therapies that activate the immune system and reduce chronic inflammation and adiposity would likely be beneficial for UTCs. As exercise frequently has demonstrated these effects, we hypothesize that regular physical activity may attenuate or even reverse some disease-related detriments in UTCs. In the next section, the effects of acute and regular exercise on MAIT, NKT, and γδ T cells are presented to begin evaluating our hypothesis as to whether physical activity has the potential to prevent declines in UTC cell counts and function.

3.UTCs and Exercise

The effects of acute and chronic exercise on UTC number and function are presented in the next section. Antigen recognition, regulation of inflammation, and barrier immunity all fall within the domain of UTCs (Pellicci et al. 2020). As these aspects are enhanced following exercise, it raises the possibility that UTCs may contribute to the improved immune function with regular physical activity. Because of a relative low number of studies for some UTC subsets, the use of acute psychological stress is included when available to provide additional context. Acute exercise was defined as a single exercise session with blood samples collected (at minimum) at baseline (rest) and then immediately following exercise. Exercise training refers to studies where blood samples were obtained before and after the exercise intervention.

3.1 Conventional T Cells

To help contextualize the UTC response to exercise, a brief overview of conventional T cells is provided. Following acute exercise, robust mobilization of conventional T cells occurs that is influenced by duration and intensity (Gabriel et al. 1992; Nieman et al. 1994; Bishop et al. 2014) and also cell type ($CD3^+CD8^+$ > $CD3^+CD4^+$) (Campbell et al. 2009). Conventional T cell counts exhibit a biphasic response, with mobilization increasing circulating cell frequency immediately following exercise with levels falling below baseline in the initial hours following recovery (Hansen et al. 1991; Gleeson and Bishop 2005; Simpson et al. 2008). This "open window" no longer represents exercise-induced immunosuppression (Campbell & Turner, 2018), rather an egress of cells into lymphoid and non-lymphoid tissues that is partially dependent on activation status (Westermann et al. 2001). Additionally, conventional T cells demonstrate a more mature effector phenotype (e.g., $CD57^+$ or $KLRG1^+$ cells) with acute exercise that is partially age-dependent (Simpson et al. 2008) along with decreased proliferation and IFNγ production (Shaw et al. 2018). Exercise training may also have beneficial effects on T cells, with cross-sectional studies reporting trained individuals have higher naïve vs. senescent T cell ratios, T cell proliferation, and IL-2, IL-4 and IFNγ levels compared to untrained (Nieman and Wentz 2019; Bartlett and Duggal 2020). Interestingly, longitudinal investigations (range 12 wk to 12 months) did not consistently support these findings, although exercise training within more "at risk" populations (e.g., obese, cancer survivors) may show greater T cell benefits (Simpson et al. 2012).

3.2 MAIT cells

MAIT cells and exercise is an emerging topic. However, MAIT cell publications have increased exponentially in the past 5 years. With the association between MAIT cell deficiencies and chronic conditions, this is an area ripe for future investigations. Exercise as a low cost, scalable option that has multiple physiological benefits that may extend to MAIT cells. The establishment of exercise efficacy would open up additional therapies to offset the side effects of low MAIT cell counts.

3.2.1 Acute Exercise

The effects of acute exercise in MAIT cells are summarized in Table 1. MAIT cell mobilization was initially investigated in recreationally active young men following a maximal effort graded exercise test on a cycle ergometer (Hanson et al., 2017). Maximal aerobic exercise increased MAIT cell counts by 2.2-fold immediately after acute exercise. There was also a 0.8% increase in MAIT cell frequency, indicating that MAIT cells are preferentially mobilized within the T cell populations. In a follow up study also using healthy young men, 40 min of sub-maximal aerobic exercise increased MAIT cell counts increased by 92% and cell frequency by 1.0% relative to total T cells (Hanson et al., 2019). One hour after exercise, counts returned to baseline while cell frequency remained elevated. Similar patterns were observed within $CD8^+$ and $CD4^-CD8^-$ MAIT cell subpopulations. Acute exercise increased the proportion of MAIT cells expressing TNFα, suggesting greater MAIT cell sensitivity to PMA and ionomycin stimulation. Neither IFNγ or chemokine (homing marker) expression changed with acute exercise and IL-17 expression was minimal, likely due to participants with normal body mass being used compared to obese individuals (Carolan et al. 2015; Magalhaes et al. 2015a). Ultimately, MAIT cell counts appear to show a dose response to exercise intensity in young men, which is consistent with conventional T cells (Scanzano and Cosentino 2015). As MAIT cells express β_2 adrenergic receptors (Fergusson et al. 2014), this response may be modulated by increasing levels of catecholamines as observed in other immune cells (Ortega et al. 2007; Scanzano and Cosentino 2015) but still needs to be confirmed.

To our knowledge, there are no published MAIT cell and exercise data in women. However, our laboratory recently examined the effects of acute aerobic and resistance exercise in older women. Compared to a lean, non-exercising reference group (n=8), overweight women (n=8) had 2-fold and 4.7 fold lower resting lymphocyte and MAIT cell counts, respectively (Bates et al. 2020 (abstract)). The lower MAIT cell count is consistent with previous reports (Carolan et al. 2015; Magalhaes et al. 2015b). Moreover, overweight women (vs. lean reference group) also

had 20% lower resting MAIT cell TNFα expression following PMA and ionomycin stimulation that suggests impaired function. Immediately following 25 minutes of walking at 70-80% heart rate reserve and performing 2 sets of 8 different resistance training exercises, lymphocyte counts increased by 63% while MAIT cell counts were unchanged. The lack of a MAIT cell response to acute exercise contrasts existing literature in healthy young male populations (Hanson et al., 2017, 2019) and is somewhat surprising given that acute exercise induced a lymphocyte response. Possible reasons for the lack of MAIT cell change are greater levels of adiposity or lower fitness levels, along with age and sex differences that may have confounded the response and need to be investigated.

3.2.2 Exercise Training

There is a lack of published exercise training studies in MAIT cells, although several recent unpublished works have been identified. Although 12 wk of aerobic training did not change circulating MAIT cell frequency, intrahepatic frequency was reduced and CD95 expression was increased during non-alcoholic fatty liver disease (Naimimohasses et al. 2019 (abstract)). Further investigations are required to determine the significance of these findings. Our group recently examined the acute exercise response before and after 16 wk of combined exercise training in 13 breast cancer survivors compared to 13 age-matched healthy controls (Bates 2020 (thesis)). Prior to exercise training, acute exercise increased MAIT cell counts in controls (137%) to a greater extent than in breast cancer survivors (46%), with preferential mobilization of MAIT cell frequency in controls only, but no change in cytokine production. Following training, breast cancer survivors now demonstrated nearly 2-fold increases in MAIT cell counts with acute exercise that approached levels in controls. These initial data are promising and suggest exercise training partially rescues the attenuated MAIT cell numbers following breast cancer treatment.

3.3 *NKT cells*

We are unaware of any human exercise studies that have specifically identified (e.g. Vα24*i* or CD161 expression) NKT cells. Instead, numerous studies use combinations of CD3, CD16, and CD56 that do not reflect the true NKT cell population (Berzins et al. 2011). As such, the effects of acute and chronic exercise on these NKT-like cells are presented, along with the phenotype of each populations. However, as the absence of NKT cells affects disease progression (Balato et al. 2009), an understanding if exercise also influences these cells and how mobilization compares to previous NKT-like cells would fill an important gap in the current literature.

3.3.1 Acute Exercise

NKT-like cells are responsive to short bouts of acute exercise in healthy young men and women (Table 2). In young healthy women, a 30 min treadmill run increased circulating $CD3^+CD56^+$ NKT-like cell numbers by 3-4 fold, before returning to pre-exercise levels one-hour later (Zelazowska et al. 1997). In young healthy men, 60 min of treadmill running elicited a similar response for $CD3^+CD56^+$ NKT-like cells (Pizza et al. 1995). Vigorous cycling for 84 min increased $CD3^+CD16^+CD56^+$ NKT-like cells by 84% (Gabriel et al. 1992) while 60 min of cycling elicited 2-3 fold increases in $CD3^+CD56^+$ NKT-like cells in young men (Timmons et al. 2004). Carbohydrate ingestion prior to cycling attenuated the $CD3^+CD56^+$ NKT-like cell increase immediately post exercise in these men; suggesting that metabolic stress plays a role in NKT-like cell mobilization that is analogous to NK cells (Wentz et al. 2018).

Similar to other effector immune cells, NKT-like cells respond differently to additional physiological stressors. Supine cycling to exhaustion in hypoxia (14% O_2) resulted in a larger $CD3^+CD16^+CD56^+$ NKT-like cell egress than normoxia (21% O_2) during 60 min of recovery (Gabriel et al. 1993). This effect was not influenced by differences between hypoxia and normoxia for cell mobilization during exercise, or catecholamine responses. In fact, NKT-like cells may be less responsive to catecholamines than NK cells, and thus preferentially respond to alternative exercise responses (Søndergaard et al. 1999). For example, muscle damage from downhill running induces greater mobilization of $CD3^+CD56^+$ NKT-like cells into the blood compared to a level gradient (Pizza et al. 1995). Elevated NKT-like cell number (as well as NK cells, $CD8^+$, and $CD4^+$ T cells) in the blood following damage-inducing exercise is suggestive of a rapid stress/damage immune response requiring specialized effector cells (Pizza et al. 1995). This is consistent with the involvement of NKT cells, specifically iNKT cells, in sterile inflammation responses such as tissue injury (Ferhat et al. 2018). Damage associated molecular patterns and alarmins (e.g., IL-33) are released from injured cells and rapidly activate iNKT cells to produce IL-17 and IFNγ, which in turn recruit neutrophils to the damaged tissue. Depending on the severity of damage, NKT cells will sequester in the tissue and be part of a coordinated regeneration process (Ferhat et al. 2018). This would explain the NKT-like and neutrophil responses during downhill running (Pizza et al. 1995), as well as the prolonged 30-70% reduction of blood NKT-like cells following a 100km ultramarathon race where severe sterile tissue damage is common (Gabriel et al., 1994). Exhaustive cycling at 10% above lactate threshold increased $CD3^+CD16^+CD56^+$ NKT cells 2-3 fold in 15 young athletes (Gabriel et al., 1998). Interestingly, when comparing the immune response to acute exercise at different periods of a training regimen, NKT-like cells were higher when athletes were overtrained (OT). The magnitude of mobilization and egress

in NKT-like cell counts were similar, but greater absolute cell numbers during OT suggesting that this may be a stimulus to increase NKT-like cell production (Gabriel et al., 1998). As no comparison were made between non-OT and OT athletes at the same point of the training program, it is difficult to determine if increased NKT-like cells in OT are because of exercise training or the exercise volume leading to OT.

3.3.2 Exercise Training

In breast cancer survivors, 12 wk of walking during chemotherapy (Kim et al. 2015) or 16 wk of resistance training following treatment (Hagstrom et al. 2016) had no effect on the frequency of $CD3^{+}CD56^{+}$ NKT-like cells. Neither study converted frequency into absolute cell number and only resistance training reduced TNFα expression after overnight mitogen stimulation (Hagstrom et al. 2016). There were no additional effects on NKT-like cell measures (e.g., IFNγ production), and serum TNFα concentrations were low and unchanged, making it difficult to determine the importance of this finding. Following 6 months of Tai Chi in healthy, middle-aged to older women, the frequency of NKT-like cell frequency increased by ~3% and the production of IFNγ and IL-4 from $CD3^{+}CD4^{+}$ lymphocytes (of which some are NKT cells) also increased (Liu 2012). In non-small cell lung cancer survivors, 16 wk of Tai Chi was associated with $CD3^{+}CD16^{+}CD56^{+}$ NKT-like cell frequency maintenance (0.2% increase) while controls decreased by 1.0% that resulted in a group difference (Liu et al. 2015). These results suggest that Tai Chi in healthy women improves function and may prevent declines during lung cancer.

No studies that we are aware of have assessed NKT-like cells following exercise interventions that improve health parameters (e.g., cardiorespiratory fitness or cardiometabolic health) in young adults. Following 1 month of intensive volleyball training, $CD3^{+}CD16^{neg}CD56^{+}$ cells (rather than NKT-like $CD3^{+}CD16^{+}CD56^{+}$) increased from baseline by ~75% after training and remained ~50% elevated after 1 wk (Suzui et al. 2004) and is consistent with acute exercise performed during OT (Gabriel et al., 1998). This cellular shift is most similar to that of $CD56^{bright}$ NK cells, a population typically defined as $CD16^{dim/negative}$ that produces greater amounts of cytokines and has lower cytolytic function compared to $CD56^{dim}$ NK cells (Poli et al. 2009). Interestingly, intensive volleyball training was associated with impaired NK cytolytic activity (Suzui et al. 2004), which is consistent with a redistribution of NK and NKT cell subsets that are less cytotoxic, although cytotoxicity on a per cell basis was not determined. As none of the athletes reported illness (Gabriel et al., 1998; Suzui et al., 2004), it may be that increased NKT cell frequency is a consequence of intensive exercise training rather than overtraining per se.

Alternatively, looking at 60d of bed rest to mimic space flight or inactivity, immune-endocrine parameters were assessed with or without resistance exercises or vibration exercises (Hoff et al. 2015). When the control group and two exercise groups were combined, there was ~60% more $CD3^+CD56^+$ NKT-like cells at the end of the study. Although exercise appeared to reduce total lymphocyte numbers, no group differences were reported for NKT-like cells, making it difficult to ascertain why cell counts increased during bed rest.

Taken together, both acute and chronic exercise training have the ability to modify NKT-like cell counts and frequency. However, there may be differential responses depending on the age, disease state, and the phenotype of the NKT-like cells, which limits comparisons.

3.4 γδ *cells*

3.4.1 Acute Exercise

Numerous studies have investigated the effects of acute exercise on γδ T cells in humans (Table 3). Long duration cycling in men evoked an ~3-fold increase in blood γδ T cell counts immediately after exercise but were nearly undetectable following 2h of recovery (Krzywkowski et al. 2001), presumably due to the exercise-induced redistribution of leukocytes to peripheral tissues (Kruger and Mooren 2007). It was strongly indicated that β-adrenergic stimulation prompts γδ T cell mobilization into circulation (Anane et al. 2009). The infusion of the β-agonist isoproterenol caused circulating γδ T cell counts to increase by >2.5 fold, and this mobilization was dose-dependent and emulated the exercise (>200%) response while exceeding acute psychological stress (53%). Akin to long duration acute exercise (Krzywkowski et al. 2001), γδ T cell sensitivity to high intensity exercise – as well as during acute psychological stress and isoproterenol infusion – was relatively greater than αβ T cells (Anane et al. 2009). The mobilization and egress of γδ T cells appears to mirror that of $CD16^+CD56^{dim}$ NK cells, which have high β-adrenergic receptor expression (Benschop et al. 1994) and are profoundly exercise-sensitive (Campbell et al., 2009), albeit to a slightly lesser extent (Krzywkowski et al. 2001; Anane et al. 2009). In a follow-on study, the phenotypic analysis of γδ T cells was extended to understand the effects of β-adrenergic stimulation on distinct γδ T cells, including memory phenotypes (naïve, central memory, effector memory, and $CD45RA^+$ effector memory) within δ1 and δ2 γδ T cell population (Anane et al. 2010). Acute psychological stress mobilized δ1 and δ2 T cells to a similar extent during and analogous to the mobilization patterns of αβ T cells observed in other studies (Campbell et al., 2009), although γδ T cells with a highly differentiated phenotype and high cytotoxic potential were preferentially mobilized (Anane et al. 2010). Examining adhesion molecules, it was apparent that γδ T cells with low CD62L and

high CD11a expression were preferentially mobilized. In addition, these preferentially mobilized γδ T cells expressed CD94 (NKG2), which is an innate receptor also expressed by NK cells, showing that the γδ T cells mobilized to tissues may play a role in cytotoxic or regulatory responses against aberrant MHC, such as those expressed by cancer or virally infected cells (Anane et al. 2010).

More recent studies have explored the effects of age and latent virus seropositivity on γδ T cell mobilization during exercise, with the intended purpose of evaluating how immunosenescence impacts γδ T cell mobilization. Healthy older adults (age 50-64 y) had fewer γδ T cells than healthy younger adults (age 23-35y) and 30 minutes of cycling evoked only a marginal increase in γδ T cell frequency in the peripheral blood of the older adults (~35%), yet a larger, archetypal increase (~120%) was observed in younger adults (Pistillo et al. 2013). Among older adults, CMV serostatus did not appear to be associated with γδ T cell sensitivity to exercise; however, a positive CMV serostatus resulted in greater γδ T cell responsivity in younger adults. One hour after exercise cessation, γδ T cells exhibited greater cytopenia in younger adults, perhaps reflecting a greater redeployment of γδ T cells for immunosurveillance in these individuals. The temporal egress of γδ T cells during the recovery from vigorous exercise has been studied in young healthy adults (Rooney et al. 2018). γδ T cell frequency in the blood was reduced by >25% after only a few minutes, somewhat mirroring heart rate reductions and likely corresponds with a rapid decline in adrenaline post-exercise, that was similar to other T cells but less than NK cells. Lastly, acute exercise led to ~3-fold increases in circulating γδ T cells following vigorous exercise in trained cyclists (Baker et al. 2020). Following *ex vivo* expansion of the δ2 subset using zoledronic acid and IL-2, exercise enhanced NKG2 receptor expression and cytotoxicity against several different tumor cell lines. In a subset of participants, mobilization was abrogated using the non-selective β_1 / β_2 antagonist nadolol but not the β_1 antagonist bisoprolol, indicating γδ T mobilization with exercise largely occurs via a β_2 adrenergic receptor activity. The ability of exercise to increase cellular expansion potentially improves the therapeutic potential of these cells, which is currently limited by the low frequency in circulation.

The effects of sleep on immune cell kinetics has become of interest to researchers in exercise immunology, due in part to a desire to understand the dysregulating effects of sleep and circadian rhythm disruption on immunity (Besedovsky et al. 2012) interact with the exercise-stress response. In young men performing vigorous cycling, there was a tendency for γδ T cell mobilization to be more pronounced following a night of sleep disruption vs. undisturbed sleep (Ingram et al. 2015). Disturbed sleep may upregulate the stress hormone response to exercise, and therefore appears to prime immune cell mobilization in a conserved evolutionary response.

3.4.2 Exercise Training

To the authors' knowledge, there are no human studies that investigated the effects of regular exercise on γδ T cells and only two rodent studies (Lee et al. 2019; Estruel-Amades et al. 2019). The lack of literature using exercise training to potentially alter γδ T cells (along with MAIT and clearly defined NKT cell populations) counts or frequency represents an important gap in the exercise immunology literature that would benefit from additional work.

3.5 Animal Models of UTCs and Exercise

While animal models of exercise in UTCs is beyond the scope of the current review, a brief summary of the existing literature is provided. We are presently unaware of acute or regular exercise in MAIT cells. However, four studies exist using murine models that examine NKT and γδ T cells, with three of them using intensive or OT protocols. Treadmill training did not change NKT cell frequency at 36h after the last session but exercise but there was a 1.5% decrease one week after training that was mostly prevented using αGalCer treatment (Ru and Chen 2009; Ru and Peijie 2009). Short-term (2 wk) treadmill training altered neither NKT cells or γδ T cells, whereby longer training (5 wk) decreased NKT frequency by 25% that was exacerbated when preceded by exhaustive acute exercise (Estruel-Amades et al. 2019) that had minimal effects on γδ T cells. Finally, compared to body temperature water, swimming in thermoneutral water resulted in 1.5-fold and 2.5 fold higher γδ T cells and NKT cell counts, respectively (Lee et al. 2019). In alignment with other exercise and tumor models used in rodents (Pedersen et al., 2016), swimming elicited reduced tumor volume and mass but only in thermoneutral water with a lack of cold stress being hypothesized to be responsible for the differences.

4. Exercise Training: A Potential Stimulus for UTCs?

Decreased UTC numbers present with aging, asthma, diabetes, cancer, and autoimmune disorders have several common links, including inflammation, excess body fat, and reduced physical activity. Sustained low-grade elevations in pro-inflammatory cytokines (e.g. IL-6, TNFα, IFNγ) are observed in aging (Brüünsgaard and Pedersen 2003), chronic disease (Head and Jurenka 2003; Lambrecht et al. 2019; Moffa et al. 2019) and faster tumor progression (Koelwyn et al. 2015) but differs from the large, transient changes seen with acute exercise (Pedersen & Febbraio, 2012). Obesity is associated with many chronic diseases and contributes to inflammation via cytokine production from activated UTCs within adipose tissues (Carolan et al. 2015; Magalhaes et al. 2015b), while sedentary behavior is one factor leading to increased adiposity (Whitaker et al. 2017).

Lifelong exposure to physical activity has well-established immunoregulatory effects (Duggal et al., 2019; Duggal et al., 2018) in both circulation and skeletal muscle that appears to confer benefits in men (Lavin et al. 2020a) more than women (Lavin et al. 2020b). There are several potential mechanisms by which regular exercise may influence UTCs (Figure 3). Exercise training reduces sympathetic nervous system activity (Mueller 2007) and increases vagal tone (Gourine and Ackland 2019) while also attenuating immune cell pro-inflammatory cytokine production (Tracey 2009) seen with aging (Woods et al. 2012), cancer (Khosravi et al. 2019), and a murine model of asthma (Vieira et al. 2014). Additionally exercise induces anti-inflammatory effects via the release of myokines such as IL-6 and IL-10 from contracting muscle fibers as well as catecholamine secretion with vigorous exercise that collectively inhibit pro-inflammatory cytokine production (Gleeson et al. 2011; Woods et al. 2012). However, chronic stress that promotes sympathetic nervous system and hypothalamic-pituitary-adrenal axis activity impairs innate and adaptive immune functions (Godbout and Glaser 2006), which likely includes UTCs. For example, MAIT cells from breast cancer survivors have reduced IFNγ expression (Bates et al., 2020) that is also observed with obesity (Carolan et al. 2015) and suggests potential cellular exhaustion (Rudak et al. 2018). Attenuated rises in epinephrine from acute exercise during breast and prostate cancer treatment (Evans et al. 2016; Hanson et al. 2018) support altered stress-induced immune dysregulation (Godbout and Glaser 2006). Reduced exercise-induced catecholamine rises may alter UTC mobilization, such as attenuated MAIT cell mobilization in breast cancer survivors that resolves following training (Bates et al. 2020). Psychosocial interventions (including exercise training) showed improvements in cytokine levels and NK and T cell frequencies and function but results were inconsistent and did not include UTCs (Subnis et al. 2014).

Additionally, increased physical activity disrupts sedentary behavior that is associated with diabetes and cancer (Gleeson et al. 2011) and improves glycemic control, insulin sensitivity, and the tumor microenvironment (Koelwyn et al. 2015; Dethlefsen et al. 2017; Hojman et al. 2018). While we are unaware of any direct effects on UTCs, these changes are likely to improve overall well-being, which includes the immune system and mental health. For example, while homing marker frequency remains constant after acute exercise (Hanson et al., 2019), overall circulating UTC levels are higher. This combination may increase the absolute number of cells that migrate to the lungs and GI tract to help alleviate the elevated pathogen exposure from increased ventilation and food and fluid intake during exercise. Exercise training also improves body composition during chronic disease (Hanson et al., 2016; Kujala, 2009; Mcleod et al., 2019), particularly when combined with nutritional interventions (Fiatarone Singh 2002;

Rozentryt et al. 2010). The loss of adipose tissue, visceral fat in particular, reduces immune cell infiltration and adipokine secretion (Gleeson et al. 2011), with bariatric surgery partially restoring MAIT cell number and function (Magalhaes et al. 2015b). Furthermore, myokines (e.g. IL-6, IL-15) released during skeletal muscle contraction inhibit TNFα production and stimulate the release of anti-inflammatory IL-1ra and IL-10 into circulation (Petersen and Pedersen 2005; Gleeson et al. 2011). IL-15 also has direct effects on UTCs, including activation of MAIT cells (Hinks and Zhang 2020), iNKT maturation and regulation (Gordy et al. 2011), and increased γδ T cells proliferation and cytotoxicity (Van Acker et al. 2016). Interestingly, plasma IL-15 levels following 1h of cycling are higher in obese individuals (Pierce et al. 2015), providing support that exercise could improve UTC function.

Lower circulating UTC levels during many chronic conditions is likely multi-factorial, but we postulate that increased egress into the diseased tissues provides a likely explanation. Exercise training may play a role in re-establishing homeostatic balance through mobilization of UTCs while also reducing the adverse effects of inflammation, sedentary behavior, and excess body fat on these cells. Presently, definitive evidence is lacking as much of the acute and regular exercise involving UTCs utilizes healthy individuals. Moreover, beyond greater cytokine frequency in MAIT cells (Hanson et al., 2019), the functional benefits have yet to be determined. However, with the expansion of exercise immunology into new diseases and cellular populations, the inclusion of UTCs will help fill in these gaps and to provide the direct evidence needed to determine the efficacy of exercise to improve UTC number and function.

5. Implications and Future Directions

UTCs contribute to immunity in multiple ways, with MAIT, NKT, and γδ T cells all being capable of cytotoxic potential and cytokine secretion (e.g., TNFα, IFNγ, and IL-17) that is potentially problematic in an aberrant inflammatory phenotype. Moreover, UTCs target a wide range of infections and contribute to tumor suppression, providing a broad degree of protection while also bridging the gap between innate and adaptive immunity. With aging, UTC frequency is lower but function may be maintained while chronic diseases adversely affects both UTC numbers and function. Greater adiposity, inflammation and sedentary behavior appear as a link between the UTCs, aging and disease.

Exercise may provide beneficial effects in rescuing UTC number and frequency. UTCs demonstrate robust changes with acute exercise in healthy individuals, with mobilization that is analogous to conventional T cell populations, with evidence that γδ T cells (but not likely MAIT or NKT cells) respond in a catecholamine-dependent

manner. Moreover, NKT cells increase during heavy training periods or with acute tissue damage, suggesting that these cells could serve as a marker of OT or injury. However, the effects of exercise in clinical populations and whether functional improvements occur both remain unknown and loom as key next steps. Regarding exercise training, evidence supporting beneficial effects are strongest in NKT-like cells, although age and disease-state may modulate this response and specific (iNKT vs. type II) cell type has yet to be assessed. Emerging work from our group provides preliminary evidence that MAIT cell mobilization may be rescued in breast cancer survivors after training. Exercise training and γδ T cells are restricted to animal work, with a clear need to examine these cells in humans. Although not central to this review, exercise and diet are often intertwined and nutritional considerations are relevant in future UTC investigations. MAIT and γδ T cells within the GI tract are influenced by the gut microbiota (Lin et al. 2020). Caloric deficiency decreases immunity and has the most prominent effects in older, clinical populations with poorer nutritional habits (Walsh 2019) and may even coincide with some populations (e.g. IBD, diabetes) who have low UTC numbers (Catalan-Serra et al. 2018; Giuffrida et al. 2018; Moffa et al. 2019; Hinks and Zhang 2020). Exercise training augments the gut microbiota [reviewed elsewhere (Monda et al. 2017)], with body composition and exercise mode influencing the training response (Nieman and Pence 2020). Additionally, advances in "multi-omics" technology are unlocking new opportunities for exercise immunology that may help contribute to the mechanisms responsible for these improvements.

In summary, there is a clear need to assess the efficacy of exercise-induced mobilization as a potential low risk, high reward means of alleviating UTC deficiencies or to expand these cells for allogenic stem cell transplant or immune therapies. The inclusion of UTCs in exercise studies, particularly within populations with low UTC frequency, is required to assess the effects of and to determine if disease burden and quality of life can be improved.

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Tables

Table 1. Summary of acute exercise and exercise training on mucosal associated invariant T (MAIT) cells.

Population	N	Age (y)	% F	Exercise	Outcomes	Reference
Acute						
Healthy YM	20	28 (5)	0	Graded exercise test	Cell # ↑ 116% and cell freq ↑ 0.8% at 0h.	Hanson 2017
Healthy YM	20	22 (4)	0	40 min at 86% of V_T	Cell # ↑ 92% and freq ↑ 1.0% at 0h. TNFα freq ↑ by 8% at 0h but IFNɣ and IL-17 ↔.	Hanson 2019
Training						
NAFLD	16	58 (range: 20-71)	56	AE 5d / wk for 12 wk	Intrahepatic cell freq % ↓ post-training; Circulating & intrahepatic CD95 MFI ↑ post-training.	Naimimohassess 2019

Data are mean (SD). #, cell counts; freq, cell frequency; ↑, increase; ↓, decrease; ↔, no change; YM, young men; V_T, ventilatory threshold; TNFα, tumor necrosis factor alpha; IFNɣ, interferon gamma; IL-17, interleukin 17; NAFLD = nonalcoholic fatty liver disease; AE, aerobic exercise; MFI, mean fluorescent intensity; d, day; wk, week;

Table 2. Summary of acute exercise and exercise training on natural killer T (NKT) cells.

Population	N	Age (y)	% F	Exercise	Outcomes	Reference
Acute						
Healthy Subjects	14	28 (4)	NR	100% of A_T to exhaustion	Cell # ↑ by 84% in first 10 min of exercise, remained ↑, then reduced to resting levels	‡ Gabriel 1992
Sedentary	10	28 (4)	NR	GXT in normoxia vs. hypoxia	2-fold ↑ in cell # at 0h (both conditions). At 1h only hypoxia caused a 50% ↓ below resting levels	‡ Gabriel 1993
Athletes	9	Range: 36-68	22	100km ultra-marathon	Cell # ↑ by 99% 10-33 min into race	‡ Gabriel 1994
Trained Runners	10	26 (5)	0	60 min at 70% of VO_{2max}	Downhill running ↑ cell # by 2.2 fold vs. 1.1 fold on level grade at 0h. ↔ during recovery	† Pizza 1995
Healthy YW	9	29 (1)	100	20 min run at 50-90% of VO_{2max}	Cell freq ↑ ~ 26% with acute exercise; ↔ time of day (morning vs. evening).	‡ Zelazowska 1997
Athletes	15	23 (7)	0	10% above L_T to exhaustion	Cycling ↑ cell # (57% ↑ normal and 49% ↑ overtrained).	‡ Gabriel 1998
Healthy Boys & YM	22	10 (1) & 22 (1)	0	60 min at 70% VO_{2max} +/- CHO ingestion	Only men without CHO ingestion had ~11% ↑ in cell freq post-cycling.	† Timmons 2004
Training						
Athletes	15	23 (7)	NR	19 (3) mo of cycling or triathlon	Overtrained condition resulted in ↑ 33% cell # vs. healthy post exercise.	‡ Gabriel 1998
Athletes	15	20 (1)	100	5h/d, 6d/wk, for 1 mo	Cell # ↑ 38% during and after intensive volleyball training vs. CON.	$ Suzui 2004
Healthy OW	60	55 (21)	100	60 min, 4d/wk for 6 mo Tai Chi	Cell freq ↑by ~3.5% in EX vs. ↔ CON.	‡ Liu 2012
Healthy YM	21	31 (8)	0	3d/wk for 2 mo RT ± vibration	Cell # ↑ by ~60% during bedrest. No differences between EX or CON.	† Hoff 2015
Breast Cancer	20	48 (3)	100	Walk 35-50 min/day, 5d/wk for 12 wk	Non-significant 20% ↓ in cell freq during walking at 40-60% of HRR.	? Kim 2015
Lung Cancer	32	E: 63 (8); C: 61 (7)	44	60min, 3d/wk, 16 wk Tai Chi	NKT cell freq ↓ ~1% in CON but ↔ in EX (~0.2%) at post-training.	‡ Liu 2015
Breast Cancer	39	52 (9)	100	16 wk for 60 min/d, 3d/wk RT	NKT cell freq ↔. EX ↓ TNFα freq by 3% vs. baseline.	† Hagstrom 2016

Data are mean (SD). NR, not reported; #, cell counts; freq, cell frequency; ↑, increase; ↓, decrease; ↔, no change; A_T, Anaerobic Threshold; GXT, graded exercise test; RT, resistance training; EX, exercise; CON, controls; L_T, lactate threshold; HRR, heart rate reserve; d, day; wk, week; mo, month; † $CD3^+CD56^+$ cells; ‡ $CD3^+CD16^+CD56^+$; ^ NKR-P1A (CD161) cells; $ $CD3^+CD16^-CD56^{dim}$ cells; ? NKT phenotype unknown;

Table 3. Summary of acute exercise and exercise training on gamma delta (γδ) T cells.

Population	N	Age (y)	% F	Exercise	Outcomes	Reference
Acute						
Elite athletes	10	37 (range: 25-48)	NR	120 min at 75% VO_2max	Cell # ↑ 3 fold at 0h. Minimal # 2h post exercise.	Krzywkowski 2001
Active YM	11	21 (2)	0	16 min at 35% or 85% of PPO	Cell # ↑ 56% with low intensity and by 219% with high intensity.	Anane 2009
Active YM & OM	34	29 (4) & 55 (4)	0	30 min at 80-85% of PPO	Cell # ↑ 140% (independent of age). Resting cell freq was 3.5% ↓ in OM vs. YM.	Pistillo 2013
Healthy YM	10	27 (8)	0	60 min at 90% of time trial wattage	Cell # ↑ by 90% in disrupted vs. normal sleep. Egress (cell #) was ↑ by 10% following sleep disruption.	Ingram 2015
Active YM & YW	11	31 (4)	36	30 min at 80% HR maximum	Cell # ↑ by 119% at 0h and remained elevated during 30 min of recovery.	Rooney 2018
Trained cyclist	14	30 (6)	14	30 min at 10-15% above L_T	Cell # ↑ by 1.8 fold after 14d expansion at 0h. 5% ↑ freq of NKG2D activation receptor and ~50% ↑ in cytotoxicity.	Baker 2020

Data are mean (SD). NR, not reported; #, cell counts; %, cell frequency; ↑, increase; ↓, decrease; ⇔, no change; PPO, peak power output; YM, young men; OM = old men; YW, young women; VO2max, maximal oxygen uptake; HR, heart rate; L_T, lactate threshold; d, day; wk, week; mo, month;

Figures

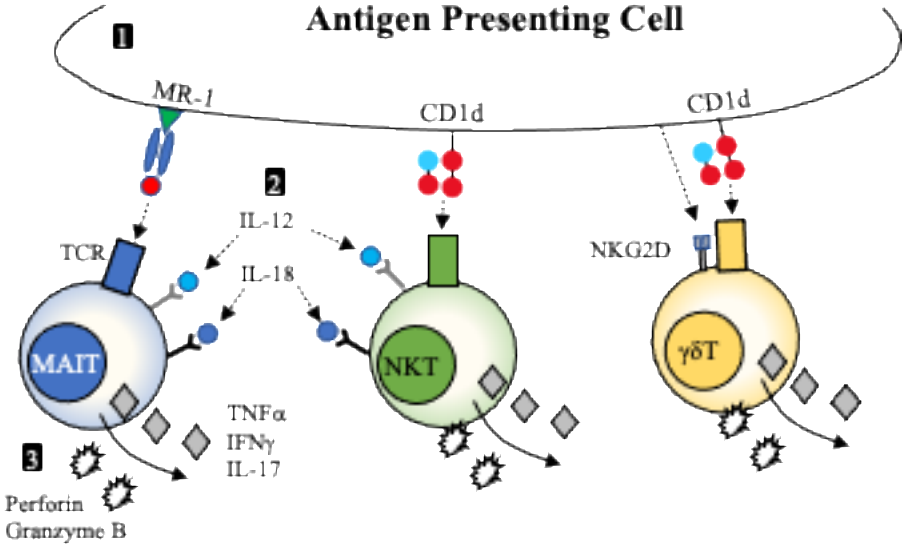

Fig. 1 Unconventional T cells (UTCs) are activated 1) via their T cell receptors (TCR) following interactions with antigen presenting cells or 2) through cytokines using TCR-independent signaling. 3) Upon activation, UTCs release cytokines and cytotoxic molecules that activate other immune cells or kill target cells, respectively. Activating signals are represented by dashed lines and effector functions via solid lines

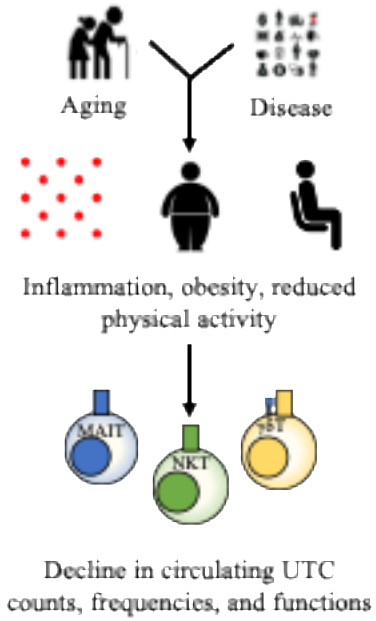

Fig. 2 Model of circulating unconventional T cell (UTC) decline and dysfunction with aging and disease

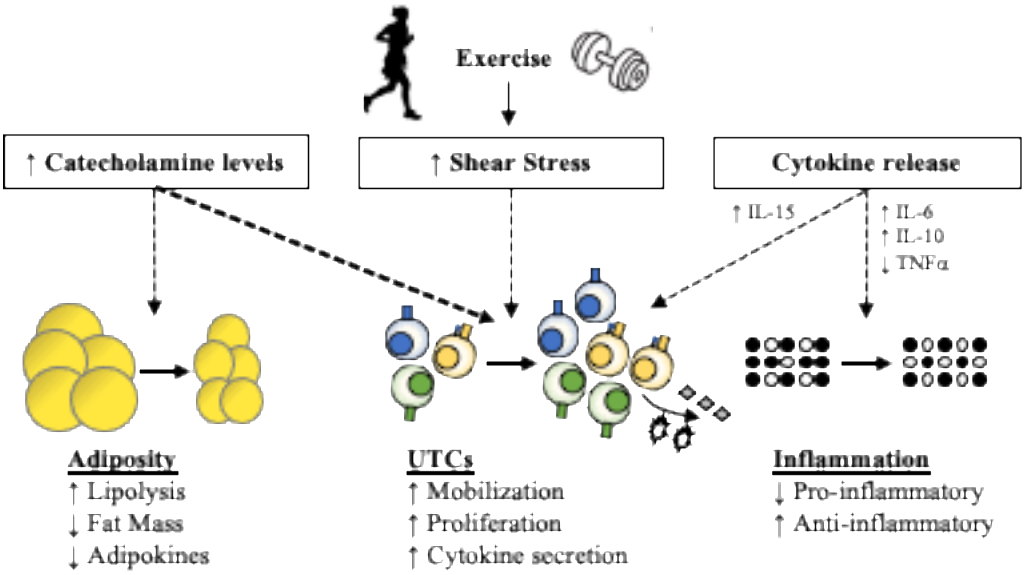

Fig. 3 Proposed mechanisms by which regular bouts of acute exercise may increase unconventional T cell (UTC) number and function. Moderate to vigorous exercise stimulates catecholamine release, increasing lipolysis and fat oxidation that reduces adipocyte mass, immune cell infiltration and adipokine secretion. Along with shear stress, catecholamines increases circulating immune cell numbers from the marginal pools. Myokines such as IL-6 and IL-15 released from contracting skeletal muscle increase UTC proliferation and cytotoxic function while inhibiting TNFα and stimulating IL-1ra and IL-10