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**Optimized Cardiac Health by Exercise: Cardiomyocytes and Immune
Microenvironment**

**Running Title: Exercise modulates cardiomyocytes-immune
microenvironment**

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39 **Abstract**

40 Exercise is a highly cost-effective and non-pharmacological intervention for
41 maintaining cardiovascular health and treating heart diseases. Exercise can protect the
42 heart through multiple effects, including regulations of cardiomyocytes and non-
43 cardiomyocytes. Immune cells can be regulated upon exercise under both physiological
44 and pathological conditions. The present review presents the current knowledge and
45 research advances about how exercise protects the heart, especially deciphering the
46 regulation of cardiomyocytes and immune microenvironment by exercise. This review
47 introduces the effect of exercise on the infiltration, phenotypic plasticity, and activation
48 of innate and adaptive immune cells, alongside their interactions with other cellular
49 components within the cardiac immune microenvironment. Moreover, we address the
50 role of lymphatic vessels in regulating immune cell trafficking and activation, as well
51 as the effects of exercise on cardiac lymphangiogenesis. It further discusses the
52 application of multi-omics approaches in investigating exercise-induced cardiac
53 adaptations, explores potential therapeutic strategies targeting the cardiac immune
54 microenvironment, and highlights the cardiotoxicity risks associated with excessive
55 exercise. A deep understanding of the effects of exercise on cardiomyocytes and cardiac
56 immune microenvironment will pave the way to promote the exercise interventions and
57 the development of exercise-mimetics in the treatment of heart diseases.

58 **Keywords:** Exercise, Cardiac Health, Cardiomyocytes, Immune Cells, Immune
59 Microenvironment, Lymphangiogenesis

60

1. Introduction

Cardiovascular diseases (CVD) are among the leading causes of death and disability worldwide(1). Although current pharmacological and surgical interventions improve outcomes in CVD, many patients progress to advanced stages or even heart failure (HF)(2). Therefore, identifying safe and cost-effective prevention and treatment strategies are still urgent and crucial. Exercise is a non-pharmacological intervention and has been extensively demonstrated to be effective to maintain cardiovascular health and improve various cardiovascular conditions(3).

For healthy adults, achieving 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic exercise per week significantly reduces risk factors of CVD(4). Secondary prevention exercise programs based on endurance training and resistance training also improve cardiovascular clinical outcomes(5, 6). For those after an onset of CVD, exercise training under doctor directions has been widely accepted as a cost-effective therapeutic intervention(6-8). A cardiovascular rehabilitation study involving 4,846 patients with coronary heart disease found that the risk of cardiovascular events remained low regardless of whether participants engaged in high-intensity or moderate-intensity exercise(9). Compared with standard percutaneous coronary intervention (PCI), exercise training via a daily 20-minute bicycle training resulted in significantly higher event-free survival rates in patients with stable coronary artery disease(10). Moreover, exercise training significantly improves cardiopulmonary function in patients with HF(11). These clinical findings have prompted further investigation into the mechanisms of exercise-mediated cardiac protection.

Early research primarily focused on the direct improvement of cardiac muscle cell functions through exercise. The heart is a complex system composed of multiple cell

86 types, including cardiomyocytes, fibroblasts, endothelial cells, immune cells, etc(12).
87 The immune microenvironment plays a crucial role in maintaining cardiac homeostasis
88 and regulating disease progression(13). However, the crosstalk between these
89 components and pathways and their synergistic mechanisms underlying the exercise's
90 cardioprotective effects remain incompletely elucidated. Moreover, the role of the
91 lymphatic vessels in the heart and its response to exercise are also crucial for
92 cardiovascular health and diseases, as it serves as a key pathway for immune cell
93 transport and fluid homeostasis(14-17).

94 This review integrates current evidence on exercise-mediated maintenance of
95 cardiac health and protection against CVD via cardiomyocyte and immune
96 microenvironment modulations. By summarizing current research advances and
97 controversies, we hope to provide new perspectives for future basic and translational
98 research on exercise-based cardiovascular interventions.

99 **2. Exercise-induced regulation of cardiomyocytes: physiological mechanisms** 100 **and protective effects**

101 Physical exercise serves as a powerful natural stimulus for the central nervous system,
102 triggering humoral responses essential for whole-body balance(18). These
103 neuroendocrine axes drive systemic release of diverse signaling molecules that work
104 together to enhance exercise capacity and exert systemic and local benefits(18, 19).
105 Notably, exercise triggers coordinated multi-organ responses to secrete a diverse
106 repertoire of signaling molecules (e.g., hormones, growth factors, cytokines,
107 metabolites) collectively defined as exerkinases(20). Skeletal muscle, liver, and adipose
108 tissues are major organs that release exerkinases(21). Interleukin (IL)-6 is the first
109 identified exercise-responsive myokine that is markedly induced after acute exercise(22,
110 23). Despite the elevation of IL-6 levels in response to acute exercise, long-term aerobic

111 exercise re-calibrates the cytokine balance in coronary artery diseases (CAD)(24, 25).
112 The reduction of IL-1, IL-6, Interferon (IFN)- γ and C-reactive protein (CRP) levels and
113 the increase in the anti-inflammatory IL-10 levels were observed in CAD patients with
114 exercise training(24, 26). To be noticed, this 12-week training shifted 46% of patients
115 from high to lower cardiovascular-risk categories, implying that cytokine modulation
116 by exercise directly translates into measurable improvement in cardiac prognosis(24).

117 In addition to neuroendocrine regulation, exercise is widely recognized as
118 beneficial for myocardial protection through its multifaceted effects on the myocardium,
119 including the regulation of cardiac redox homeostasis(27-29), mitochondrial biogenesis
120 and function(30-32), cardiac energy metabolism(33-35), and myocardial excitation-
121 contraction coupling and contractility(36-38). Moreover, chronic regular exercise is an
122 efficient stimulus to induce physiological cardiac hypertrophy, which is characterized
123 by enlarged cell size and increased proliferation activity of cardiomyocytes(39-42).
124 Different from pathological cardiac hypertrophy, physiological cardiac hypertrophy
125 represents a healthy adaptation to physiological stimuli such as long-term regular
126 exercise or pregnancy(43). The molecular mechanisms underlying exercise-induced
127 physiological cardiac hypertrophy, may also have the potential to protect against
128 myocardial apoptosis or pathological hypertrophy(44-46).

129 **3. Exercise-mediated cardiac immune microenvironment modulations**

130 Increasing evidence has shown that exercise not only regulates cardiomyocytes directly
131 but also modulates cardiac immune microenvironment(47). The healthy myocardium
132 harbors substantial leukocyte populations, including mononuclear phagocytes,
133 neutrophils, mast cells, and lymphocytes, which collectively form the cardiac immune
134 microenvironment(48). Notably, under disease conditions, growing evidence indicates
135 that a complex network of immune cells, together with cardiomyocytes, fibroblasts,

endothelial cells, and others, actively regulates disease pathogenesis(49). In this section, we first summarize the multifaceted roles of immune cells and interactions between immune and non-immune cells during cardiac injuries. We then focus on the effect of exercise in regulating immune cells and microenvironment in cardiac protection and repair.

3.1 Immune cells and cardiac immune microenvironment involved in cardiac injuries

In response to cardiac injury, damaged or stressed cardiac cells, particularly impaired cardiomyocytes, actively release damage-associated molecular patterns (DAMPs), thereby recruiting and polarizing immune cells(50). Meanwhile, the activation of resident cardiac cells such as macrophages and fibroblasts, the expression of vascular endothelial adhesion molecules and endothelial barrier disruption, as well as the activation of neurohumoral axis sophisticatedly participate in the recruitment and infiltration of inflammatory and immune cells(51). These recruited cells further secrete a spectrum of inflammatory and immunomodulatory factors to influence the functional states of different cardiac cells, by modulating cardiomyocyte survival, fibroblast activation, extracellular matrix remodeling, endothelial barrier integrity, and angiogenic capacity(52). These responses following cardiac injury play a dual role in maintaining cardiac function and promoting repair. On one hand, the acute inflammatory response helps prevent myocardial rupture and initiate repair. On the other hand, chronic or excessive immune responses lead to myocardial fibrosis and worsening cardiac function(53, 54). The interactions between immune and non-immune cells in the cardiac microenvironment under heart disease conditions are discussed in detail below, with schematic representation in **Figure 1**.

3.1.1 Immune cells and cardiomyocytes

161 Under acute pathological conditions, a large number of myocardial cells die and release
162 DAMPs. Recognition of DAMPs by pattern recognition receptors (PRRs) triggers
163 activations of downstream mitogen-activated protein kinase (MAPK) and NF- κ B
164 signaling pathways, leading to increased secretion of pro-inflammatory cytokines and
165 chemokines(55, 56). This drives the infiltration of leukocytes into the heart, including
166 monocytes/macrophages, neutrophils, natural killer (NK) cells and adaptive immune
167 cells(57-59). Damaged cardiomyocytes also mediate the infiltration of immune cells
168 via chemokines. Cardiomyocyte-derived chemokine C-X-C motif ligand 1 (CXCL1)
169 and monocyte chemoattractant protein-1 (MCP-1) have been demonstrated to
170 participate in monocyte infiltration during pressure overload (transverse aortic
171 constriction, TAC)-induced injury in mice(60). In cardiac ischemia/reperfusion (I/R)
172 injury, cardiomyocytes produce MCP-1 and IL-1 via the CaMKII- δ 9 pathway, thereby
173 promoting the infiltration and activation of CD68⁺ macrophages within the heart(61).
174 Moreover, in doxorubicin-induced cardiotoxicity, gasdermin E (GSDME) mediates
175 Chemokine ligand 2 (CCL2) secretion from cardiomyocytes. GSDME can be cleaved
176 by caspase-3, thereby altering non-inflammatory apoptosis into pyroptosis(62). This
177 cardiomyocyte-derived CCL2 subsequently promotes the recruitment of C-C
178 chemokine receptor type 2 (CCR2) positive macrophages into the myocardium, thereby
179 driving cardiac inflammation and doxorubicin-induced myocardial injury and HF (63).

180 The efficient clearance and degradation (phagocytosis) of apoptotic/necrotic
181 cardiomyocytes is crucial for the resolution of inflammation and tissue repair following
182 cardiac injury. Legumain (Lgmn) is a lysosomal cysteine protease that demonstrates
183 high specificities for cleaving protein substrates(64). Macrophages, particularly
184 cardiac-resident macrophages expressing Lgmn, have the capacity to phagocytose
185 necrotic cardiomyocytes, while Lgmn deficiency in mice increases the infiltration of

186 MHCII^{high} CCR2⁺ macrophages into the heart, suppresses the anti-inflammatory
187 mediators and promotes the expression of pro-inflammatory mediators after myocardial
188 infarction (MI)(65). Cardiomyocytes in both basal and during cardiac stress actively
189 release dysfunctional mitochondria encapsulated in membrane vesicles, which could be
190 efficiently cleared by macrophages via the myeloid-epithelial-reproductive tyrosine
191 kinase (Mertk) receptor, which is a crucial biomarker of impaired innate macrophage
192 phagocytosis(66), thereby preventing extracellular waste accumulation, inflammasome
193 activation, and autophagic dysfunction, collectively maintaining cardiac
194 homeostasis(67). On the other hand, evidence also shows that the post-phagocytic
195 macrophages can initiate interferon regulatory factor 3 (IRF3)-dependent amplification
196 of post-MI inflammation(68). Following MI, cardiomyocytes undergo necrosis, with
197 their cellular debris and released DNA being phagocytosed by macrophages. This
198 process induces the interferon response within cardiac macrophages through activating
199 the cGAS-STING-IRF3 signaling pathway, thereby inducing leukocyte accumulation
200 and amplifying inflammatory responses in MI(68).

201 Immune cells also participate in the regulation of cardiomyocytes fate via secreting
202 immunomodulators such as cytokines and immunoglobins. CD8⁺ T cells rapidly
203 accumulate within ischemic myocardial tissue and release granzyme B, a substance
204 with cytotoxic activity that promotes cardiomyocyte death(69). IgM produced by B
205 cells initiates acute inflammatory responses in the myocardium following I/R injury,
206 while knockout of IgM in mice markedly reduces cardiomyocyte apoptosis, diminishes
207 infarct size, and decreases neutrophil infiltration(70). Conversely, following MI in both
208 humans and mice, elevated levels of eosinophils have been observed in both blood and
209 cardiac tissue, which might mitigate cardiomyocyte apoptosis by releasing IL-4 and
210 cationic protein mEar1(71).

211 **3.1.2 Immune cells and fibroblasts**

212 Cardiac fibroblasts are key effector cells in cardiac fibrosis(72, 73). Tissue-resident
213 fibroblasts differentiate from multiple sources during early cardiac development,
214 forming a self-sustaining cell population(74). Under homeostatic conditions, these
215 cardiac fibroblasts primarily mediate extracellular matrix secretion and maintenance(75,
216 76). When stimulated by DAMPs or during other cardiac stress, fibroblasts are capable
217 of secreting substantial quantities of inflammatory cytokines and chemokines(77). With
218 the treatment of anti-cytotoxic T lymphocyte antigen-4 m2a antibody, the CXCL1
219 derived from cardiac fibroblasts promotes CCL5⁺ neutrophil infiltration within the heart
220 of autoimmune myocarditis mice via the CXCL1-CXCR2 signaling axis(78). This
221 subsequently enhances cytokine production and adaptive immune responses and
222 activates the NF- κ B signaling pathway(78). A new fibroblast subset, the CD248⁺
223 fibroblasts, was found to enhance T-cell retention by upregulating fibroblast ACKR3
224 expression post MI(79). The CD248-mediated T cell-fibroblast communication, in turn,
225 promotes fibroblast activation and cardiac remodeling in mouse MI models(79).

226 TGF- β is a key regulator of tissue fibrosis, by activating the Smad2/3 signaling
227 pathway in fibroblasts(80, 81). Cardiac fibroblast activation undergoes precise
228 regulation by multiple cytokines derived from a variety of cells including immune
229 cells(82). WWP2-expressing Ly6C^{high} monocytes constitute a major source of
230 macrophage expansion during the early stages of cardiac fibrosis. WWP2, an E3
231 ubiquitin ligase, is induced in pro-fibrogenic Ly6C^{high} monocytes under fibrotic stress,
232 where it upregulates CCL5 expression, thereby promoting macrophage infiltration and
233 activation as well as the trans-differentiation of myofibroblasts(83). Multiomic single-
234 cell gene expression, epitope mapping and chromatin accessibility profiling of acutely
235 infarcted and chronically failing human hearts revealed the immune-fibroblast cell

communication(84). It has been further demonstrated that the IL-1 β signaling pathway mediates the interactions between CCR2⁺ macrophages and fibroblasts; the activation of IL-1 β receptor expressed by fibroblasts drives the emergence of fibroblast activator protein (FAP) and periostin (POSTN)-expressing fibroblasts which contribute to cardiac fibrosis and HF in mice (84).

3.1.3 Immune cells and endothelial cells

Endothelial cells constitute a critical interface between the cardiovascular system and the immune system(85). They actively participate to immunomodulation during both acute injury such as MI and chronic adverse remodeling associated with HF(86). By expressing cell adhesion molecules such as E-selectin, P-selectin, intercellular adhesion molecule (ICAM), and vascular cell adhesion protein (VCAM), endothelial cells regulate leucocyte infiltration into tissues at inflammatory sites (85, 87). Moreover, endothelial cells can function as antigen-presenting cells by expressing MHC class I and II molecules and presenting endothelial antigens to T cells(88).

Immune cell migration is a critical process of the immune response to tissue injury. Adenosine deaminase acting on RNA type 2 (ADAR2), an enzyme that converts adenosine to inosine nucleotides in double-stranded RNA(89), regulates IL-6 signaling in endothelial cells and the recruitment of immune cells to the vascular endothelium. Knockout of ADAR2 in endothelial cells impairs the rolling and adhesion capabilities of immune cells on the vascular wall, thereby reducing immune cell infiltration within ischemic tissues(90). Neutrophils constitute the primary leukocyte population interacting with damaged endothelium, triggering the initial pro-inflammatory response during acute vascular injury(91). Overexpression of interleukin-8 receptor alpha (IL8RA) and interleukin-8 receptor beta (IL8RB) in endothelial cells attenuates neutrophil infiltration, suppresses inflammatory responses, and promotes structural

261 repair following vascular injury(92).

262 Immune cells are also crucial for maintaining endothelial cell function(93, 94).

263 The monocytes/macrophages-derived cytokines meteorin-like (METRNL) act as a
264 driver of angiogenesis, whose deficiency however inhibits the angiogenic response and
265 exacerbates post-infarction HF in mice (95). Following MI, M1 macrophages transfer
266 miR-155 to endothelial cells via exosomes, which inhibits the angiogenic capacity of
267 endothelial cells thereby exacerbating cardiac injury(96).

268 **3.2 Exercise regulates cardiac immune microenvironment in cardiac protection** 269 **and repair**

270 Exercise does not comprehensively suppress or activate the immune system, but rather
271 functions as a dynamic regulator, selectively recruiting, reprogramming, and
272 redistributing immune cell subsets. In physiological status, acute exercise can rapidly
273 mobilize large numbers of immune cells into the circulatory system, including
274 monocytes, neutrophils, NK cells, CD8⁺ T cells, CD4⁺ T cells, and B cells(97-104).
275 Comparatively, long-term or regular physical exercise can change the number and
276 distribution of immune cells accompanied by their functional changes. For example,
277 long-term exercise can reduce the number of B cells in human peripheral blood(105),
278 enhance NK cell activity and immune surveillance(106), delay the ageing of T
279 cells(107), and modulate monocyte/macrophage polarization(108). Under pathological
280 conditions, exercise plays a crucial role in regulating immune cell numbers, cellular
281 polarization responses, and levels of immune cell-mediated cytokines. Exercise training
282 can transform the pro-inflammatory cardiac immune microenvironment into an anti-
283 inflammatory state, promoting the repair of damaged cells and thereby improving the
284 progression of CVD including sepsis- or obesity-induced cardiomyopathy, myocardial
285 ischemic injury, and doxorubicin-induced cardiomyopathy(109-115).

286 Studies have shown that exercise-responsive immune cells fall into two major
287 categories: innate immune cells (including monocytes/macrophages, neutrophils, and
288 NK cells) and adaptive immune cells (including T cells and B cells)(116). These cells
289 exert distinct regulatory effects on cardiac microenvironment to participate in the
290 benefits of exercise(117). This section reviews the mechanisms governing exercise-
291 induced immune cell modulations, and further focuses on how these processes and
292 signals integrate cardiac cells with their immune microenvironment to maintain cardiac
293 homeostasis and to improve cardiac protection and repair following injury. Both clinical
294 and animal studies have revealed that exercise modulates diverse innate and adaptive
295 immune cell populations, which serve as key mediators of exercise-induced cardiac
296 protection and repair (**Figure 2**).

297 **3.2.1 Innate immune cells involved in exercise-induced cardiac protection and** 298 **repair**

299 *Exercise regulates monocytes and macrophages*

300 Innate immune cells serve as the first line of defense for the body which response
301 rapidly after cardiac injury (116). Their activation, trafficking, and polarization are
302 tightly regulated by exercise(47). Among them, monocytes/macrophages are the most
303 extensively studied innate immune cell population involved in exercise-mediated
304 cardiac immunomodulation(47). Monocytes develop from the common myeloid
305 progenitors in the bone marrow and constitute the largest type of leukocytes in the blood,
306 though they possess a short lifespan. These cells are released from bone marrow into
307 the circulation then migrate into tissues where they mature into macrophages and
308 dendritic cells. Monocytes and macrophages are present in numerous tissues and organs
309 including the heart, where they participate in both initial inflammatory response and
310 subsequent wound healing process following cardiac injury(118).

311 Following 10 weeks of moderate-to-vigorous physical activity in healthy adults,
312 peripheral blood CD16⁺ monocyte counts decreased, simultaneously with reduced
313 expressions of CD16 and Toll-like receptor (TLR) 2 and 4 on monocytes (119). Acute
314 exercise also alters the expression of TLR and human leukocyte antigen DR (HLA-DR)
315 on the surface of blood monocytes. After completion of an ergometer 60 km time trial,
316 cyclists exhibited elevated expression levels of TLR2 and TLR4 in their peripheral
317 blood monocytes, alongside reduced expression of HLA-DR(98). It is noteworthy that
318 sex-specific effect exists in the monocyte/macrophage response to exercise. For
319 example, an acute bout of moderate-intensity cycle ergometry significantly reduced
320 CCR2 expression on monocytes/macrophages in women, though it had no such effect
321 in men(108). Furthermore, post-exercise anti-inflammatory macrophage polarization
322 was markedly higher in women than in men, suggesting that an acute moderate-
323 intensity aerobic exercise differentially regulate monocyte CCR2 expression and
324 macrophage polarization in women and men(108).

325 In animal experiments, although exercise has been shown to improve the
326 inflammatory environment of the heart by upregulating anti-inflammatory factors such
327 as IL-10 and suppressing pro-inflammatory signaling, mechanistic studies specifically
328 focusing on the roles of monocytes/macrophages remain limited. A 4-week treadmill
329 running exercise was demonstrated to sufficiently increase the proportion of myeloid-
330 derived suppressor cells (MDSC) via macrophage-derived IL-10, which further triggers
331 STAT3/S100A9 signaling to regulate the differentiation of MDSC(120). This
332 mechanism mediates the protective effect of exercise in isoproterenol-induced HF by
333 improving cardiac function and reducing myocardial remodeling(120). In addition to
334 regulating macrophage functions, research indicates that exercise can diminish
335 inflammatory cell generation and ameliorate cardiovascular inflammation through

336 reducing hematopoietic output of inflammatory cells(121). Mechanistic studies
337 revealed that voluntary running exercise can reduce leptin production in mice adipose
338 tissues and enhance quiescence-promoting hematopoietic niche factors in leptin-
339 receptor-positive stromal bone marrow cells(121). This consequently diminishes
340 hematopoietic stem and progenitor cell (HSPC) proliferation and leukocyte production,
341 as well as cardiac inflammation post MI, without altering emergency hematopoiesis in
342 mice(121).

343 The heterogeneous responses of macrophage subpopulations to exercise stimuli
344 have emerged as a critical determinant of cardiac homeostasis. Compared to earlier
345 research suggesting that exercise reduces macrophage antigen-presenting capacity and
346 surface major histocompatibility complex II (MHCII) expression(122, 123), recent
347 study indicates that low-intensity treadmill running for 5 weeks in mice increases the
348 percentage of MHCII^{low} cardiac-resident macrophages, while decreases the percentage
349 of MHCII^{high} cardiac-resident macrophages(124). Moreover, exercise can differentially
350 regulate monocytes/macrophages in physiological and disease states. In left circumflex
351 coronary artery-occluded female pig, exercise training significantly reduces numbers
352 of pro-inflammatory M1 macrophages, upregulates anti-inflammatory genes such as
353 peroxisome proliferator-activated receptor gamma (PPAR γ), and weakens intercellular
354 communication between adipocytes and immune cells, thereby alleviating
355 inflammatory responses in epicardial adipose tissue of female pigs(111).

356 ***Exercise regulates neutrophils***

357 Neutrophils, another key innate immune cell population, are closely involved in cardiac
358 repair and participate in early-stage debris clearance and inflammatory regulation(125,
359 126). As the first-line defenders against bacterial infection within the innate immune
360 system, neutrophils constitute 50%–60% of all circulating immune cells. Neutrophils

are implicated in the development of various CVD. During myocardial I/R injury, neutrophils exhibit enhanced migration and release neutrophil extracellular traps (NETs) through S100A9 protein lactylation, exacerbating cardiomyocyte death(127). In atrial fibrillation, NETs can induce mitochondrial damage and autophagy-dependent cell apoptosis, prompting cardiomyocytes to release mitochondrial DNA and other substances that in turn, amplify NET formation. Conversely, DNase I-induced degradation of NETs can alleviate atrial fibrillation-related fibrosis(128).

In human studies, it has been shown that a single bout of moderate-intensity or high-intensity treadmill running for 60 min in well-trained male runners reduce the expression of the neutrophil surface receptor CD16(129). The effect of high-intensity exercise is more pronounced than that of moderate-intensity exercise. However, this reduction does not impair neutrophil degranulation or respiratory burst activity(129). Clinically, an 8-month exercise intervention involving 98 patients with cardiovascular risk factors revealed that exercise increases plasma deoxyribonuclease (DNase) activity, enhancing the degradation capacity of NETs networks(130). This elevation in DNase activity was not merely a compensatory response to cell-free DNA release following exercise, but rather an independently enhanced homeostatic regulatory mechanism that contributes to reduce pro-inflammatory and pro-thrombotic risks associated with NETs(130). These observations imply that exercise is beneficial for training and optimizing the immune system function of neutrophils.

Exercise has been suggested to regulate neutrophil infiltration and activation, initiating tissue repair cascades, and facilitating adaptive remodeling via modulating oxidant-antioxidant balance(131, 132). In animal studies, eighteen-month-old aged mice undergoing a four-week swimming training program exhibited reduced migration of Gr-1⁺ neutrophils in the heart following myocardial I/R injury, accompanied by a

386 significant downregulation of inflammatory markers (IL-6, IL-8, and TNF- α) as well
387 as ICAM and VCAM proteins, thereby ameliorating I/R injury in the aged heart(32). A
388 9-week swimming training program activated the endothelial nitric oxide system to
389 regulate the oxidant-antioxidant balance, reduced neutrophil infiltration
390 (myeloperoxidase activity), and alleviated rat cardiac/endothelial dysfunction and
391 oxidative damage induced by renovascular hypertension(133). Exercise via a voluntary
392 wheel running for six weeks in mice was found to enhance hematopoietic progenitor
393 cell quiescence and reduce the numbers of neutrophils, monocytes, and lymphocytes in
394 peripheral blood, thereby improving cardiovascular inflammation(121). However, the
395 molecular mechanisms linking exercise-mediated neutrophil function to cardiac repair
396 remain to be further studied and it requires further investigation to clarify their
397 synergistic roles with other immune cells.

398 Moreover, it should be mentioned that the regulation of neutrophils is closely
399 related to exercise intensity and duration in animal studies. For example, an exhaustive
400 exercise in mice was reported to activate neutrophils and increase their infiltrations in
401 renal tissues, which might induce acute renal injury(134). Exhaustive exercise also
402 increased neutrophil infiltrations in skeletal muscles that further recruited immune cells
403 like macrophages, leading to muscle injury(135). Following the elimination of
404 neutrophils by neutralizing antibodies, the inflammatory levels could be decreased and
405 tissue damage was effectively mitigated(134, 135).

406 ***Exercise regulates NK cells***

407 NK cells, as core cells of the innate immune system, also play a pivotal role in cardiac
408 immune microenvironment(136). In patients with acute MI, the abundance of NK cells
409 is negatively correlated with the expression of apoptosis-related genes following
410 MI(137). NK cells, as a subset of innate lymphoid cells, can alleviate viral myocarditis

411 by suppressing eosinophil-associated chemokines produced by cardiac fibroblasts(138).
412 NK cells can suppress cardiac inflammatory responses by releasing IL-10, thereby
413 repairing the damaged myocardium(139). Research indicates that the mobilization of
414 bone marrow-derived NK cells and angiogenic cells contributes to improved cardiac
415 remodeling and function following MI(140)

416 Extensive research indicates that exercise serves as a potent physiological stimulus
417 for regulating both the distribution and activity of NK cells. Acute exhausted exercise
418 session rapidly mobilizes NK cells from peripheral reservoirs such as the spleen into
419 the circulating pool, causing their numbers to surge several-fold during exercise(141,
420 142). There is no conclusive evidence demonstrating that exercise can alter the number
421 of NK cells and such changes in NK cells are more likely attributable to the
422 redistribution of immune cells within tissues and organ(104). NK cells express β_2 -
423 adrenergic receptors on their surface, whose activation has been proved to be necessary
424 to mediate the effect of exercise on the mobilization of NK cells into the circulation(101,
425 143).

426 A study in older women found that chronic resistance exercise promotes the
427 activity of NK cells(102). A moderate-intensity exercise training via 45 min of brisk
428 walk, 5 sessions/week for 6 weeks did not alter NK cell counts, but enhanced their
429 activity, accompanied by an improvement of cardiorespiratory fitness and a reduction
430 in upper respiratory tract infection symptoms, but these effects were no longer present
431 after 15 weeks of exercise(106). Some studies have found that despite an increase of
432 NK cell activity during acute exercise, the NK cell activity can rapidly decrease to
433 almost half the pre-exercise level within 1 hour following acute exercise, which
434 returned to baseline levels after 2 hours of recovery(100, 103).

435 In animal experiments, research indicates that a 4-week swimming exercise

436 training prevents stress-induced myocardial hypertrophy by suppressing the IL-
437 6/JAK/STAT pathway and reducing inflammatory response(144). Other studies
438 indicated that IL-6 blocking antibodies could attenuate voluntary wheel running-
439 induced NK cell mobilization and activation in tumor-bearing mice(145). Although the
440 anti-inflammatory effects of exercise on CVD may partially involve NK cells, whether
441 and how exercise regulates NK cells and the related mechanisms require further
442 investigation.

443 **3.2.2 Adaptive immune cells involved in exercise-induced cardiac protection and** 444 **repair**

445 *Exercise regulates T cells*

446 Adaptive immune cells, including T cells and B cells, exert precise and sustained
447 regulatory effects on cardiac immune homeostasis and repair processes. T cells,
448 particularly CD8⁺ T cells and Treg, complement B cells' humoral regulation as key
449 adaptive immune regulators in exercise-mediated cardiac protection. Exercise
450 dynamically regulates the mobilization, activation, metabolic adaptation, and
451 senescence processes of CD8⁺ T cells through multiple integrated pathways involving
452 neuroendocrine, vascular, and metabolic regulations(146).

453 T cells originate from lymphoid stem cells in the bone marrow. After
454 differentiating and maturing in the thymus, they circulate throughout the body and
455 distribute to immune tissues. As the core effector cells of adaptive immunity, they
456 primarily mediate cellular immune responses(147). CD8⁺ T cells are crucial for
457 maintaining cardiac immune homeostasis especially under healthy status(148). While
458 in specific disease status such as cardiac ischemic stress, CD8⁺ T cells are an important
459 driver of myocardial injury (146, 149). A bout of acute aerobic exercise or
460 supramaximal high-intensity exercise was shown to promote transient mobilization and

461 activation of CD8⁺ T cell subsets in healthy human subjects(150, 151). Similar to NK
462 cells, β 2-adrenergic receptor signaling is involved in the mobilization of differentiated
463 subsets of CD8⁺ T cells to the blood in response to acute exercise in humans(101). In
464 addition to mobilization, physical exercise is able to maintain the function of CD8⁺ T
465 cells and delay immune aging in elder man by enhancing mitochondrial function(107).
466 Functional characterization of CD8⁺ T cells has shown that high-intensity interval
467 training in healthy subjects significantly increased the circulating CD8⁺ T cell counts
468 and enhanced their cytotoxic capacity, which may improve the immune surveillance
469 function(151). Moreover, regular physical activity also promotes an increase in Treg in
470 the human blood(152).

471 In patients with ischemic heart diseases, the post-exercise serum IL-35 and IL-33
472 levels and FoxP3 gene expression in peripheral blood mononuclear cells show a
473 significant increase, suggesting that aerobic exercise may improve the inflammatory
474 state of atherosclerosis by regulating Treg(153). The transcription factor Foxp3 is a key
475 regulator of Treg development, driving the conversion of naive CD4⁺ T cells into
476 immunosuppressive Tregs(154). Conversely, high-intensity endurance exercise
477 (marathon and half-Ironman triathlon) may markedly increase Th17 cell numbers while
478 concomitantly reducing peripheral blood Treg(155). Meanwhile, serum concentrations
479 of IL-6 and TGF- β were significantly elevated. These exercise-induced cytokine
480 alterations drive shifts within Treg and Th17 cell populations, potentially biasing the
481 immune response toward inflammation(155).

482 Animal experiments revealed a significant increase in Th17 cells and a marked
483 decrease in Treg cells in a rat model of ischemic cardiomyopathy(156). Regarding
484 cytokines, peripheral blood level of IL-6, IL-17, and TNF- α were markedly elevated,
485 while TGF- β levels were significantly reduced. After 12 weeks of treadmill running,

the Th17/Treg ratio in the exercised group was significantly lower than that in the non-exercise group, accompanied by a recovery of cytokines(156). These findings indicate that aerobic exercise may improve the Th17/Treg imbalance, thereby enhancing cardiac function in HF(156). Moreover, in pigs with ischemia-induced cardiomyopathy, a 14-week running exercise significantly reduced the number of CD8⁺ T cells in epicardial adipose tissue and upregulated the anti-inflammatory genes such as PPAR γ , thereby alleviating inflammatory responses(111). In regards of cell-cell communication, CD8⁺ T cells directly induce cardiomyocyte apoptosis through the perforin-granzyme pathway and the Fas-Fas ligand (FasL) pathway, while simultaneously secreting proinflammatory factors such as IFN- γ and TNF- α to amplify the inflammatory cascade(69, 157). However, how exercise modulates T cell interactions with other cells remains to be further investigated.

Exercise regulates B cells

B cells, the primary mediators of humoral immunity, also play a role in the effects of exercise on cardiac health and diseases(158, 159). The number, proportion, and immunoglobulin production levels of B cells are modulated by exercise, though these changes may vary in dependent of the type, intensity and duration of exercise(160). B cells, as a vital component of the immune system, play a pivotal role in the development and progression of HF(161). They not only directly damage myocardial tissue by producing autoantibodies targeting cardiac antigens but also function as antigen-presenting cells to activate other immune cells(162). Furthermore, they regulate inflammatory responses and influence myocardial fibrosis and remodeling by secreting chemokines and cytokines(161).

A study of healthy men demonstrated that circulating absolute CD19⁺ B-cell counts were significantly reduced at 30 minutes and 24 hours after a total duration of

511 53 minutes of high-intensity interval exercise, sprint interval exercise, or moderate-
512 intensity continuous exercise(105). However, no changes in B cell counts were
513 observed among participants undertaking low-intensity cycling or eccentric leg
514 exercise, indicating that the response of circulating B cells are highly dependent on
515 exercise modality(99, 163). Compared to short-term exercise, chronic exercise training
516 has been shown to reduce both the number and proportion of B cells, whereas acute
517 bouts of peak aerobic exercise transiently increased B cell count immediately post-
518 exercise (164, 165). Moreover, an increase in the proportion of bone marrow-derived
519 naïve B cells was observed following 14 weeks of endurance exercise in healthy
520 human(166). Animal studies have shown that bone marrow-derived naïve B cells can
521 improve cardiac function in mice following MI(167). The potential of exercise to
522 ameliorate CVD through modulation of bone marrow-derived naïve B cell abundance
523 and function warrants further investigation.

524 Long-term exercise training can increase levels of secretory IgA (s-IgA) and
525 plasma IgA, suggesting that regular physical activity may help enhance mucosal and
526 humoral immunity, offering potential benefits for infection prevention(168, 169).
527 Different from IgA or s-IgA, chronic exercise commonly maintains circulating IgG
528 levels(170), while high-intensity endurance exercise like exhaustive marathon or
529 overtraining may reduce serum levels of IgG and IgM, which may be responsible for
530 the increased risk of infection(171, 172). Compared to chronic exercise training, acute
531 bouts of high-intensity exercise could transiently increase the serum concentrations of
532 IgG associated with hemoconcentration; IgG levels will subsequently fall below
533 baseline as B cells redistribute to lymphoid tissues, and finally return to baseline within
534 24–78 hours post-exercise(159).

535 Beyond general subset and immunoglobulin regulation, exercise can also regulate

536 B cell receptors and their intercellular communications to alleviate cardiac injury. Eight
537 weeks of treadmill running was shown to effectively suppress doxorubicin-induced
538 cardiotoxicity in mice by upregulating the expression of the inhibitory receptor FcγRIIB
539 on B cell surfaces(113). The increased FcγRIIB expression elevates the activation
540 threshold of B cells, via inhibiting the phosphorylation of proto-oncogene tyrosine-
541 protein kinase SRC (Src), spleen tyrosine kinase (Syk), Bruton tyrosine kinase (Btk),
542 and phospholipase gamma 2 (PLCγ2) (113). These molecular alterations ultimately
543 reduce B cell activation and their release of antibodies and inflammatory
544 mediators(113). Moreover, exercised mice-derived B cells isolated from the spleen
545 tissues significantly inhibited cardiomyocyte apoptosis and fibroblast activation *in vitro*,
546 when compared to the B cells derived from sedentary mice(113). However, this study
547 did not consider the sex differences and the influence of different types and intensity of
548 exercise. The effect of exercise-modulated B cells on the cardiac microenvironment
549 across various cardiac injury contexts also remains to be fully characterized.

550 **4. Exercise-regulated cardiac lymphatic vessels: Implications for cardiac** 551 **microenvironment**

552 The cardiac lymphatic system plays pivotal roles in cardiac development, homeostasis
553 maintenance, and cardiac repair after injury(173, 174). This network begins forming
554 during the embryonic period and continues to mature postnatally, with its core functions
555 in regulating myocardial fluid homeostasis and immune surveillance(173, 175).
556 Following cardiac injury such as MI, the cardiac lymphatic system contributes to reduce
557 excess tissue oedema, mediate immune cell trafficking, and regulate functions of
558 immune cells as well(176). These processes are crucial for controlling inflammation
559 and initiating repair after cardiac injury(177, 178).

560 Macrophages play a crucial role in cardiac regeneration, and cardiac lymphatics

561 in postnatal day 1 (P1) mice contained zipper-like junctions with continuous VE-
562 cadherin expression, thus retaining LYVE-1⁺ macrophages which play an essential role
563 to promote cardiac regeneration and repair in neonatal mouse(179). However, the
564 button junctions were more evident compared to the zipper-like junctions in postnatal
565 day 7 (P7) mice heart, which increased the permeability of cardiac lymphatic vessels
566 and macrophage trafficking(179). In adult mice, prompt and effective lymphatic
567 formation and functional enhancement following MI have been shown to accelerate the
568 clearance of inflammatory cells, necrotic cell debris, and excessive inflammatory
569 mediators from cardiac tissues, which facilitates the transition from the acute
570 inflammatory response phase to the tissue repair phase(180, 181). Bone Morphogenetic
571 Protein 9 (BMP9), also known as growth differentiation factor 2 (GDF2), is a member
572 of the TGF- β superfamily(182). Exogenous supplementation of BMP9 in mice was
573 shown to improve MI by enhancing lymphatic drainage function(183). On the contrary,
574 impaired branched-chain amino acid (BCAA) catabolism in lymphatic endothelial cells
575 via the branched-chain ketoacid dehydrogenase kinase triggers lymphangiogenic
576 defects, ultimately emerging as a key factor in the onset of HF with preserved ejection
577 fraction (HFpEF) in mice(184). Increasing evidence has suggested that delivery of
578 vascular endothelial growth factor (VEGF)-C to the heart stimulates lymphatic vessel
579 formation, thereby reducing myocardial edema and cardiac fibrosis following
580 myocardial injury and ultimately improving cardiac function(185, 186).

581 Exercise can promote both angiogenesis and lymphangiogenesis in multiple
582 organs including the heart, by upregulating VEGF, hypoxia-inducible factor-1 α (HIF-
583 1 α), and endothelial nitric oxide synthase (eNOS)(14). It was shown that swimming
584 exercise can significantly enhance cardiac lymphatic vessel density in a vascular
585 endothelial growth factor receptor 3 (VEGFR3)-dependent manner, which is necessary

586 to mediate exercise-induced physiological cardiac hypertrophy(16). The conditioned
587 culture medium from lymphatic endothelial cells was found to promote both
588 physiological hypertrophy and proliferation of cardiomyocytes *in vitro*, through
589 activating AKT and modulating the CCAAT/enhancer binding protein β (C/EBP β)-ED-
590 rich carboxyterminal domain 4 (CITED4) pathway(16). The insulin-like growth factor-
591 1 (IGF-1) and the extracellular protein Reelin (RELN) may serves as mediators of cell-
592 cell communication between lymphatic endothelial cells and cardiomyocytes in
593 exercise-induced physiological cardiac hypertrophy(16).

594 Exercise has been recently shown to induce cardiac lymphatic remodeling which
595 mitigates cardiac inflammation in the aged mice(17). Compared to young mice, aged
596 mice exhibited a significantly reduced density of cardiac lymphatic vessel networks,
597 which is closely associated with chronic immune cell infiltrations (e.g. CD3⁺ T cells
598 and CD68⁺CD206⁺ macrophages), fibrosis, and increased perivascular fat deposition in
599 the aged mouse heart. Interestingly, eight weeks of voluntary wheel running was
600 efficient to enhance cardiac lymphatic vessel density and branching while reducing
601 their dilation in aged mice, thus alleviating inflammatory responses, fibrosis, and lipid
602 deposition and simultaneously facilitating physiological cardiomyocyte
603 hypertrophy(17). The interplay between exercise, cardiac lymphatic vessels, and
604 immune microenvironment dynamics in CVD requires further exploration.

605 **5. Exercise-induced protective effects from a multi-omics perspective**

606 The application of multi-omics technologies has greatly promoted our understanding of
607 the molecular responses triggered by exercise. Various ‘omics’ platforms, including
608 transcriptomics, epigenomics, proteomics and metabolomics, have been used to explore
609 how exercise improves health and contributes to disease management.

610 Following a five-week course of voluntary wheel running training in young and

611 aged mice, single-cell transcriptomic analyses of skeletal muscle, subventricular zone
612 (SVZ) of the brain, hematopoietic stem and progenitor cells (HSPCs) of the bone
613 marrow, and peripheral blood immune cells were performed which found that exercise
614 exerts substantial effects on the phenotypic composition and transcriptional profiles of
615 both circulating and tissue-resident immune cells. Especially, exercise alleviates the
616 upregulation of multiple inflammatory pathways in aged mice, restored the number of
617 resident CD206⁺ monocytes in skeletal muscles of aged mice, and increased the
618 expression of Osteopontin in skeletal muscles and promoted muscle regeneration(187).
619 A 12-month wheel running exercise program in young and aged mice, conducted in a
620 model of lipopolysaccharide (LPS)-induced infectious injury, revealed through single-
621 cell sequencing analysis of 14 tissues and organs that exercise protects tissues from
622 infectious injury and promotes tissue renewal by inhibiting inflammatory aging. In
623 particular, exercise delays aging and improves infectious injury by resetting the
624 circadian rhythm program via the circadian rhythm protein basic helix-loop-helix
625 ARNT like 1 (BMAL1)(188), which is one of the most important regulatory proteins
626 of the circadian clock and is closely associated with the regulation of metabolism, cell
627 growth and physiological functions(189).

628 Multi-omic response to endurance exercise training at different exercise training
629 time points have recently been reported (<https://motrpac-data.org/>)(190). Male and
630 female rats aged six months underwent eight weeks of treadmill endurance training. It
631 was found that the male group experienced an 18% increase in aerobic capacity (VO₂
632 max) and a 5% reduction in body fat percentage, compared to the female group, which
633 exhibited a 16% increase in aerobic capacity; however, whilst body fat percentage did
634 not decrease in the female group, it increased in the sedentary control group. Whole
635 blood, plasma and 18 solid tissues (including the muscle, heart, liver, white adipose

636 tissue, lungs, kidneys, brain, etc.) were collected for multi-time-point, multi-omics
637 analysis including transcriptome, proteome, metabolome, lipidome, phosphoproteome,
638 acetylproteome, ubiquitylproteome, epigenome and immunome(190). The findings
639 revealed that exercise-induced molecular adaptations are highly tissue-specific, with
640 shared pathways across tissues (such as the heat shock response and mitochondrial
641 metabolism), and that gender differences are widespread across multiple tissues and
642 time points. Immune, metabolic, stress responses and mitochondrial pathways all
643 respond to the effects of exercise. Furthermore, the rat data show a high degree of
644 consistency with human health, including cardiovascular health and injuries(190).

645 Recently, researchers have undertaken a systematic integration and in-depth
646 analysis of existing exercise-related transcriptomic data. To address the challenges
647 posed by the diversity of exercise modalities, complex individual variations, and multi-
648 tissue coordinated responses, the ExerGeneDB database (<https://exergenedb.com>) has
649 been established to systematically collect and re-analyze 6,194 samples from humans,
650 mice and rats, including skeletal muscle, blood, heart, liver, adipose tissue, brain, spinal
651 cord, bone marrow, and more than 13 other tissues and organs(191). It integrates
652 multiple data types, including RNA-seq, microarrays and single-cell transcriptomics,
653 and standardizes clinical and exercise parameters such as sex, age, body mass index
654 (BMI), exercise mode, intensity and frequency. ExerGeneDB provides a vital platform
655 for investigating the molecular mechanisms underlying exercise-induced
656 adaptations(191).

657 These studies, ranging from the single-cell to the whole-tissue level, from single
658 time point to temporal dynamic research, and from single-sex to sex-comparative
659 analyses, have collectively constructed a molecular map of the protective effects of
660 exercise and will promote further exploration for the mechanistic understanding of

661 exercise's systemic and local effects for maintaining homeostasis and improving health.

662 **6. Exercise-related therapeutic strategies targeting cardiac immune**
663 **microenvironment**

664 Accumulating evidence has reported that a deep understanding of the cellular and
665 molecular changes in response to exercise may provide potential therapeutic targets or
666 strategies for CVD(192, 193).

667 A three-month treadmill exercise program in mice revealed that exercise induces the
668 reprogramming of mice monocytes via histone acetylation (H3K18la), transforming
669 them into iNOS⁺Arg1⁺ macrophages with pro-inflammatory and pro-repair functions,
670 thereby restoring cardiac immune homeostasis. The adoptive transfer of these modified
671 monocytes can mimic the cardioprotective effects of exercise in a sepsis-induced
672 cardiomyopathy mouse model, offering a new direction for cell therapy strategies(109).

673 Additionally, it has been shown that exercise training activates macrophages to secrete
674 IL-10, which in turn amplifies cardiac myeloid-derived suppressor cells (MDSCs) via
675 the STAT3/S100A9 signaling pathway; depletion of MDSCs attenuates the exercise-
676 induced cardioprotective effect, suggesting that MDSC amplification may serve as a
677 potential therapeutic target for HF(120). Investigators employed a two-sample
678 Mendelian randomization (MR) method to assess the causal relationship between
679 physical activity and CVD, and found that physical activity partially mediates its
680 cardioprotective effects by modulating immune pathways (particularly IL-10 receptor
681 subunit beta signaling). Exercise reduces the risk of CVD through immune modulation,
682 suggesting that targeting the IL-10 signaling pathway may serve as a potential
683 therapeutic strategy to mimic the cardioprotective effects of exercise(194). Research
684 has also shown that moderate-intensity treadmill training, at a speed of 10 m/min for
685 30 minutes per time over an 8-week period, can alter the microbial composition of the

spleen in mice fed a high-fat diet and increase the abundance of *Lactobacillus johnsonii*, a bacterial species that is positively correlated with Tregs and can improve cardiac function. This suggests that probiotic or metabolite intervention may serve as an indirect strategy to mimic the immunomodulatory effects of exercise(195). An integrated multi-omics analysis revealed that repeated exercise boost circulating metabolite betaine partly through renal synthesis, a metabolite that may serve as an exercise “memetic” to reduce senescence and inflammation and promote multi-organ geroprotection(196).

Collectively, the cardioprotective effects of exercise may be mimicked or enhanced through cell adoptive transfer, targeting specific immune cell subsets (such as MDSCs) or key signaling pathways (such as IL-10, histone lactylation, etc), as well as by modulating gut microbiota or metabolites. These findings provide important foundational theory and potential targets for the development of “exercise mimetics”.

7. Beyond the benefits: Potential cardiotoxicity of excessive exercise

Although extensive research demonstrates that regular exercise effectively improves cardiovascular health, others have reviewed the potential dangers of excessive exercise, such as marathons, ironman distance triathlons, and very long distance bicycle races, that may induce adverse cardiac remodeling(197). The study of long-term marathon participation found that the total coronary artery plaque volumes, calcified plaque volumes, and non-calcified plaque volumes may be increased in marathon runners compared to the sedentary matched group(198). Extreme endurance training may lead to atherosclerotic plaque formation and myocardial cytotoxicity and increase cardiovascular disease mortality(199). A prospective observational cohort study involved 106 asymptomatic male competitive cyclists and triathletes (age $\geq$ 50 years, exercising $\geq$ 10 hours per week for $\geq$ 15 years). Cardiac magnetic resonance imaging

711 (MRI) revealed that 47.2% of the athletes had myocardial fibrosis. During exercise
712 testing, athletes with fibrosis had a higher incidence of ventricular premature beats, and
713 fibrosis was associated with a 4.7-fold increased risk of ventricular arrhythmias(200).
714 Using cardiac MRI, the researchers examined 93 highly trained endurance athletes
715 (who had trained for at least 12 hours per week over the past 5 years; mean age 36 ± 6
716 years; 53% male) *versus* 72 age- and sex-matched control subjects. The prevalence of
717 cardiac fibrosis was significantly higher in high-level endurance athletes than in
718 sedentary individuals, and cardiac fibrosis was positively correlated with training load
719 (annual training volume and years of training), suggesting that long-term, high-intensity
720 endurance exercise may promote the development of cardiac fibrosis(201).

721 In animal experiments of mice subjected to three different overtraining protocols
722 (including overtrained by downhill running, uphill running, or running without
723 inclination), it was found that overtraining significantly reduced the adenosine
724 monophosphate-activated protein kinase (AMPK) activation, promoted the expression
725 of proinflammatory cytokines IL-6, and upregulated pathological cardiac hypertrophy
726 marker gene β -isoform of myosin heavy-chain (β -MHC) (202). A rat experimental
727 study demonstrated that long-term intensive exercise training induced cardiac fibrosis,
728 accompanied by ventricular dysfunction and increased susceptibility to
729 arrhythmias(203). In another eight-week program of forced treadmill running in mice
730 with induced myocarditis via Cocksackievirus B3 (CVB), it was found that endurance
731 exercise led to an increase in pro-inflammatory immune cells, including M1
732 macrophages and CD8⁺ T cells and promoted cardiac fibrosis(204).

733 The mechanisms through which the health and longevity benefits of moderate
734 exercise begin to diminish when training intensity exceeds a critical threshold remain
735 to be elucidated(205). Emerging evidence has suggested that high-intensity training is

736 closely associated with immune dysfunction and inflammatory responses(206, 207).
737 NK cells and CD8⁺ T cells decreased significantly within 1-2 hours following acute
738 exercise(100, 103). However, there is currently no conclusive evidence demonstrating
739 that strenuous exercise increases the risk of opportunistic infections. Moreover, it has
740 been proposed that the marked decline in lymphocyte numbers and function observed
741 shortly after exercise represents a redistribution of immune cells within tissues rather
742 than immune suppression(208).

743 Thus, exercise intensity and duration warrant careful consideration when
744 evaluating exercise effects, particularly in vulnerable populations such as the elderly,
745 individuals with genetic predispositions, or those with underlying viral infections. The
746 cardiac fibrosis, immune-inflammatory dysregulation, and metabolic pathway
747 disturbances induced by excessive exercise may increase the risk of arrhythmias and
748 myocardial damage. These findings will provide important evidence for developing
749 personalized exercise prescriptions, defining safe exercise limits, and identifying high-
750 risk populations.

751 **8. Perspectives and conclusions**

752 The present review summarizes exercise as a cardioprotective strategy via coordinated
753 modulation of cardiomyocytes and cardiac immune microenvironment. Future studies
754 are expected to go deep into elucidating the molecular mechanisms, deciphering
755 intercellular communication signals, and advancing translational applications of
756 exercise-induced cardiac protection.

757 First, despite characterization of exercise-responsive signaling mediators, their
758 spatiotemporal coordination of intercellular communication across distinct cardiac cell
759 populations, particularly among immune cells, cardiomyocytes, and other cell types,
760 requires further investigation. Moreover, it is of considerable significance to investigate

761 the specific immune cell subsets and signaling molecules regulated by exercise. Single-
762 cell RNA sequencing, spatial transcriptomics and proteomics, metabolomics, and novel
763 genetic tools will be preferentially applied to investigate the dynamic changes and
764 interactions of cardiac cell populations before and after exercise, thereby elucidating
765 the molecular mechanisms and intercellular crosstalk underlying exercise-induced
766 cardioprotection.

767 Second, the development of exercise prescriptions represents an urgent clinical
768 priority. The functional roles of exercise in cardiovascular protection and its specific
769 regulations on immune cells may be closely related to the mode of exercise (aerobic or
770 resistance exercise), as well as the intensity, frequency, and duration of exercise.
771 Moreover, the immunomodulatory effects of exercise exhibit temporal specificity,
772 varying markedly between the acute injury, reparative, and chronic remodeling stages
773 of CVD. Developing more refined animal disease models and integrating these with
774 clinical cohort studies will promote the translational application of exercise-induced
775 cardiac protection.

776 Third, individual differences must be taken into careful consideration. Genetic
777 background, sex, age, and gut microbiota may influence the response to exercise. By
778 integrating genomic, metabolism, immunological, and metagenomic data through
779 artificial algorithms, it is possible that we might develop machine-learning models to
780 help predict how well an individual may benefit from exercise-induced cardioprotection.

781 In conclusion, elucidating the mechanisms through which exercise modulates the
782 myocardium and cardiac immune microenvironment will provide a scientific
783 foundation for designing personalized exercise prescriptions and potentially “exercise
784 mimetics”, to achieve precision prevention and treatment of CVD.

785

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1543

1544 **Figure legends**

1545 **Figure 1. Immune cells in the cardiac microenvironment under heart disease**
1546 **conditions.** During myocardium injury, the dying myocardial cells release DAMPs,
1547 which drive the infiltration of monocytes/macrophages, neutrophils, NK cells, T cells
1548 and B cells into the injured myocardium. This figure presents some examples of the
1549 immune cells and cell-cell communication in the microenvironment of the injured heart.
1550 **Monocytes/Macrophages:** Ly6C^{high} monocytes infiltrate into the injured heart and
1551 release pro-inflammatory factors such as TNF- α . Circulating monocytes release
1552 cytokines METRNL to enhance the endothelium angiogenic response. The Ly-6C^{high}
1553 CCR2⁺ monocyte/macrophage cells secrete IL-1 β and directly regulate inflammation-
1554 driven FAP⁺/POSTN⁺ fibroblasts to promote cardiac fibrosis. The M1 macrophages
1555 cause the damage of endothelium through EVs containing miR-155. **Neutrophils:**
1556 Neutrophils initiate inflammation in the injured myocardium, while IL8R
1557 overexpression in endothelial cells suppresses neutrophil infiltration during
1558 endothelium damage. Neutrophils further migrate into the injured myocardium and
1559 release NETs, leading to cardiomyocyte death. **NK cells:** NK cells can alleviate viral-
1560 induced myocarditis by suppressing eosinophil-associated chemokines produced by
1561 cardiac fibroblasts. **T cells:** Endothelial cells regulate T cell infiltration via presenting
1562 endothelial antigens (MHC I/II) to T cells. In myocardial infarction, T cells infiltrate to
1563 the damaged myocardium and CD8⁺ T cell release granzyme B to induce
1564 cardiomyocyte death. **B cells:** Recruited B cells in the injured myocardium produce
1565 chemokines, cytokines, and autoantibodies, triggering cardiomyocyte injury and
1566 fibroblast activation. This figure is created with Biorender.

1567 **Abbreviations:** DAMPs, damage-associated patterns; NK cells, natural killing cells;
1568 Ly6C, lymphocyte antigen 6C; TNF- α , tumor necrosis factor- α ; CCR2, CC-chemokine
1569 receptor 2; FAP, fibroblast activator protein; POSTN, periostin; EVs, Extracellular
1570 vesicles; IL8R, Interleukin-8 receptor; NETs, neutrophil extracellular traps; MHC I/II,
1571 major histocompatibility complex class I and II molecules.

1572

Figure 2. Exercise regulates immune cells and cardiac microenvironment in cardiac protection and repair. This figure summarizes how immune cells serve as mediators of exercise-induced cardiac protection and repair. In human studies of physical activity and exercise training, as well as in animal exercise training studies, exercise has been shown to regulate different types of immune cells, including monocytes/macrophages, neutrophils, NK cells, T cells and B cells.

Monocytes/Macrophages: Exercise turned the monocytes and macrophages into anti-inflammatory phenotypes in both human and mouse studies. Chronic moderate-to-vigorous physical activity exercise training reduces CD16⁺ monocyte counts, alters their surface marker profiles, and influences macrophage polarization in humans. In animal experiments, voluntary running exercise reduces leptin secretion and diminishes HSPC proliferation, leading to the beneficial effect against myocardial infarction. Treadmill running increases the proportion of MDSC through the IL-10/STAT3/S100A9 signaling pathway, and protects against heart failure.

Neutrophils: In clinical, exercise increases plasma DNase activity, and reduces neutrophils-induced NETs. In animal studies, voluntary wheel running in mice can reduce the neutrophil numbers by enhancing hematopoietic progenitor cell quiescence, leading to the improvement of cardiovascular inflammation.

NK cells: Chronic exercise can improve the activity of NK cells, while acute exercise can mobilize NK cells into the circulation by activating β_2 -adrenergic receptor signaling in humans. In animal studies, aerobic exercise can prevent cardiac hypertrophy with the suppressed IL-6/JAK/STAT pathway and reduced inflammatory responses in the myocardium. Relationship between IL-6 and NK cells remain further investigation.

T cells: Healthy human with acute aerobic exercise or supramaximal high-intensity exercise can lead to the mobilization and activation of CD8⁺ T cell in the blood. Exercise training attenuates atherosclerotic inflammation in patients with ischemic heart disease, as evidenced by elevated serum levels of IL-35 and IL-33 and increased FoxP3 expression in PBMC. In animal studies, treadmill running can reduce the Th17/Treg ratio and improve the cardiac function in heart failure model. Running exercise can protect against ischemia-induced cardiomyopathy in pig animal models, via reducing the number of CD8⁺ T cells in epicardial adipose tissues and upregulating the anti-inflammatory genes such as PPAR γ .

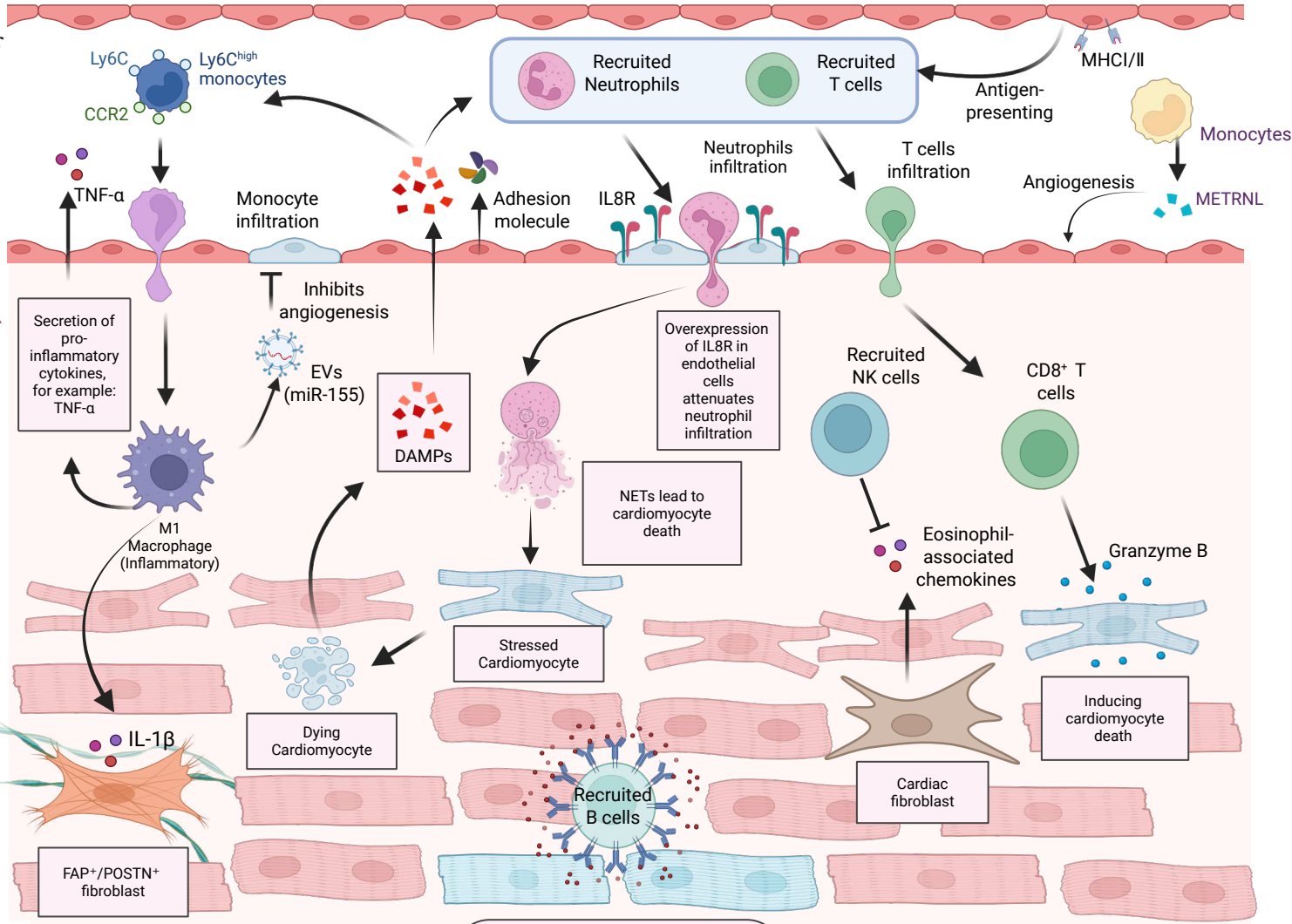
B cells: High-intensity interval exercise, sprint interval exercise, moderate-intensity continuous exercise, or chronic exercise training, can reduce the B cell counts in circulation from healthy people. Low-intensity cycling or eccentric leg exercise has no effect on the number of B cells. Chronic exercise can induce s-IgA and plasma IgA, while maintaining circulating IgG levels. In animal studies, long-term treadmill running protects against doxorubicin-induced cardiotoxicity via upregulating the Fc γ RIIB receptor expression on B cell surfaces. Exercise-derived B cells elicit anti-apoptosis and anti-fibrosis effects on cardiomyocytes and cardiac fibroblasts under doxorubicin stress. This figure is created with Biorender.

Abbreviations: NK cells, natural killing cells; HSPC, hematopoietic stem and progenitor cell; MDSC, myeloid-derived suppressor cell; DNase, Deoxyribonuclease; NET, neutrophil extracellular traps; PBMC, peripheral blood mononuclear cell; PPAR γ , proliferator-activated receptor gamma; s-IgA, secretory Immunoglobulin A; IgG,

1617 Immunoglobulin G; Fc γ RIIB, Fc gamma receptor IIB.
1618

Blood vessel

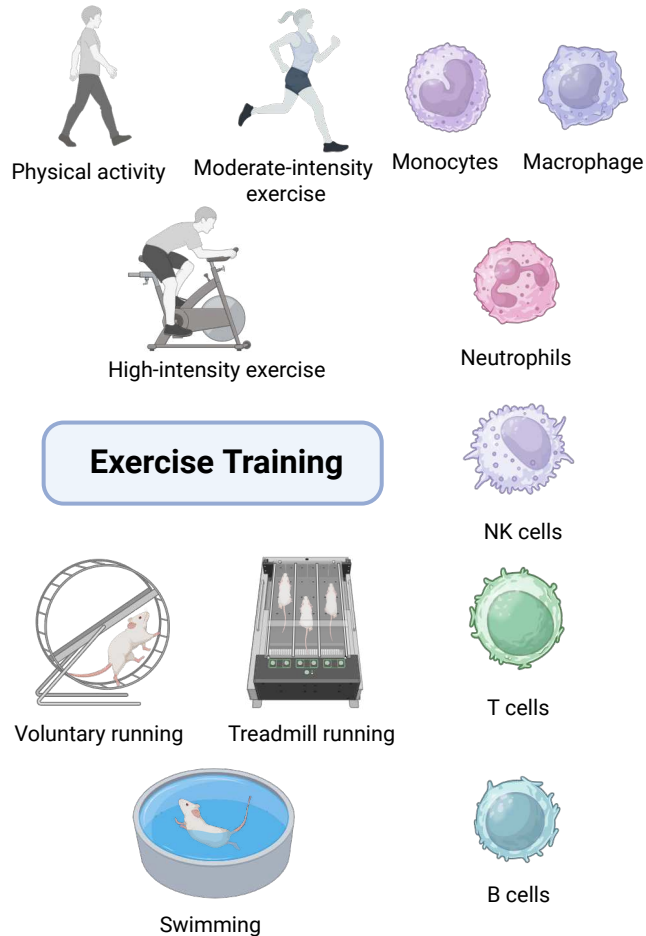
Endothelium



Myocardium

Inducing cardiomyocyte death or activating fibrosis via secreting autoantibodies, chemokines and cytokines

Exercise Immunology



Exercise mediated Cardiac Protection and Repair

