

骨骼肌是調節免疫反應的主要關鍵

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摘要

運動係藉由骨骼肌之收縮而完成身體所有的活動，同時骨骼肌有如內分泌器官，可以產生許多種類肌細胞激素。許多肌細胞激素能促進免疫細胞增生及增加細胞吸附分子之表現，進而促使更多的免疫細胞移動，達到免疫系統之活化。介白素-6 最早被發現，也是最重要的肌細胞激素之一，可抑制促發炎細胞激素的作用，因而具抗發炎之功效，有助於預防或治療因長期慢性發炎所導致的心血管疾病及代謝症候群。透過運動所誘發產生的肌細胞激素可負責骨骼肌、免疫系統與其他器官組織之間的對話，維持生理之恆定與健康。過去的研究發現，規律適度運動者比久坐者出現上呼吸道感染症狀的時間較短，而且嚴重程度也較輕。因此，藉由適度的運動，促使骨骼肌提升免疫功能乃是提升免疫力的最佳作法之一。

關鍵字：骨骼肌、肌細胞激素、免疫系統、適度運動

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壹、前言

全球正面臨人口老化、代謝性疾病、身體活動量不足與新興傳染性疾病侵襲等狀況所威脅，維持良好的個人免疫力與健康管理，為大眾所追求身體健康的最佳對策。當免疫細胞被不適當的活化並誘發身體局部發炎時，往往進而造成免疫力下降及代謝相關病灶的發生。透過規律且適度的運動提升自身的免疫系統功能，目前被認為是對抗外在病原菌最好的武器之一，如此方可達到健康生活的最終目標。

貳、骨骼肌與免疫系統的對話

免疫系統是由許多不同功能的細胞及各種大小不同的蛋白質分子所組成一個複雜且堅固的網狀連結，針對人體執行保護的工作。包括：清除入侵的病原菌與外來物、消滅內生性不正常的物質與壞死的細胞殘骸或是生病的細胞等。因此，當免疫功能低下時，容易受到感染進而危及人體健康。自然殺手細胞 (natural killer cells) 具毒殺能力及分泌細胞激素的能力，被認為是免疫細胞中最易受到運動所影響，除了直接對抗感染症外，也可以跟其他免疫細胞如：T 細胞、樹突細胞 (dendritic cells)、吞噬細胞 (macrophages) 一起合作，達到提升免疫與保護的功效 (Idorn & Hojman, 2016; Spits et al., 2013)。細胞激素 (cytokines) 是一群很龐大的蛋白質家族，早期研究免疫系統功能時，發現其負責細胞與細胞之間的訊息傳遞，單一種細胞激素常同時具有多種功能，將依據所受到的刺激源、作用目標細胞及是否有其他細胞激素一起作用而決定細胞激素的功用 (Peake, Della Gatta, Suzuki, & Nieman, 2015)。

過去二十多年來，由於運動科學的發展中包含許多有關骨骼肌的科學研究，目前已知骨骼肌是體內重量最大的器官，約占男性體重的 40% 及女性體重的 30% (Kim, Wang, Heymsfield, Baumgartner, & Gallagher, 2002)。許多證據顯示骨骼肌像是一個內分泌器官，可以產

生超過 300 種蛋白質，這群蛋白質分子被稱為肌細胞激素 (myokine) (Henningsen, Rigbolt, Blagoev, Pedersen, & Kratchmarova, 2010; Yoon et al., 2009)，可以透過自泌 (autocrine)、旁泌 (paracrine) 或是內分泌 (endocrine) 的方式 (Pedersen et al., 2003) 而作用到其他的組織。研究亦顯示肌細胞激素可負責骨骼肌、免疫系統與其他器官組織之間的對話與聯繫，主要與代謝及抗發炎相關的作用有關連性，並調控運動所產生的生理適應現象，形成許多有助健康的功效 (Benatti & Pedersen, 2015; Karstoft & Pedersen, 2016)。

參、肌細胞激素種類與功能

肌細胞激素產生的種類與含量受到不同運動的特性及強度所影響，其中與免疫系統功能相關的肌細胞激素如：介白素-6 (Interleukin-6, IL-6)、IL-7 及 IL-15 等特別受到關注，過去研究發現阻力訓練後使 IL-6 及 IL-15 增加 (Nielsen & Pedersen, 2007; Riechman, Balasekaran, Roth, & Ferrell, 2004)，由這些肌細胞激素的作用方式，顯示出骨骼肌因可分泌出相關細胞激素，進而具有調節免疫系統的能力。

一、IL-6

IL-6 是最早被發現、也是由骨骼肌收縮後所分泌出最重要的肌細胞激素之一，其最主要的功能是促進骨骼肌內葡萄糖代謝並調節肌肉衛星細胞 (satellite cells)，以協助肌纖維細胞再生，使得運動後的骨骼肌達到生理恆定 (Munoz-Canoves, Scheele, Pedersen, & Serrano, 2013)。

1. IL-6 與免疫反應的相關性

除了由收縮的骨骼肌產生之外，IL-6 也是巨噬細胞活化後所釋放出的主要細胞激素之一，IL-6 可以在促發炎 (pro-inflammatory) 或是抗發炎 (anti-inflammatory) 的免疫反應過

程扮演不同的角色 (Almuraikhy et al., 2016; Pal, Febbraio, & Whitham, 2014)。在促發炎反應時，IL-6 可以促進 T 細胞增生、促使 B 細胞產生抗體及增加細胞吸附分子 (cell adhesion molecules) 表現，進而誘導更多的淋巴細胞進行移動，達到活化免疫系統的功能 (Schaper & Rose-John, 2015)。但在運動的情況下，IL-6 扮演著抗發炎細胞激素的角色。運動誘發產生的 IL-6 可以抑制促發炎細胞激素腫瘤壞死因子 α (Tumor necrosis factor- α , TNF- α) 及 IL-1 β 的作用 (Steinbacher & Eckl, 2015)。

2. IL-6 與碳水化合物及脂肪代謝的相關性

IL-6 可促進胰臟細胞的生長、降低因代謝壓力所引起的細胞凋亡、誘導胰島素分泌、增加葡萄糖轉運蛋白 4 (Glucose transporter type 4, GLUT4) 表現而提升對胰島素的敏感性 (Ikeda et al., 2016)、促進肝醣分解以維持血糖恆定及脂肪分解進而調控脂肪代謝 (Herder, Dalmas, Boni-Schnetzler, & Donath, 2015; Karstoft & Pedersen, 2016; Kelly, Gauthier, Saha, & Ruderman, 2009) 等作用。

3. IL-6 與控制腫瘤生長的相關性

動物實驗證實運動後產生的腎上腺素及 IL-6 均會使自然殺手細胞的移動與活化增加，尤其在 C57BL/6 黑色小鼠所產生腫瘤移植模式中，當有較多的自然殺手細胞浸潤到腫瘤內，可使腫瘤生長大小減少 50-60% (Pedersen et al., 2016)。IL-6 與自然殺手細胞可能在運動與抗癌之間扮演著橋樑的角色。

二、IL-7

在肌肉衛星細胞分化為肌管 (myotube) 時釋放出 IL-7 (Haugen et al., 2010)，IL-7 可促進多功能造血幹細胞 (multipotent hematopoietic stem cells) 分化為淋巴前趨細胞 (lymphoid progenitor cells)，再分化為 T 及 B 細胞 (Ceredig & Rolink, 2012)。另外，IL-7 可影響運動後產生的體溫升高作用，促使自然殺手細胞調控分配進入腫瘤組織內而毒殺體內癌細胞，進而影響其免疫作用 (Idorn & Hojman, 2016)。

三、IL-15

IL-15 可由許多器官如：心、肺、肝、腎、腦及骨骼肌等細胞所製造 (Grabstein et al., 1994; Quinn, Haugk, & Grabstein, 1995)，過去研究已顯示不管是訓練過後或是未受訓練者在經過運動後，血清中 IL-15 的濃度均提高 (Bazgir, Salesi, Koushki, & Amirghofran, 2015)。

1. IL-15 與免疫反應的相關性

IL-15 具有調控自然殺手細胞及 T 細胞的增生、活化與分布等作用 (Conlon et al., 2015; Marçais et al., 2014; Satoh-Takayama et al., 2010)。同時可以刺激單核球細胞分泌發炎的細胞激素 TNF- α (McInnes, Leung, Sturrock, Field, & Liew, 1997)。

2. IL-15 與碳水化合物及脂肪代謝的相關性

IL-15 可以調控肌細胞攝入葡萄糖 (Krolopp, Thornton, & Abbott, 2016)、維持血中葡萄糖的恆定、提高胰島素敏感性 (Quinn, Anderson, Conner, & Wolden-Hanson, 2013)、分解脂肪組織促進脂肪酸的利用 (Kalinkovich & Livshits, 2017)，與骨骼肌的合成作用有密切關係 (Quinn, Haugk, & Grabstein, 1995)。另外，對於過氧化氫 (hydrogen peroxide) 所造成的氧化壓力具有保護的作用 (Li et al., 2014)，可增加骨骼肌及皮膚細胞內粒線體的活性，延緩皮膚細胞老化 (Crane et al., 2015; Thornton, Krolopp, & Abbott, 2016)。

肆、骨骼肌調控免疫發炎與抗發炎反應

發炎反應與抗發炎作用猶如蹺蹺板互相平衡。免疫系統依據身體防禦、維持恆定等需要，適時的調控以達到抵抗病原菌感染及組織修復的功能。適度運動對身體而言是短暫的壓力並具有提升免疫功能的效果。骨骼肌與其他免疫細胞的不同點在於骨骼肌不會隨著血液移動，僅會在運動時肌肉收縮釋放大量肌細胞激素，進而影響其附近的免疫細胞。

過去許多研究指出在運動中及運動後幾小時內壓力荷爾蒙及發炎反應會短暫降低。若是持續規律運動，則可增加免疫抵抗能力、降低疾病風險及全身性發炎等生理現象 (Duggal, Pollock, Lazarus, Harridge, & Lord, 2018; Lavin et al., 2020; Shanely et al., 2013)。由於運動的過程中，肌肉難免會出現損傷，當組織受損時，體內的纖維細胞或是內皮細胞就會釋放出 IL-33 (Liew, Pitman, & McInnes, 2010)。IL-33 像是一個警報器的角色，藉由傳遞訊號活化 $CD4^+FoxP3^+$ 調節 T 細胞 (T regulatory cells) 以促進肌原細胞的再生 (Kuswanto et al., 2016)；在受損的骨骼肌組織切片染色中可以發現調節 T 細胞，故 IL-33 透過活化調節 T 細胞而促進肌原細胞再生 (Burzyn et al., 2013; Schiaffino, Pereira, Ciciliot, & Rovere-Querini, 2017)。另外 IL-33 能活化免疫反應，可能藉由修補肌肉的發炎與抗發炎過程，同時調節免疫功能 (Liew et al., 2010)。

由分析肌肉發炎病人的病理組織切片亦發現，骨骼肌細胞雖非為典型的抗原呈現細胞 (antigen presenting cells)，卻可以表現第二型主要組織相容性複合體 (class II major histocompatibility complex) 呈現抗原，活化輔助型 T 細胞，肌細胞表面還能出現共同刺激分子 (co-stimulatory molecules) 如：CD40、CD80、CD86、NKG2DL、CTLA、ICAM1 等，及細胞激素接受器如：CCR1、CCR5 等；同時，肌細胞可釋放出許多可溶性分子 (soluble molecules) 如：IL-1 β 、IL-6、IL-15、TNF- α 、IFN- γ 等，這些特性都顯示骨骼肌扮演著調控免疫細胞的功能，調控促發炎或是抗發炎的免疫反應 (Afzali, Muntefering, Wiendl, Meuth, & Ruck, 2018; Watanabe, Kawamoto, Ohtani, & Hara, 2017)。

伍、骨骼肌調控免疫防禦功能

上呼吸道感染 (upper respiratory tract infection, URTI) 可由超過 200 種不同的病毒引起，特別是鼻病毒 (Rhinovirus) 家族及冠狀

病毒家族 (*Coronaviridae*) (Fendrick, Monto, Nightengale, & Sarnes, 2003; Monto, 2002; “National Institute of Allergy,” 2010)。然而，對經常運動（每週運動次數多於 5 次）的人比起坐式生活者（每週運動次數少於 1 次），出現上呼吸道感染症狀的天數減少 43-46%，而且症狀的嚴重程度也減輕 32-41% (Nieman, Henson, Austin, & Sha, 2011)。另有一項針對歐美地區問卷調查，研究 1 千 4 百多萬一般人及 18 萬多癌症患者的休閒運動時間表與 26 種腫瘤發生率的相關性，結果發現休閒運動時間較短與罹患惡性黑色素癌跟前列腺癌具有高度相關性 (Moore et al., 2016)。對癌症而言，組織浸潤的免疫細胞數目可以作為預後良好與否的一個重要指標 (Fridman, Pages, Sautes-Fridman, & Galon, 2012; Remark et al., 2013)。在運動後可以觀察到免疫細胞在循環系統中的數目短暫的增加，可能因而增加保護組織的作用；同時也發現循環中的調節 T 細胞增加，顯示運動可能藉由調控免疫反應以達到預防甚至治療的效果 (Gleeson et al., 2011)。

陸、骨骼肌透過調控免疫系統影響其他代謝功能

許多心血管疾病及代謝症候群都與體內長期慢性發炎的現象有關，在這些病人周邊血液循環中可以發現 IL-6、TNF- α 、C 反應蛋白 (C-reactive protein, CRP) 等發炎指標，這些與疾病如：胰島素阻抗、第二型糖尿病、動脈粥狀硬化 (atherosclerosis) 等有密切的關係。運動可能是透過減緩體內發炎的現象，一直被認為有助於預防或是治療肥胖、第二型糖尿病、肌少症、骨質疏鬆、心臟病、焦慮等疾病，其可能的作用機轉如下：

一、調節碳水化合物代謝

透過骨骼肌收縮後分泌出的各種肌細胞激素（如上述的 IL-6、IL-7、IL-15）作用到不同器官後的現象 (Catoire & Kersten, 2015; Huh, 2018; Pedersen & Febbraio, 2012; Ye, 2015)。具有與碳水化合物

代謝相關能力的肌細胞激素，可能就是運動改善糖尿病的作用因子。

二、增加骨骼肌內抗發炎激素產生

透過運動收縮的骨骼肌釋放抗發炎的細胞激素及降低單核細胞表面的類鐸受體 4 (Toll-like receptor 4, TLR4) 含量，進一步傳遞訊息，以減少單核細胞活化後產生過多的促發炎細胞激素 (Gleeson et al., 2011; Hung & Suzuki, 2017)。

三、降低骨骼肌內堆積的脂肪

運動可提高增加骨骼肌內脂肪酸的利用，導致肌肉內脂肪量下降，而減少吸引吞噬細胞的聚集，降低發炎的程度 (Rayavarapu, Coley, & Nagaraju, 2012)。

四、降低發炎反應

1. 運動會誘發非骨骼肌產生的抗發炎細胞激素如：介白素-1 接受器的拮抗物 (IL-1 receptor antagonist, IL-1ra)，IL-1ra 結合至 IL-1 接受器後並不會啟動活化的訊號，因此藉由與 IL-1 α 及 IL-1 β 競爭 IL-1 接受器而降低全身發炎的程度 (Ostrowski, Rohde, Asp, Schjerling, & Pedersen, 1999)。
2. 運動誘發產生的皮質醇 (cortisol) 具有抗發炎的作用 (Cupps & Fauci, 1982)。此外，兒茶酚胺 (catecholamines) 也會降低多醣體刺激免疫細胞產生的發炎細胞激素如：TNF- α 、IL-1 β (Bergmann et al., 1999)。
3. 運動會降低吞噬細胞表現吞噬細胞發炎性蛋白-1 (macrophage inflammatory protein-1)、C 反應蛋白、TNF- α 、IL-1 β 等發炎相關細胞激素分泌 (Speaker et al., 2014)。

柒、結語

全世界正面臨老化、肥胖及身體活動量不足等危害健康相關的議題，許多研究已證實這些現象將導致免疫細胞不適當的活化並誘發局部發炎，進而出現免疫防禦力降低及代謝相關疾病發生 (Booth, Roberts, & Laye, 2012; Nieman, 2020)。世界衛生組織建議每週 150-300 分鐘的中等強度運動或是 75-150 分鐘高強度運動有益人體健康。此外，針對 18-64 歲年齡層的人，每週 2 次阻力訓練可以具有重建骨骼強度與肌肉力量、增加脂肪燃燒及促進代謝等益處 (Australian Government Department of Health, 2014)。故適當運動，可以調節發炎激素產生，並有效提升黏膜免疫保護力，以提升人體免疫力。這些方式是最好預防威脅疾病的對策之一。

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Skeletal Muscle is a Major Key to Regulate Immune Response

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Abstract

Exercise refers to body activities through skeletal muscle contractions. Skeletal muscles produce various myokines like an endocrine organ, and many myokines promote the proliferation of immune cells while increasing the expression of cell adhesion molecules, thereby enhancing the movement of more immune cells and activating the immune system. Interleukin-6, the first identified important myokine, exhibits inhibition on the activities of pro-inflammatory cytokines that could prevent cardiovascular diseases and metabolic syndrome caused by long-term chronic inflammation. The myokines induced by exercise are also responsible for the cross-talk among skeletal muscle, the immune system and other tissues to maintain physiological stability and health. Past studies have reported that persons maintaining exercise habits experience shorter and less severe periods of upper respiratory tract infection. In conclusion, regular and moderate exercises enhance the regulatory activities of skeletal muscles on the immune system, and is one of the best ways to improve immunity.

Keywords: Skeletal muscle, myokines, immune system, moderate exercise

