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Short Review

Can yoga therapy stimulate stem cell trafficking from bone marrow?

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ABSTRACT

It has been established that mesenchymal stromal cells (MSCs) from bone marrow enter the peripheral circulation intermittently for possible tissue regeneration, repair and to take care of daily wear and tear. This is evident from the detection of MSCs from peripheral blood. The factors governing this migration remain elusive. These MSCs carry out the work of policing and are supposed to repair the injured tissues. Thus, these cells help in maintaining the tissue and organ homeostasis. Yoga and *pranayama* originated in India and is now being practiced all over the world for positive health. So far, the chemical stimulation of bone marrow has been widely used employing injection of colony stimulating factor. However, the role of physical factors such as mechanical stimulation and stretching has not been substantiated. It is claimed that practicing yoga delays senescence, improves the physiological functions of heart and lung and yoga postures make the body elastic. It remains to be seen whether the yoga therapy promotes trafficking of the stem cells from bone marrow for possible repair and regeneration of worn out and degenerating tissues. We cover in this short review, mainly the role of physical factors especially the yoga therapy on stem cells trafficking from bone marrow.

1. Background

It is believed from a long time that healthy spirit results in healthy body [1]. The thought that interactions between the mind and body influence physical health has existed for a long time [2]. The system of the movement and breathing exercises meant to promote the connection between mind and body is yoga. Yoga originated in India, was practiced by ancient Indians and was systemized by the writer Patanjali in the first or second century BC. Yoga consists of breathing exercises called *pranayama* and postures called *asanas* and *mudras*. Yoga has gradually gained popularity, and many of them who practice it say that it improves their health. The bending, stretching, and deep breathing have become a type of oxygen for the modern soul. There are several evidences that prove yoga to be extremely beneficial for patients with back pain, asthma, depression, anxiety and hypertension [3].

Deep breathing modulates oxidative stress. It is established that deep breathing enhances the antioxidant defense status of athletes after exercise, which is accompanied by concomitant decrease in cortisol, increase in melatonin resulting in lesser oxidative stress [4]. A theoretical description by Jerath et al. explains a common physiological mechanism underlying *pranayama* and reveal the role of the respiratory and cardiovascular system on modulating the autonomic nervous system [5].

All the beneficial effects of yoga are well documented in literature. However, the mechanism of action of yoga in improving the organ function is not yet revealed. It is likely that yoga and *pranayama* stimulate stem cell trafficking from the stem cell depots to the peripheral circulation. Pattern formation and remodeling of the organ is facilitated by stem cell trafficking. Hence, we postulate that yoga and *pranayama* act as a cargo to carry stem cells to their destination wherever needed. It is presumed that the yogic practices provide mechanical stimulation for mobilization of stem cells from bone marrow and tissue resident stem cell depots. It is claimed that yoga and related practices result in rapid gene expression alterations which may be the basis for their long term cell biological and higher level health effects [6].

2. Mesenchymal stem cells (MSCs)

MSCs are non-hematopoietic stromal cells present in the bone marrow and most of the connective tissues. They are capable of differentiating into mesenchymal tissue such as bone, cartilage,

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adipose tissue and muscle [7]. MSCs have been found in almost all the post-natal organs as resident stem cell population. It acts as a reserved pool of undifferentiated cells which play an important role in tissue homeostasis. MSCs have their own paracrine secretions. They are well known to have immunomodulatory and angiogenic properties. They are anti-ageing, anti-apoptotic, anti-scarring and antioxidant [8]

3. Stem cell trafficking

Stem cells undergo regulated trafficking from the developmental stages to the adulthood. Their migration is critical in organogenesis of developing organs. It likely contributes postnatally to tissue regeneration [9,10]. It is claimed that undifferentiated populations of stem cells found in the post natal organs are contributed by bone marrow stem cell trafficking [11]. In addition to bone marrow, there are many other organs which exhibit this phenomenon of stem cell trafficking such as endometrium, placenta, breast milk etc. There are three US-FDA approved drugs available for HSPC mobilization: granulocyte colony stimulating factor (G-CSF, Filgrastim), granulocyte/macrophage colony stimulating factor (GM-CSF, Sargramostim), and AMD3100 (Plerixafor). It has been reported that in humans, Hematopoietic Stem Progenitor Cell (HSPC) mobilization can occur without the use of pharmacological agents. For example, the quantity of HSPC in peripheral blood fluctuates throughout the day and is governed by circadian rhythms [12]. Likewise, HSPC content in peripheral blood can increase rapidly and transiently due to acute physiological stress [13]. There is a lot of evidence to support the concept that exercise can mobilize HSPCs into circulation and it is transient but the effect on quantity remains to be elucidated [14,15]. HSPC mobilization following acute exercise is believed to be dependent on age, exercise intensity, and training status. Factors involved in HSPC mobilization reported so far are as follows:

1. Activation of sympathetic nervous system (SNS) – may participate in G-CSF-induced HSPC mobilization.
2. A number of redundant pathways in the niche exist to mediate HSPC mobilization into peripheral circulation.
3. By acute and chronic inflammatory stimuli – Acute exercise-induced inflammation may be a potential mechanism responsible for HSPC mobilization [16].

Moreover, it has been established that beneficial effects of exercise include improving physical fitness and quality of life [17,18]. Thus, exercise may provide a safe, feasible, low-cost approach to enhance HSPC mobilization. An important suggested purpose of this circulation is that various types of such circulating stem cells play a role in “patrolling” peripheral tissues to prevent infections and tissue damage. Based on the earlier evidences it has been investigated and found that very small embryonic-like stem cells (VSELs) also mobilize in parallel with HSPC after endurance exercise. There is a positive effect of exercise on expansion of the primitive pool of stem cells in bone marrow. Since these small cells may differentiate into several types of cells across the three germ layers, their increase may explain, in a novel way, the positive effect of regular exercise on tissue and organ rejuvenation and on improving life quality by directly affecting the pool of the most primitive stem cells residing in adult tissues [19]. Haas et al. reported that the most desirable and beneficial life style pattern includes enhanced physical activity prior to the advance of peripheral arterial disease (PAD) limitations [20]. These observations will be crucial for the development and optimization of novel treatment strategies aimed at prolonging human life span, and physical activity being an important part of this.

However, it is not known that stem cell trafficking is facilitated in all these circumstances by yoga and *pranayama* as there is a scarcity of literature on this particular issue. Hence, it is very important to undertake such a study to prove the relation between yoga and stem cell trafficking. Yoga practice involves stretching, bending and twisting which is likely to release stem cells from bone marrow to peripheral circulation which is required for homeostasis.

4. *Pranayama* as a means to induce intermittent hypoxia (IH)

A short cyclic episode of hypoxia followed by normoxia is the characteristic feature of intermittent hypoxia. It can occur during intense exercise, obstructive sleep apnoea and obstructive lung disease. Increased intracellular reactive oxygen species (ROS) generation during the reoxygenation phase is associated with IH which further affects cell proliferation and neuronal differentiation [21]. In diabetic patients, *pranayama* is likely to play a major role in activating beta cells for insulin production. Transplantation efficacy of mesenchymal stem cells and cardiac progenitor cells in animal models of myocardial infarction has been shown to improve due to hypoxic preconditioning [22]. *Nisshesha rechaka pranayama* may offer benefits through the mechanism of intermittent hypoxia. Disease conditions where self-administered brief intermittent hypoxia can work are type 2 diabetes mellitus, coronary artery disease, osteoarthritis, Parkinson's disease, chronic renal failure and many more [23].

5. Yoga therapy and disease

There are several reports which suggest that yoga therapy may have a synergistic effect with conventional modalities of treatment in preventing cancer progression and recurrences [24]. Possible antidepressant effects with yoga intervention in breast cancer patients undergoing conventional treatment and in reducing postoperative distress and preventing immune suppression following surgery has also been reported [25,26]. A report by Diorio et al., standardized yoga program and an approach to monitoring that are now ready for incorporation in clinical trials. They suggest that future work should include the adaptation of the program to different pediatric populations and clinical settings [27]. It has been reported that increased telomerase activity and stem cells count in peripheral blood from mind and body therapies (MBT) retreat participants that may lead to increased longevity and better quality of life at latter age [28]. Yoga, massage and Reiki decrease stress and anxiety, improve mood and enhance cancer center patrons' perceived overall health and quality of life [29]. Yoga has beneficial effects on various health conditions. The available evidence suggests that yoga helps in lowering oxidative stress and blood pressure; enhances pulmonary and autonomic function, mood, sleep, and quality of life; and reduces medication providing benefits to adult patient with type 2 diabetes mellitus [30,31]. There are evidences that yoga practice is generally effective in reducing body weight, blood pressure, glucose level and high cholesterol. However, only few studies examined long-term adherence [32].

6. Proposed hypothesis

We hypothesize that practicing yoga stimulates the bone marrow stem cells (both hematopoietic and mesenchymal stem cells) trafficking to the peripheral blood. These circulating stem cells then help in reduction of inflammation, prevent apoptosis, help in restoring the lost cells and delay senescence. We further state that the combination of yoga with *pranayama* exposes the