Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Gautam et al., J Mol Genet Med 2018, 12:2
DOI: 10.4172/1747-0862.1000351

Short Communication Open Access

A Possible Link between Dysregulated Mitochondrial Calcium Homeostasis and Citrullination in Rheumatoid Arthritis

Gautam S, Goswami A, Chaurasia P and Dada R*

All India Institute of Medical Sciences, New Delhi, India

***Corresponding author:** Dr. Rima Dada, All India Institute of Medical Sciences, New Delhi, India, Tel: 011 2658 8500; E-mail: rima_dada@rediffmail.com

Rec date: April 19, 2018; **Acc date:** May 16, 2018; **Pub date:** May 21, 2018

Abstract

Rheumatoid arthritis (RA) is characterized by citrullination of peptides and proteins mediated by calcium-dependent peptidyl arginine deiminase enzymes (PADs). Various mechanisms of intracellular and extracellular protein citrullination have been elucidated so far. Here, we highlight one more important possible mechanism that could lead to intracellular citrullination due to dysregulated mitochondrial Ca^{2+} homeostasis i.e., inability of mitochondrial uptake of Ca^{2+} during physiological signaling and triggering the generation of autoimmune disease. Spontaneous secretion of intracellular PAD may be the result of high cytosolic Ca^{2+} due to a disturbance in mitochondrial calcium homeostasis secondary to oxidative damage without any compromise to the cell membrane. Various environmental triggers like air pollutants also induce oxidative stress (OS) which may compromise the mitochondrial integrity and disturb Ca^{2+} homeostasis. Adoption of simple lifestyle modification like yoga and meditation optimizes reactive oxygen species (ROS) levels and maintains mitochondrial integrity by increasing COX activity, thus may curb citrullination process and its sequelae.

Keywords: Calcium homeostasis; Citrullination; Mitochondrial integrity; Peptidyl Arginine Deaminases (PAD); Rheumatoid arthritis; Yoga and meditation

Introduction

Citrullination is an essential contributor to the pathogenesis of rheumatoid arthritis (RA). This post-translational conversion of arginine to citrulline residues requires peptidyl arginine deiminase enzymes (PADs) which are calcium-dependent. Under physiological conditions, calcium stimulation is required to activate the mostly inactive PADs resulting in citrullination of a number of structural proteins e.g., vimentin, fibrinogen, filaggrin, and keratin and proteins involved in the regulation of gene transcription e.g., histones [1]. Hence, the enzymatic activity of PADs may impact gene expression by directly citrullinating transcription factors or by regulating histones and thus impact the epigenome. Recently, it has been reported that hypoxia promotes citrullination and PAD production in human fibroblast-like synoviocytes [2]. Although, the mechanisms promoting citrullination in RA are not fully elucidated but heightened citrullination propagates inflammation in an NF-κB-dependent expression of IL-1β and TNFα [3]. Zhou Y et al. highlights novel pathways of extracellular protein citrullination, cellular localization of calcium (Ca^{2+}) dependent peptidyl arginine deiminases (PAD) and their activity in physiological and pathological conditions. This finding also sheds light upon mechanisms responsible for intracellular protein citrullination which are distinct from the ones mediated by PAD activation via Ca^{2+} influx due to the compromised cell membrane [4]. Various other pathologies have also been associated with the abnormal protein citrullination like multiple sclerosis, Alzheimer's disease, prion diseases, psoriasis as well as cancer [5-8].

Millimolar Ca^{2+} levels are required by intracellular PAD activity, but how citrullination takes place even in the presence of an intact cell membrane remains uncertain. One possibility could be dysregulation of mitochondrial Ca^{2+} homeostasis i.e., inability of mitochondrial uptake of Ca^{2+} during physiological signaling [9]. Mitochondria play a crucial role in different intracellular pathways of signal transduction, ranging from energy production to cell death. The fine modulation of mitochondrial Ca^{2+} homeostasis plays a fundamental role in various pathophysiological processes. It regulates different cell processes controlled by buffering intracellular cytosolic Ca^{2+} as well as exerts a positive role on oxidative metabolism within mitochondria by regulating Ca^{2+} dependent Krebs' cycle enzymes [10]. However, excessive mitochondrial Ca^{2+} entry consequent to stress stimuli causes opening of the mitochondrial permeability transition pore (mPTP) and release of proapoptotic factors which eventually lead to cell death [11]. The mPTP is voltage-gated inner membrane channel which is activated by matrix calcium overloading and reactive oxygen species (ROS) [12]. Full opening of the mPTP results in increased production of mitochondrial reactive oxygen species (mROS) and release of most matrix metabolites including mROS, calcium, NAD^+, and glutathione. As a result, the mitochondrial membrane potential collapses, oxidative phosphorylation and mitochondrial metabolism are inhibited, the matrix swells, and on prolonged opening the outer membrane ruptures, releasing intermembrane space proteins [13]. Prolonged pore opening in a large number of mitochondria in the cell can lead to cell death by necrosis or similar pathways.

Discussion

Activation of mPTP by mitochondrial calcium overloading and mROS is seen enhanced during aging and in aging-associated degenerative diseases like depression, osteoarthritis, RA [14]. The oxidative damage to mitochondria is more severe and persistent than damage to nuclear DNA. The process of immunosenescence is accelerated and occurs prematurely in RA [15]. There is accelerated telomere length attrition in antigen-unprimed naive T cells of RA patients due to inefficient telomere maintenance resulting in loss of telomeres, unraveling of heterochromatin, low expressions of DNA

repair nucleases like MRE11A, changed the expression of cell-cycle regulators which leads to accumulation of T cell aging [16]. Oxidative stress (OS) is responsible for the fragmentation of nuclear/mitochondrial DNA, increased oxidative DNA damage, inefficient DNA mismatch repair system and accumulation of DNA adducts like 8-oxo-hydroxy-7,8-dihydro-2'-deoxyguanosine, 1,N(6)-etheno-2'-deoxyadenosine, and heptanone-etheno-2'-deoxycytidine which results in progression of autoimmune disease like RA [17]. Excessive physiological buffering capacity due to ROS generation during respiratory bursts results in OS. There is perturbation in mitochondrial homeostasis leading to excessive ROS production, impaired mitochondrial dynamics, electron transport chain defects, bioenergetics imbalance and increased AMPK activity, decreased mitochondrial NAD^+ and altered metabolism, and mitochondrial calcium accumulation. Such mitochondrial signals activate p53/p21 and/or p16/pRb pathways resulting in cellular senescence [18]. Oxidative damage to calcium transporters leads to calcium overload and hence inducing more frequent opening of mPTP. Intracellular Ca^{2+} levels in normal cells are much lower than the optimal Ca^{2+} levels required for PAD activation. Hence, it has been proposed that PAD activation occurs only during cell death or necrosis when PAD enzymes leak out into the extracellular matrix from dying cells, or vice versa, with the high Ca^{2+} concentration activating PADs [19].

Hence, spontaneous secretion of intracellular PAD may be the result of high cytosolic Ca^{2+} due to a disturbance in mitochondrial calcium homeostasis secondary to oxidative damage to mitochondria and flares of RA is seen with increased environmental exposure especially air pollution. Air pollutants also induce OS which may compromise the mitochondrial integrity and disturb Ca^{2+} homeostasis. Mitochondria are the powerhouse organelle, a place where oxidative metabolism takes place, which plays a pivotal role in health and disease. Most of the mitochondrial activities are driven in a Ca^{2+} dependent manner, in turn affecting the activities of various Ca^{2+} dependent enzymes like PADs. Development of specific drugs that act on mitochondrial Ca^{2+} homeostasis is being developed which may open the way to new biochemically designed therapeutic approaches in the treatment of several disabling disorders like RA. Studies in our laboratory have shown yoga-based lifestyle intervention (YBLI) improves mitochondrial integrity as is evident by increasing COX activity, reducing OS, upregulating the total anti-oxidant capacity and telomerase enzymes, which both aid in maintenance of telomere length and genomic stability, thus reducing and delaying onset of age-related chronic diseases and complex lifestyle disorders [20-23]. Also, YBLI reduces the levels of acute phase reactants like CRP, pro-inflammatory cytokines, OS levels in RA [24].

Conclusion

The ongoing studies in our laboratory on the impact of yoga and meditation have shown significant upregulation in the expression of antioxidant, anti-inflammatory genes, genes of cell cycle control, DNA repair genes and elevation of tolerogenic molecules which both aid in immune-modulation and reversal of autoimmunity. Improvement in mitochondrial integrity with normal Ca^{2+} levels by maintaining homeostasis, thus prevent activation of PAD and citrullination of tissue fibrinogen. This may prevent numerous sequelae of excessive citrullination and dysregulated gene expression. Thus, we hypothesize that activation of PAD may be due to loss of mitochondrial integrity secondary to OS. OS can be induced due to various exogenous and endogenous factors. Majority of factors that induce oxidative stress are modifiable like quitting smoking, decreasing intake of fast nutritionally depleted processed food, minimizing alcohol consumption, minimize exposure to xenobiotics and insecticides and pesticides and adopt simple mind body stress reduction techniques to delay accelerated aging and improve mitochondrial integrity. Thus, simple lifestyle intervention may maintain optimal ROS levels, mitochondrial integrity, Ca^{2+} homeostasis and prevent activation of PADs and thus reduce the incidence/severity of RA.

Author Contributions

RD and SG conceived the idea behind this commentary; SG wrote the manuscript; SG, AG and PC generated experimental data and; RD finalized the article.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This study was funded by Science and Technology of Yoga and Meditation (SATYAM) (SR/SATYAM/55/2016), Government of India, Ministry of Science and Technology, Department of Science and Technology (DST).

References

1. Wang S, Wang Y (2013) Peptidylarginine deiminases in citrullination, gene regulation, health and pathogenesis. Biochim Biophys Acta 1829: 1126-1135.
2. Yu R, Li C, Sun L, Jian L, Ma Z, et al. (2018) Hypoxia induces production of citrullinated proteins in human fibroblast-like synoviocytes through regulating HIF1alpha. Scand J Immunol 87: e12654.
3. Sun B, Dwivedi N, Bechtel TJ, Paulsen JL, Muth A, et al. (2017) Citrullination of NF-kappaB p65 promotes its nuclear localization and TLR-induced expression of IL-1beta and TNFalpha. Sci Immunol 2: 1-2.
4. Zhou Y, Chen B, Mittereder N, Chaerkady R, Strain M, et al. (2017) Spontaneous secretion of the citrullination enzyme PAD2 and Cell surface exposure of PAD4 by neutrophils. Front Immunol 8: 1200.
5. Lillico R, Zhou T, Ahmad KT, Stesco N, Gozda K, et al. (2018) Increased post-translational lysine acetylation of myelin basic protein is associated with peak neurological disability in a mouse experimental autoimmune encephalomyelitis model of multiple sclerosis. J Proteome Res 17: 55-62.
6. Ishigami A, Masutomi H, Handa S, Nakamura M, Nakaya S, et al. (2015) Mass spectrometric identification of citrullination sites and immunohistochemical detection of citrullinated glial fibrillary acidic protein in Alzheimer's disease brains. J Neurosci Res 93: 1664-1674.
7. Jang B, Ishigami A, Maruyama N, Carp RI, Kim YS, et al. (2013) Peptidylarginine deiminase and protein citrullination in prion diseases: Strong evidence of neurodegeneration. Prion 7: 42-46.
8. Witalison EE, Thompson PR, Hofseth LJ (2015) Protein arginine deiminases and associated citrullination: Physiological functions and diseases associated with dysregulation. Curr Drug Targets 16: 700-710.
9. Giorgi C, Agnoletto C, Bononi A, Bonora M, De Marchi E, et al. (2012) Mitochondrial calcium homeostasis as potential target for mitochondrial medicine. Mitochondrion 12: 77-85.
10. Rao VK, Carlson EA, Yan SS (2014) Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. Biochim Biophys Acta 1842: 1267-1272.

11. Briston T, Roberts M, Lewis S, Powney B, Szabadkai G (2017) Mitochondrial permeability transition pore: sensitivity to opening and mechanistic dependence on substrate availability. Sci Rep 7: 10492.
12. Bernardi P, Forte M (2007) The mitochondrial permeability transition pore. Novartis Found Symp 287: 157-164.
13. Zorov DB, Juhaszova M, Sollott SJ (2014) Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 94: 909-950.
14. Rottenberg H, Hoek JB (2017) The path from mitochondrial ROS to aging runs through the mitochondrial permeability transition pore. Aging Cell 16: 943-955.
15. Weyand CM, Yang Z, Goronzy JJ (2014) T-cell aging in rheumatoid arthritis. Curr Opin Rheumatol 26: 93-100.
16. Li Y, Shen Y, Hohensinner P, Ju J, Wen Z, et al. (2016) Deficient activity of the nuclease MRE11A induces t cell aging and promotes arthritogenic effector functions in patients with rheumatoid arthritis. Immunity 45: 903-916.
17. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N (2016) Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PLoS One 11: e0152925.
18. Ziegler DV, Wiley CD, Velarde MC (2015) Mitochondrial effectors of cellular senescence: Beyond the free radical theory of aging. Aging Cell 14: 1-7.
19. Gazitt T, Lood C, Elkon KB (2016) Citrullination in rheumatoid arthritis-A process promoted by neutrophil lysis? Rambam Maimonides Med J 7: 1-3.
20. Tolahunase M, Sagar R, Dada R (2017) Impact of yoga and meditation on cellular aging in apparently healthy individuals: A prospective, open-label single-arm exploratory study. Oxidat Med Cellu Longev 2017: 1-9.
21. Bisht S, Faiq M, Tolahunase M, Dada R (2017) Oxidative stress and male infertility. Nat Rev Urol 14: 470-485.
22. Kumar M, Tanwar M, Faiq MA, Pani J, Shamsi MB, et al. (2013) Mitochondrial DNA nucleotide changes in primary congenital glaucoma patients. Mol Vis 19: 220-230.
23. Tolahunase MSR, Faiq M, Dada R (2018) Yoga and meditation-based lifestyle intervention increases neuroplasticity and reduces severity of major depressive disorder: A randomized controlled trial. Restora Neurol Neurosci 2018: 1-20.
24. Gautam S, Kumar U, Kumar A, Chaudhary S, Dada R (2017) Yoga and meditation-based lifestyle intervention on rheumatoid arthritis: A pilot study. J Anat Soc India 66: S45.