Molecular Science

AIMS Molecular Science, 13(1): 1–9.
DOI: 10.3934/molsci.2026001
Received: 09 September 2025
Revised: 18 November 2025
Accepted: 25 November 2025
Published: 12 January 2026

https://www.aimspress.com/journal/Molecular

Commentary

Focal adhesion kinase activation plays a critical role in the restoration of simulated microgravity-inhibited osteoblast differentiation by triggering transcriptional Wnt/B-Catenin-BMP2-COL1 and metabolic SIRT1-PGC1a-CPT1A pathways

Eric Zhao[1,2], Zhaojia Wu[1,2] and Jim Xiang[1,2,*]

[1] Research Unit, Saskatchewan Cancer Agency, 20 Campus Drive, Saskatoon, Saskatchewan S7N 4H4, Canada
[2] Division of Oncology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 5E5, Canada

* **Correspondence:** Email: jim.xiang@usask.ca; Tel: +13069667039.

Abstract: Background: Aerospace microgravity (AMG) poses a major threat during spaceflight, impairing osteoblast differentiation (OBD) and causing bone loss. To replicate AMG conditions for ground-based experimental procedures, simulated microgravity (SMG) has been implemented to explore the molecular mechanisms of AMG-induced alterations in osteoblast differentiation. However, SMG's metabolic implications contributing to defective osteoblast differentiation remain unexplored. **Methods**: To investigate this, we investigated effects of SMG on pre-osteoblast MC3T3-E1 cells using Western-blotting to analyze expression of metabolic regulators and Seahorse assays to characterize cellular metabolism. The cytotoxic necrotizing factor-1 (CNF1), an activator of focal adhesion kinase (FAK), was applied to assess its ability to modulate SMG-inhibited OBD. **Results**: Our results showed that, besides its established inhibition of FAK and the Wnt/β-catenin signaling cascade, SMG also induced a metabolic shift from fatty acid oxidation (FAO) to glycolysis by decreasing mitochondrial content and reducing expression of metabolic regulators [sirtuin-1 (SIRT1), peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), and carnitine palmitoyl transferase-1α (CPT1A)] that are critical for mitochondrial biogenesis and FAO capacity. CNF1 exposure was found to counteract the SMG's inhibitory influence by upregulating expression of above metabolic regulators and restoring mitochondrial content and FAO as the primary cellular metabolism and thereby rescuing OBD.

Altogether, our findings emphasize that FAK activation plays a critical role in restoration of SMG-inhibited osteoblast differentiation by triggering transcriptional Wnt/B-Catenin-BMP2 (bone morphogenic protein-2)-COL1 (type-1 collagen) and metabolic SIRT1-PGC1a-CPT1A pathways. **Conclusion**: Our data shed light on FAK as a potential therapeutic target to mitigate SMG-driven bone-loss for astronauts and attenuate bone defectiveness for clinical osteoporosis.

Keywords: Osteoblast metabolism; Simulated microgravity; FAK; CNF-1; Wnt/β-catenin; BMP2; COL1; SIRT1; PGC-1α; CPT1A

Abbreviations

ALP: alkaline phosphatase
AMG: Aerospace microgravity
AMPK: AMP-activated protein kinase
AQP9: aquaporin-9
BMP2: bone morphogenetic protein-2
CNF1: The cytotoxic necrotizing factor-1
COL1: type I collagen
CPT1A: carnitine palmitoyl transferase-1α
ECAR: extracellular acidification rate
ECM: extracellular matrix
ERK: extracellular signal-regulated kinase
FAK: focal adhesion kinase
FAO: fatty acid oxidation
FAs: Focal adhesions
HU: Hindlimb unloading
IAPs: intracellular adaptor proteins
LEF: lymphoid-enhancing-binding factor
MSCs: mesenchymal stem cells
mTORC1: mechanistic target of rapamycin complex-1
OBD: osteoblast differentiation
OCR: oxygen consumption rate
OXPHOS: oxidative phosphorylation
PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α
PPARγ: proliferator-activated receptor-γ
Rho: Ras homolog
RPM: random positional machine
SMG: stimulated microgravity
TCF1: T-cell factor-1

1. Introduction

Astronauts encounter a range of stressors that can have adverse effects on their physiological well-being during spaceflight explorations [1]. In particular, aerospace microgravity (AMG) poses a prominent threat to bone homeostasis as it inhibits osteoblast differentiation (OBD), leading to decreased bone mass and osteopenia [2,3]. To replicate AMG conditions for ground-based experimental procedures, simulated microgravity (SMG) has been implemented to explore the molecular mechanisms of AMG-induced alterations in osteoblast differentiation.

In regulating OBD and skeletal homeostasis, the Wnt/β-catenin pathway plays a prominent role in these processes [4]. Upregulation of Wnt/β-catenin leads to the downregulation of glycogen synthase kinase-3β, resulting in the hypo-phosphorylation of β-catenin, further stabilizing the β-catenin protein since it concentrates in the cytosol before localizing in the nucleus [4,5]. When in the nucleus, β-catenin binds to the transcription factors lymphoid-enhancing-binding factor (LEF) and T-cell factor-1 (TCF1), leading to the increased expression of the osteoblast maturation markers such as bone morphogenic protein-2 (BMP2) and type-1 collagen (COL1) [6,7]. Osteoblasts also enhance the expression of alkaline phosphatase (ALP), an enzyme responsible for the regulation of the mineralization and calcification of bones [8].

It has been found that osteogenic differentiation of bone marrow mesenchymal stem cells (MSCs) can also be inhibited through alterations in cellular energy metabolism [9]. Specifically, SMG has been reported to impair OBD by inhibiting fatty acid oxidation (FAO), while other studies demonstrated that SMG downregulates the NAD+-dependent histone deacetylase sirtuin-1 (SIRT1) and diminishes oxidative phosphorylation (OXPHOS), resulting in suppressed osteogenesis in MSCs [10,11]. Complementary findings have further revealed that the restoration of SIRT1 expression and OXPHOs activity reversed the SMG-induced inhibitory effects [12]. However, the precise impact of SMG on osteoblast energy metabolism and its contribution to defective OBD remains understudied.

Focal adhesions (FAs) are formed from the interactions between cell surface integrins and the extracellular matrix (ECM), enabling cells to sense and adapt to external biochemical and mechanical cues [13]. By anchoring the cytoskeleton to ECM, these specialized contact sites act as the central point of force transmission by converting forces generated by actin filaments and contractile myosin into cell movement [14]. FAs are multiprotein structures that are primarily built from a multitude of structural and mechano-sensing macromolecules, such as α/β-integrin transmembrane receptors, intracellular adaptor proteins (IAPs) consisting of scaffolds paxillin, vinculin, and talin, and IAP-associated signaling proteins such as focal adhesion kinase (FAK) and Ras homolog gene (Rho) family GTPases [15]. Within this network, FAK plays an especially vital role, concurrently acting as a scaffold that organizes other FA substituents and as a signaling hub that triggers various downstream pathways such as mechanistic target of rapamycin complex-1 (mTORC1) and extracellular signal-regulated kinase (ERK1/2) through its interactions with paxillin and Src [16].

We previously investigated SMG's effect on tumor cell biology using a mouse melanoma BL6-10$_{OVA}$ cell line and demonstrated that SMG drastically reduced FA formation, resulting in decreased expression of FAK and declined tumor cell proliferation, adhesion and invasiveness [17], and increased tumor cell apoptosis [18]. Interestingly, the addition of FAK activator cytotoxic necrotizing factor-1 (CNF1), an *Escherichia coli* toxin, to SMD-treated tumor cell culture resumed tumor cell biological activity through AMP-activated protein kinase (AMPK) and mTORC1 signaling [17], rescuing SMG-induced tumor cell apoptosis through ERK1/2 and mTORC1/NF-κB signaling [18].

This indicated that FAK activation is central in the counteraction of SMG-inhibited tumor cell functional alterations. FAK was reported to control OBD and bone regeneration [19]. Therefore, we assumed that FAK activation may also control the Wnt/β-catenin-BMP2-COL1 pathway to restore SMG-inhibited OBD.

2. FAK activation plays a critical role in restoring SMG-inhibited OBD by triggering the transcriptional Wnt/β-Catenin-BMP2-COL1 pathway

It has been reported that SMG inhibits OBD and induces bone loss via the inhibition of the Wnt/β-catenin pathway [20]. To investigate whether FAK activation controls the Wnt/β-catenin-BMP2-COL1 pathway to restore SMG-inhibited OBD, a three-dimensional clinostat random positional machine (RPM) was utilized to simulate the SMG (μg) condition for culturing a mouse pre-osteoblast cell line MC3T3-E1, compared to ground (1g) control condition, followed by analysis of cells and cell lysates by fluorescence microscopy and Western blotting, respectively [21]. We demonstrated that SMG not only decreased FA formation but also reduced FAK activity and inhibition of OBD by downregulating Wnt/β-catenin signaling and its downstream targets: BMP2 and COL1 and alkaline phosphatase (ALP) [21], as previously reported [4,6,7]. This further led to decreased ALP activity and impaired *in vitro* cell mineralization capacity, the two hallmarks of defective OBD, compared to ground (1g) control condition. The addition of the FAK activator CNF1 to the SMG-treated MC3T3-E1 cell culture also counteracted SMG's ability to reduce FA formation and FAK activity, down-regulate the Wnt/β-catenin-BMP2-COL1 signaling pathway, and block ALP activity and cellular mineralization [21]. Hindlimb unloading (HU) is a common mouse or rat model for studying SMG-induced bone demineralization *in vivo* [22,23]. Our HU-treated mice demonstrated a significant decrease in tibia trabecular bone density and overall bone loss, compared to control (1g) mice, using mouse tibia trabecular bones measured by 3D-CT scanning and histopathologic analysis [21], as previously described [23,24]. Interestingly, pharmacological activation of FAK by administration of HU-treated mice with CNF1 also restored tibia trabecular bone density in HU-treated mice [21]. Our data thus indicated that FAK activation plays a critical role in restoration of SMG-inhibited OBD by triggering the transcriptional Wnt/B-Catenin-BMP2-COL1 pathway.

3. FAK activation plays a critical role in restoring SMG-inhibited OBD by triggering the SIRT1-PGC-1α-CPT1A pathway

Bone metabolism has a substantial yet underrecognized role in bone remodeling, as osteogenic differentiation is strongly dependent on the metabolic state of the bone cells [25,26]. To illustrate, FAO induces OBD by stimulating β-catenin acetylation [27,28], and mitochondrial oxidative phosphorylation (OXPHOS) influences osteogenic differentiation in MSCs [27,29]. The SIRT1 and proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) are potent regulators of FAO and mitochondrial function [30–32], with SIRT1 particularly being able to promote OBD and bone deposition [33–35]. When PGC-1α is deacetylated by SIRT, its transcription factor properties are upregulated, enabling it to enhance mitochondrial biogenesis by increasing the expression of mitochondrial regulators [31,32]. These regulatory molecules are crucial for mitochondrial functions including glycerol channel aquaporin-9 (AQP9), a glycerol-specific transporter important for fatty acid esterification and fat storage, and carnitine palmitoyl transferase-1α (CPT1A), a key rate-limiting

enzyme for FAO [36–39].

To investigate the mechanism underlying SMG-modified metabolic programming, we performed the same experiments using pre-osteoblast cell line MC3T3-E1 as previously described [21]. We observed that SMG markedly reduced the abundance of the crucial metabolic regulators, including SIRT1, CPT1A, and PGC-1α, relative to the control (1g) condition [40]. The mitochondria, an organelle important for energy synthesis and homeostatic regulation [27–29], were also assessed under SMG conditions. Our results showed that SMG-cultured cells exhibited significantly decreased mitochondrial content compared to the control, further exacerbating SMG's ability to alter metabolic function [40]. Furthermore, the complementary Seahorse assay revealed that SMG induced a distinct metabolic reprogramming, characterized by elevated extracellular acidification rate (ECAR), reduced oxygen consumption rate (OCR), and diminished FAO [40]. Collectively, these findings demonstrate that SMG reduces mitochondrial content and function while promoting a shift from FAO toward glycolysis as the primary source of ATP, thereby impairing the bioenergetic capacity of osteoblasts [40], consistent with a previous study for SMG-induced metabolism switch from FAO to glycolysis in MSCs [41]. In parallel to our previous findings [21], the addition of CNF1 also counteracted SMG's effects on metabolism alteration. We demonstrated CNF1 restored mitochondrial composition, reinstated expression levels of the metabolic regulators (SIRT1, CPT1A, and PGC-1α), and reversed the SMG-associated reprogramming of energy metabolism, reestablishing FAO as the dominant energy pathway over glycolysis, indicating that FAK activation plays a critical role in restoration of SMG-inhibited OBD by triggering the metabolic SERT1-PGC-1α- CPT1A pathway.

4. Conclusions

Altogether, our previous and recent findings [21,40] illustrate SMG's ability to suppress osteoblast differentiation via two convergent pathways: (i) Inhibition of the transcriptional Wnt/β-Catenin-BMP2-COL1 signaling cascade, and (ii) downregulation of the metabolic SIRT1–PGC-1α–CPT1A axis, driving pre-osteoblast MC3T3-E1 cell from its FAO into a glycolytic-dependent metabolism (**Figure 1**). Importantly, FAK activation via CNF1 alleviated these SMG-altered pathways and SMG-inhibited OBD (**Figure 1**), illustrating that FAK activation plays a critical role in the restoration of SMG-inhibited OBD by triggering transcriptional Wnt/β-Catenin-BMP2-COL1 and metabolic SIRT1-PGC-1α-CPT1A pathways. TCF1, as a tolerated pharmaceutical reagent, has been applied to the treatment of rodent neuro diseases [42,43]. In applying these findings to therapeutic interventions, alongside the previously established focus on targeting Wnt/β-catenin signaling [44], our results also shed light on FAK as a potential therapeutic target to mitigate SMG-driven bone loss for astronauts and attenuate bone defectiveness for clinical osteoporosis.

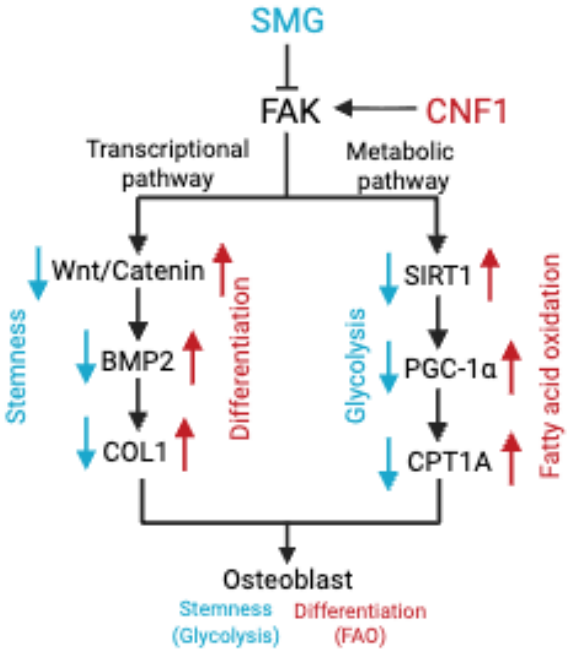

Figure 1. Schematic diagram demonstrating that SMG inhibits FAK, leading to downregulation of FAK-regulated transcriptional Wnt/β-catenin, BMP2 and COL1 factors and metabolic SIRT1, PGC-1α and CPT1A molecules for osteoblast differentiation, respectively. The FAK activator CNF1 reverts the suppressive effects of SMG by activating the above molecules and restoring the osteoblast differentiation. Note: Red arrows represent upregulation and blue arrows denote downregulation.

Author contributions

JX: Conceived the project. EZ and JX: Manuscript writing. ZW: Manuscript editing. All authors have read and approved the final version of the manuscript for publication.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgements

This work was supported by a research grant (*#421820*) from the Natural Sciences and Engineering Research Council of Canada (NSERC) for JX.

Conflict of interest

The authors declare that they have no conflicts of interest in this paper.

References

1. Williams D, Kuipers A, Mukai C, Thirsk R, et al. (2009) Acclimation during space flight: Effects on human physiology. *CMAJ* 180: 1317–1323. https://doi.org/10.1503/cmaj.090628
2. Juhl IV OJ, Buettmann EG, Friedman MA, et al. (2021) Update on the effects of microgravity on the musculoskeletal system. *NPJ Microgravity* 7: 28. https://doi.org/10.1038/s41526-021-00158-4
3. Zhang C, Li L, Jiang Y, et al. (2018) Space microgravity drives transdifferentiation of human bone marrow-derived mesenchymal stem cells from osteogenesis to adipogenesis. *FASEB J* 32: 4444–4458. https://doi.org/10.1096/fj.201700208RR
4. Houschyar KS, Tapking C, Borrelli MR, et al. (2019) Wnt Pathway in bone repair and regeneration–What do we know so far. *Front Cell Dev Biol* 6: 170. https://doi.org/10.3389/fcell.2018.00170
5. Enzo MV, Rastrelli M, Rossi CR, et al. (2015) The Wnt/β-catenin pathway in human fibrotic-like diseases and its eligibility as a therapeutic target. *Mol Cell Ther* 3: 1. https://doi.org/10.1186/s40591-015-0038-2
6. Li Z, Xu Z, Duan C, et al. (2018) Role of TCF/LEF transcription factors in bone development and osteogenesis. *Int J Med Sci* 15: 1415–1422. https://doi.org/10.7150/ijms.26741
7. Gioia M, Michaletti A, Scimeca M, et al. (2018) Simulated microgravity induces a cellular regression of the mature phenotype in *human primary* osteoblasts. *Cell Death Discovery* 4: 59. https://doi.org/10.1038/s41420-018-0055-4
8. Sugawara Y, Suzuki K, Koshikawa M, et al. (2002) Necessity of enzymatic activity of alkaline phosphatase for mineralization of osteoblastic cells. *Jpn J Pharm* 88: 262–269. https://doi.org/10.1254/jjp.88.262
9. Ning K, Liu S, Yang B, et al. (2022) Update on the effects of energy metabolism in bone marrow mesenchymal stem cells differentiation. *Mol Metab* 58: 101450. https://doi.org/10.1016/j.molmet.2022.101450
10. Nguyen HP, Tran PH, Kim KS, et al. (2021) The effects of real and simulated microgravity on cellular mitochondrial function. *NPJ Microgravity* 7: 44. https://doi.org/10.1038/s41526-021-00171-7
11. Liu L, Cheng Y, Wang J, et al. (2020) Simulated microgravity suppresses osteogenic differentiation of mesenchymal stem cells by inhibiting oxidative phosphorylation. *Int J Mol Sci* 21: 9747. https://doi.org/10.3390/ijms21249747
12. Dai S, Kong F, Liu C, et al. (2020) Effect of simulated microgravity conditions of hindlimb unloading on mice hematopoietic and mesenchymal stromal cells. *Cell Biol Int* 44: 2243–2252. https://doi.org/10.1002/cbin.11432
13. Geiger B, Spatz JP, Bershadsky AD (2009) Environmental sensing through focal adhesions. *Nat Rev Mol Cell Biol* 10: 21–33. https://doi.org/10.1038/nrm2593
14. Stutchbury B, Atherton P, Tsang R, et al. (2017) Distinct focal adhesion protein modules control different aspects of mechanotransduction. *J Cell Sci* 130: 1612–1624. https://doi.org/10.1242/jcs.195362
15. Legerstee K, Houtsmuller AB (2021) A layered view on focal adhesions. *Biology* 10: 1189. https://doi.org/10.3390/biology10111189

16. Sulzmaier FJ, Jean C, Schlaepfer DD. (2014) FAK in cancer: Mechanistic findings and clinical applications. *Nat Rev Cancer* 14: 598–610. https://doi.org/10.1038/nrc3792
17. Tan X, Xu A, Zhao T, et al. (2018) Simulated microgravity inhibits cell focal adhesions leading to reduced melanoma cell proliferation and metastasis via FAK/RhoA-regulated mTORC1 and AMPK pathways. *Sci Rep* 8: 3769. https://doi.org/10.1038/s41598-018-20459-1
18. Zhao T, Li R, Tan X, et al. (2018) Simulated microgravity reduces focal adhesions and alters cytoskeleton and nuclear positioning leading to enhanced apoptosis via suppressing FAK/RhoA-mediated mTORC1/NF-κB and ERK1/2 pathways. *Int J Mol Sci* 19: 1994. https://doi.org/10.3390/ijms19071994
19. Dai ZQ, Wang R, Ling SK, et al. (2007) Simulated microgravity inhibits the proliferation and osteogenesis of rat bone marrow mesenchymal stem cells. *Cell Prolif* 40: 671–684. https://doi.org/10.1111/j.1365-2184.2007.00461.x
20. Chen Z, Luo Q, Lin C, et al. (2016) Simulated microgravity inhibits osteogenic differentiation of mesenchymal stem cells via depolymerizing F-actin to impede TAZ nuclear translocation. *Sci Rep* 6: 30322. https://doi.org/10.1038/srep30322
21. Fan C, Wu Z, Cooper DML, et al. (2022) Activation of focal adhesion kinase restores simulated microgravity-induced inhibition of osteoblast differentiation via Wnt/β-catenin pathway. *Int J Mol Sci* 23: 5593. https://doi.org/10.3390/ijms23105593
22. Aguirre JI, Plotkin LI, Stewart SA, et al. (2006) Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *J Bone Miner Res* 21: 605–615. https://doi.org/10.1359/jbmr.060107
23. Friedman MA, Zhang Y, Wayne JS, et al. (2019) Single limb immobilization model for bone loss from unloading. *J Biomech* 83: 181–189. https://doi.org/10.1016/j.jbiomech.2018.11.049
24. Bullock WA, Hoggatt AM, Horan DJ, et al. (2019) Expression of a degradation-resistant β-catenin mutant in osteocytes protects the skeleton from mechanodeprivation-induced bone wasting. *J Bone Miner Res* 34: 1964–1975. https://doi.org/10.1002/jbmr.3812
25. Suzuki A, Minamide M, Iwaya C, et al. (2020) Role of metabolism in bone development and homeostasis. *Int J Mol Sci* 21: 8992. https://doi.org/10.3390/ijms21238992
26. Choi IA, Umemoto A, Mizuno M, et al. (2024) Bone metabolism–An underappreciated player. *NPJ Metab Health Dis* 2: 12. https://doi.org/10.1038/s44324-024-00010-9
27. Shares BH, Busch M, White N, et al. (2018) Active mitochondria support osteogenic differentiation by stimulating β-catenin acetylation. *J Biol Chem* 293: 16019–16027. https://doi.org/10.1074/jbc.RA118.004102
28. Kushwaha P, Wolfgang MJ, Riddle RC. (2018) Fatty acid metabolism by the osteoblast. *Bone* 115: 8–14. https://doi.org/10.1016/j.bone.2017.08.024
29. Shen Y, Wu L, Wang J, et al. (2018) The role of mitochondria in methamphetamine-induced inhibitory effects on osteogenesis of mesenchymal stem cells. *Eur J Pharmacol* 826: 56–65. https://doi.org/10.1016/j.ejphar.2018.02.049
30. Cantó C, Gerhart-Hines Z, Feige JN, et al. (2009) AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity. *Nature* 458: 1056–1060. https://doi.org/10.1038/nature07813
31. Jones AWE, Yao Z, Vicencio JM, et al. (2012) PGC-1 family coactivators and cell fate: Roles in cancer, neurodegeneration, cardiovascular disease and retrograde mitochondria–nucleus signalling. *Mitochondrion* 12: 86–99. https://doi.org/10.1016/j.mito.2011.09.009

32. Lin J, Handschin C, Spiegelman BM. (2005) Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab* 1: 361–370. https://doi.org/10.1016/j.cmet.2005.05.004
33. Wang H, Zhang Y, Cao J, et al. (2019) Sirt1 promotes osteogenic differentiation and increases alveolar bone mass via Bmi1 activation. *J Bone Miner Res* 34: 1169–1181. https://doi.org/10.1002/jbmr.3677
34. Wang Y, Chen G, Yan J, et al. (2018) Upregulation of SIRT1 by Kartogenin enhances antioxidant functions and promotes osteogenesis in human mesenchymal stem cells. *Oxid Med Cell Longev* 2018: 1368142. https://doi.org/10.1155/2018/1368142
35. Li M, Yan J, Chen X, et al. (2018) Spontaneous up-regulation of SIRT1 during osteogenesis contributes to stem cells' resistance to oxidative stress. *J Cell Biochem* 119: 4928–4944. https://doi.org/10.1002/jcb.26730
36. Xu A, Leary SC, Islam MF, et al. (2022) Prosurvival IL-7–stimulated weak strength of mTORC1-S6K controls T cell memory via transcriptional FOXO1-TCF1-Id3 and metabolic AMPKα1-ULK1-ATG7 pathways. *J Immunol* 208: 155–168. https://doi.org/10.4049/jimmunol.2100452
37. Ara A, Wu Z, Xu A, Ahmed KA, Leary SC, Islam MF, et al. (2022) The critical role of AMPKα1 in regulating autophagy and mitochondrial respiration in IL-15-stimulated mTORC1^{Weak} signal-induced T cell memory: An Interplay between Yin (AMPKα1) and Yang (mTORC1) energy sensors in T cell differentiation. *Int J Mol Sci* 23: 9534. https://doi.org/10.3390/ijms23179534
38. Cui G, Staron MM, Gray SM, et al. (2015) IL-7-induced glycerol transport and TAG synthesis promotes memory CD8$^+$ T cell longevity. *Cell* 161: 750–761. https://doi.org/10.1016/j.cell.2015.03.021
39. van der Windt GJW, Everts B, Chang CH, et al. (2012) Mitochondrial respiratory capacity is a critical regulator of CD8$^+$ T cell memory development. *Immunity* 36: 68–78. https://doi.org/10.1016/j.immuni.2011.12.007
40. Bai Y, Wu Z, Leary SC, et al. (2025) Focal adhesion kinase alleviates simulated microgravity-induced inhibition of osteoblast differentiation by activating transcriptional Wnt/β-Catenin-BMP2-COL1 and metabolic SIRT1-PGC-1α-CPT1A pathways. *Int J Mol Sci* 26: 1669. https://doi.org/10.3390/ijms26041669
41. Ning K, Liu S, Yang B, et al. (2022) Update on the effects of energy metabolism in bone marrow mesenchymal stem cells differentiation. *Mol Metab* 58: 101450. https://doi.org/10.1016/j.molmet.2022.101450
42. Travaglione S, Loizzo S, Ballan G, et al. (2014) The *E. coli* CNF1 as a pioneering therapy for the central nervus system diseases. *Toxin* 6: 270–282. https://doi.org/10.3390/toxins6010270
43. Tantillo E, Colistra A, Vannini E, et al. (2018) Bacterial toxins and targeted brain therapy: New insights from cytotoxic necrotizing factor 1 (CNF1). *Int J Mol Sci* 19: 1632. https://doi.org/10.3390/ijms19061632
44. Baron R, Gori F (2018) Targeting WNT signaling in the treatment of osteoporosis. *Curr Opin Pharmacol* 40: 134–141. https://doi.org/10.1016/j.coph.2018.04.011

© 2026 the Author(s), licensee AIMS Press. This is an open access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0)