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Evaluation of Synergic Effects of Molybdenum Disulfide Treatment and Near-Infrared Radiation on Human Mesenchymal Stem Cells

Alireza Omidi Farzin[1], Babak Arjmand[2,3], Nastaran Asri[4], Zahra Razzaghi[5*], Farideh Razi[6], Fatemeh Bandarian[7], Reza M Robati[8], Mitra Rezaei[9,10], Reza Vafaee[11], Parnia Rahnamay Farnood[5]

[1]Department of Cardiovascular Surgery, Modarres Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Hematology-Oncology and Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology, and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran
[3]Iranian Cancer Control Center (MACSA), Tehran, Iran
[4]Celiac Disease and Gluten Related Disorders Research Center, Research Institute for Gastroenterology and Liver Disease, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[7]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[8]Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[10]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[11]Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Correspondence to**
Zahra Razzaghi,
Email: z.razaghi@gmail.com

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Abstract

Introduction: Molybdenum disulfide (MoS2), as an anticancer reagent, can absorb near-infrared (NIR) wavelengths in phototherapy. In the present study, the synergic effect of MoS2 (in nanostructure) and NIR radiation on human mesenchymal stem cells (hMSCs) was evaluated via protein-protein interaction (PPI) network analysis.

Methods: Gene expression profiles of hMSCs were extracted from the Gene Expression Omnibus (GEO) database and analyzed via PPI network analysis. The validity of findings was assessed via the Kaplan-Meier Plotter.

Results: FN1, ACTA2, CCL2, CXCL8, FBN1, and LEP genes were selected as hub genes among 121 recognized differentially expressed genes (DEGs) as the targeted genes by the synergic effects of MoS2 and NIR radiation. Kaplan-Meier Plotter analysis demonstrated that FN1 suppression by MoS2 and NIR radiation can significantly increase the overall survival of patients with gastric cancer, lung cancer, ovarian cancer, and myeloma.

Conclusion: In conclusion, findings indicate that the anticancer property of MoS2 is intensified in the condition of NIR radiation. Therefore, MoS2 is a suitable photosensitizer reagent in photodynamic therapy.

Keywords: Human, Mesenchymal stem cell, Near-infrared, Anticancer, Molybdenum disulfide

Introduction

Molybdenum disulfide (MoS2) has a visible-light-responsive photocatalytic property and is used widely in energy conversion and storage.[1] The unique optical, physiochemical, and electrical properties of MoS2 nanostructures led to the application of this material in industry. However, its biological application, especially in tissue engineering, is a new trend.[2] Recently, MoS2 has attracted experts' attention in the field of cancer. Due to the versatile properties of MoS2, it can be used as a specific biomarker identifier and tumor-targeting reagent. MoS2 has a strong optical absorption in the near-infrared (NIR) spectrum, the property that makes it an efficient reagent for NIR-driven phototherapy.[3]

Mesenchymal stem cells (MSCs) are known as the cells with multi-directional differentiation capability

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and play a crucial role in tissue repair, hematopoiesis, and immunomodulation.[4] Since photobiomodulation, as a non-invasive method, can affect cell proliferation, viability, and migration, MSCs are investigated via this method.[5] There are many documents about the association of light phototherapy and gene expression change in the treated samples.[6, 7] A gene expression change study via RNA sequencing showed that NB-UVB phototherapy has a significant effect on inflammatory molecules in patients with lesional psoriasis.[8] photodynamic therapy is a safe and non-invasive treatment against tumors. Investigations revealed that the near-infrared second region (NIR-II), due to its deep penetration and other suitable properties, is a highlighted tool in phototherapy.[9]

Bioinformatics, especially PPI network analysis, as a complementary method, has a considerable impact on genomics and proteomics findings. PPI network analysis showed HSPA5, DDIT3, PTGS2, HMOX1, and GDF15 as the key targeted genes by a NIR laser in 143B cells.[10, 11] By using PPI network analysis, a large number of genes can be screened to find the central genes and also the regulatory interactions between the studied individuals. Hubs are the nodes of the PPI network that make directly high values of interactions with the neighboring genes. Investigations indicate that the hub node plays critical roles in the constructed PPI networks.[12,13] In the present study, the dysregulated genes under the synergic effects of NIR radiation and MoS2 on hMSCs were extracted from GSE141456 and evaluated via PPI network analysis to find the critical individuals. To validate the findings, the role of the top critical gene in patient survival was investigated across several cancer types using the Kaplan-Meier Plotter.

Methods

Data Collection

Since two-dimensional (2D) molybdenum disulfide (MoS2) nanomaterials are sensitive to near-infrared wavelengths (NIR), GSE141456 was extracted from the GEO database to find the synergic effect of 2D MoS2 and NIR radiation. There were the gene expression profiles of four groups of human bone marrow-derived mesenchymal stem cells (hMSCs) in this gene set. The gene expression profiles of the control hMSCs, the hMSCs treated with MoS2 (hMSCs MoS2), the hMSCs treated with NIR (hMSCs NIR), and the hMSCs treated with NIR and MoS2 (hMSC NIR MoS2) were recorded in this gene set (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE141456). More details are presented in the report of Carrow JK et al.[14]

Pre-Evaluation and Statistical Analyses

In the first step, the gene expression profiles of three treated groups were compared separately with the gene expression profiles of control hMSCs by using the GEO2R program. The significant DEGs were identified based on an adjusted *P*-value < 0.05. The significant DEGs of hMSC NIR MoS2 - hMSC analysis, minus the possible significant DEGs of hMSC NIR – hMSC and hMSC MoS2 – hMSC analyses (as the targeted genes via the synergic effect of NIR radiation and MoS2 treatment), were selected for further investigation.

PPI Network Analysis

The DEGs of the synergic effect of NIR radiation and Mos2 treatment were assessed via PPI network analysis by using the STRING database and Cytoscape software. A confidence score of 0.1 was considered to create the PPI network. The hub genes were identified based on a degree value of mean + 2SD (standard deviation). The critical genes were determined based on the amounts of degree value and betweenness centrality via the visualization of a scatter plot.

Kaplan-Meier Plotter Assessment

To validate findings, the role of the top central gene in the survival of patients with ALM, breast cancer, gastric cancer, lung cancer, ovarian cancer, and myeloma was investigated via Kaplan-Meier Plotter analysis.

Gene Ontology Assessment

The critical hubs were evaluated via gene ontology assessment to find the possible relative pathways, biological processes, and molecular functions via the ClueGO plugin of Cytoscape software.

Results

Pre-Evaluation Analysis

The findings indicated that NEFM and ARC were the significant DEGs of hMSC NIR – hMSC, while there were 166 significant DEGs which separated hMSC MoS2 from the hMSC group. After cleaning the data and deleting the uncharacterized individuals, we identified 158 significant DEGs. An assessment revealed that 237 significant DEGs were related to the effect of NIR and MoS2 on hMSCs. A total of 223 cleaned data remained. Since ARC was common in hMSC NIR – hMSC and hMSC NIR MoS2 – hMSCs analyses with approximately the same fold change amount, it was ignored for further assessments. After the deletion of the common genes between hMSC NIR MoS2 – hMSCs and hMSC MoS2 – hMSCs analyses which were characterized by a similar "fold change" difference, 129 DEGs related to the synergic effect of MoS2 and NIR remained.

PPI Network Analysis

The 129 DEGs were included in the PPI network. A total of 121 genes (including 5 isolated DEGs and a main connected component of 116 individuals) were recognized by the STRING database. The network was constructed

with a confidence score = 0.1 and 869 edges. The scatter plot and the degree distribution of nodes are demonstrated in Figures 1 and 2. Six genes, including FN1, ACTA2, CCL2, CXCL8, FBN1, and LEP, were identified based on a cutoff value of degree = 39 (Table 1). These 6 genes appear as the spots with a degree value > 40 in Figures 1 and 2.

Kaplan-Meier Plotter Assessment

The top central gene (FN1) was evaluated via the Kaplan-Meier Plotter. The survival of patients with ALM, breast cancer, gastric cancer, lung cancer, ovarian cancer, and myeloma in the conditions of high and low expression of FN1 was investigated. There was no significant difference between high and low values of FN1 expression in ALM and breast cancer, but the survival of patients with gastric cancer, lung cancer, ovarian cancer, and myeloma decreased in the condition of high-value expression of FN1 relative to the condition of low expression of this gene. The Kaplan-Meier Plots of the effect of the high value expression of FN1 in patients with gastric cancer and myeloma are shown in Figure 3.

Gene Ontology Assessment

Four groups of biological processes and molecular functions were identified for the six critical hubs (Figure 4).

Table 1. List of hub genes from PPI network analysis.

No.	Hub gene	Degree value	Betweenness centrality	Dysregulation
1	FN1	69	0.16	Down-regulated
2	ACTA2	48	0.07	Down-regulated
3	CCL2	43	0.02	Up-regulated
4	CXCL8	43	0.03	Up-regulated
5	FBN1	43	0.04	Down-regulated
6	LEP	41	0.07	Down-regulation

Discussion

The highlighted role of MoS2 in cancer treatment due to its tunable structure is well documented in the literature. This property allows MoS2 to absorb chemotherapeutic drugs with minimal nonspecific cellular death and side effects. Besides this property, MoS2 is used in photothermal and photodynamic therapy.[15] The synergic effects of Mos2 and NIR radiation were studied in the present study. As depicted in Figures 1 and 2, FN1, ACTA2, CCL2, CXCL8, FBN1, and LEP are the hub genes that are targeted by the synergic effect of NIR radiation and MoS2 treatment.

The correlation between the overexpression of fibronectin-1 and the promotion of breast cancer is highlighted in Zhang XX et al's investigation.[16] FN1 is down-regulated in response to NIR radiation and MoS2 treatment. FN1 which is pointed out as the potent hub-bottleneck gene is characterized by the top degree value and betweenness centrality of 69 and 0.16, respectively (see the top spot in Figures 1 and 2). Ashok G et al have introduced FN1 as an essential signaling gene in response to therapeutic intervention in pancreatic cancer.[17] The second hub gene is actin alpha 2, smooth muscle (ACTA2) with a degree value of 48. Based on Park S et al's report, the overexpression of ACTA2 in 567 patients with gastric cancer was associated with overall survival.[18] The down-regulation of ACTA2 by the synergic effect of MoS2 and NIR radiation refers to the efficient inhibition of this gene against cancer promotion. ACTA2 not only appears as the top second hub but also is characterized as the second bottleneck gene (its betweenness centrality is 0.07). The third hub is C-C motif chemokine ligand 2 (CCL2) that is up-regulated by intervention. Chemokine CCL2, which is known as "monocyte chemoattractant protein-1, MCP-1", plays a vital role in the control of infiltration and the migration of macrophages/monocytes.[19] Wang XM et al

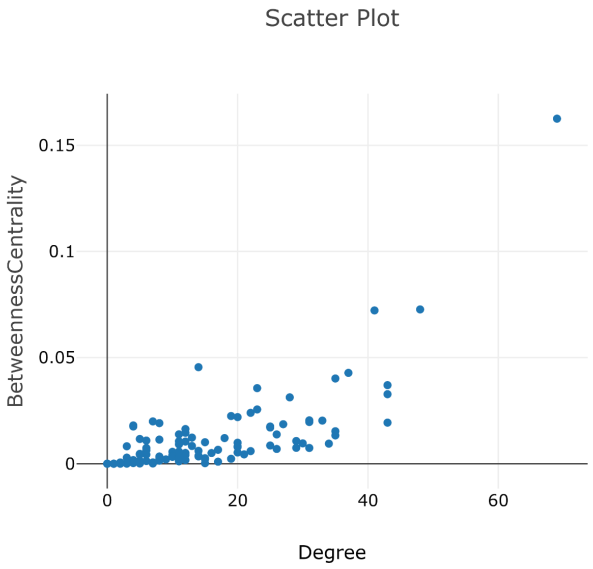

Figure 1. Scatter plot of the PPI network for the 121 DEGs related to the synergic effect of NIR radiation and MoS2 treatment on hMSCs

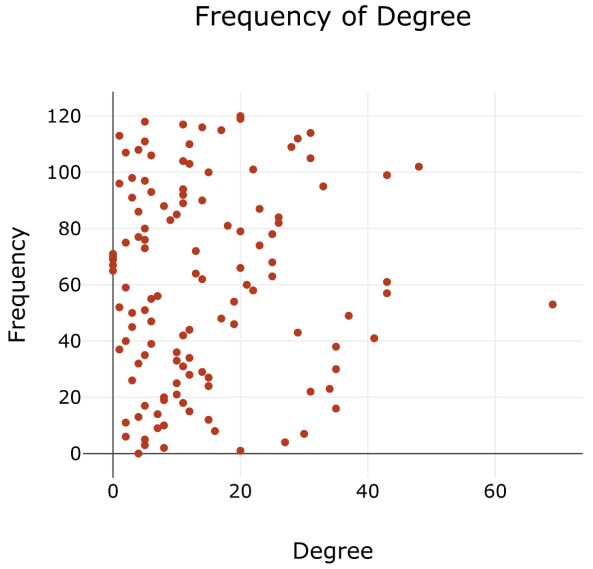

Figure 2. Node degree distribution of the PPI network for the 121 DEGs related to the synergic effect of NIR radiation and MoS2 treatment on hMSCs

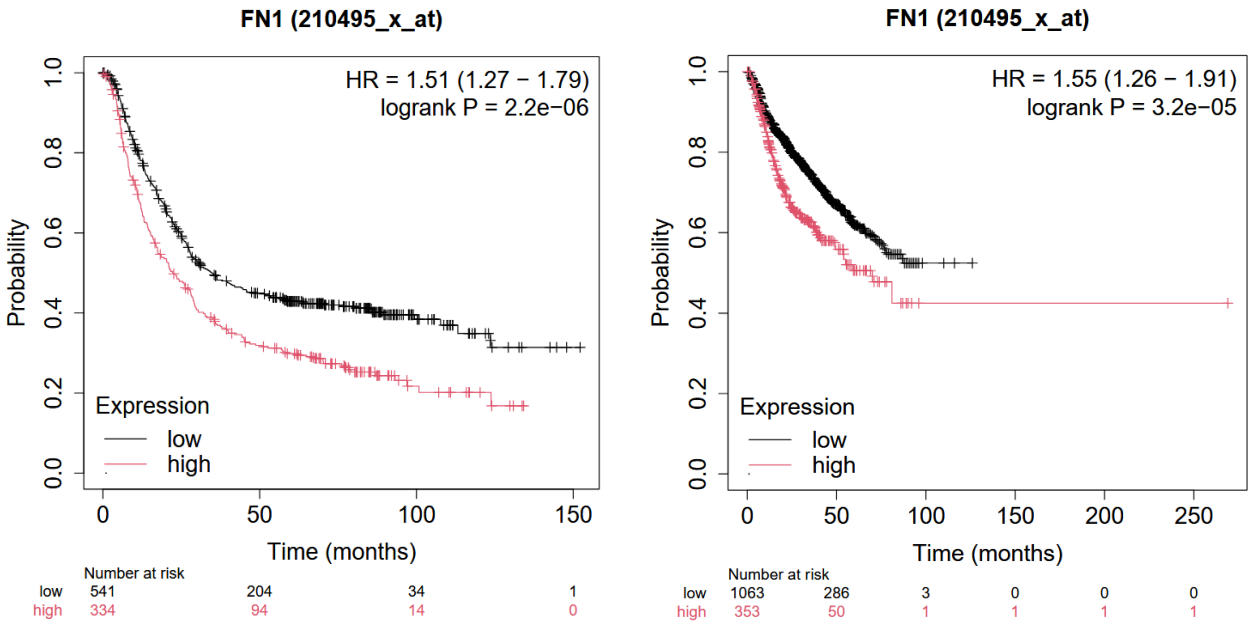

Figure 3. Kaplan-Meier Plots for the effect of high-value expression of FN1 versus a low value in patients with gastric cancer (up) and myeloma (down)

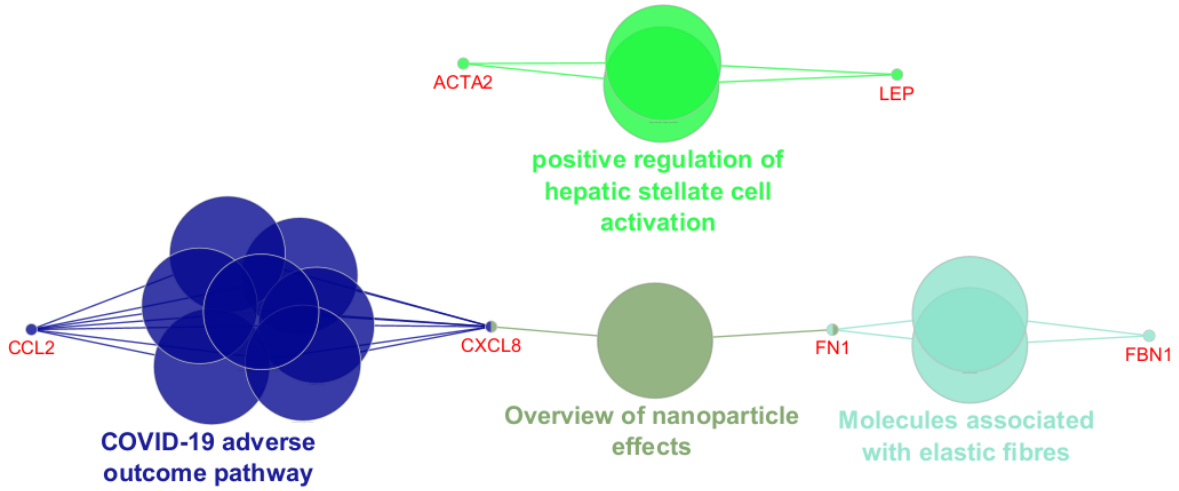

Figure 4. Gene ontology result for six hub genes. The associated genes are presented in red. The biological processes and molecular functions are grouped in four classes and presented in related colors

have reported that IL6, IL8, CCL2, CXCL2, and ANXA1 are up-regulated significantly in tissue injury. A significant correlation between the up-regulation of IL6 and CCL2 is experienced. This molecular event is accompanied by pain intensity.[20] The upregulation of CCL2 in response to MoS2 and NIR application can be considered as the unfavorable side effect of treatment. C-X-C motif chemokine ligand 8 (CXCL8) is the fourth up-regulated hub. It is demonstrated that CXCL2 is involved in inflammatory cell infiltration. It also facilitates the survival of triple-negative breast cancers.[21,22] Similar to the up-regulation of CCL2, the overexpression of CXCL2 versus MoS2 and NIR radiation can be interpreted as a harmful event in this treatment.

Fibrillin-1 (FBN1) is the fifth down-regulated hub. An investigation has indicated that FBN1 up-regulation is accompanied by the early recurrence of ovarian cancer.[23] On the other hand, the overexpression of COL6A1, which is associated with the suppression of invasion, migration, and viability of bladder cancer cell lines, is positively correlated with the expression of FBN1.[24] There are controversial effects of FBN1 in cancer promotion. The last down-regulated hub is the leptin receptor (LEP). The role of leptin in the promotion of proliferation of prostate cancer cells and the inhibition of apoptosis is reported by XuCJ et al[25] The down-regulation of leptin by MoS2 and NIR radiation can be considered a beneficial effect of treatment. As depicted in Figure 1, there are three hubs (including FN1, ACTA2, and LEP) that are characterized by higher values of betweenness centrality. Therefore, targeting FN1, ACTA2, and LEP by the mentioned intervention is the main finding of this study. As discussed above, the down-regulation of these three hub-bottleneck

genes is associated with tumor suppression. To validate findings, the overall survival of patients with ALM, breast cancer, gastric cancer, lung cancer, ovarian cancer, and myeloma in the presence of a higher value of FN1 relative to the lower level of its expression was evaluated. The findings indicate that the survival of patients with gastric cancer, lung cancer, ovarian cancer, and myeloma decreases significantly in the condition of high expression of FN1. Therefore, the down-regulation of FN1 in treated samples refers to the beneficial therapeutic effects of synergic application of MoS2 and NIR radiation. As depicted in Figure 4, interactions between FN1, CCL2, CXCL8, and FBN1 and the related biological terms refer to the important role of this gene set in response to treatment.

Conclusion

In conclusion, the anticancer property of MoS2 is intensified in the condition of NIR radiation. This finding indicates that MoS2 is a suitable photosensitizer reagent in photodynamic therapy. The suppression of FN1, ACTA2, and LEP is the core of the molecular event in this regard. Future experimental investigations will explore the efficiency of the therapeutic method.

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Authors' Contribution

Conceptualization: Alireza Omidi Farzin.
Data curation: Mitra Rezae, Reza Vafaee.
Formal analysis: Zahra Razzaghi.
Investigation: Babak Arjmand, Zahra Razzaghi.
Methodology: Zahra Razzaghi.
Project administration: Reza Vafaee.
Resources: Nastaran Asri, Alireza Omidi Farzin.
Supervision: Reza M Robati.
Writing–original draft: Farideh Razi, Fatemeh Bandarian, Reza M Robati.
Writing–review & editing: Alireza Omidi Farzin, Nastaran Asri, Parnia Rahnamay Farnood.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

This project was approved by the Research Ethics Committee of the Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, with the ethical code of IR.SBMU.LASER.REC.1404.015.

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