IJMCM
Winter 2019, Vol 8, Suppl 1
DOI: 10.22088/IJMCM.BUMS.8.2.30

Review Article

Metabolomics Analysis of Mesenchymal Stem Cells

Parisa Goodarzi[1], Sepideh Alavi- Moghadam[2], Moloud Payab[3], Bagher Larijani[4], Fakher Rahim[5], Kambiz Gilany[6, 7], Nikoo Bana[8], Akram Tayanloo- Beik[2], Najmeh Foroughi Heravani[2], Mahdieh Hadavandkhani[2], Babak Arjmand[2,8*]

1. Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.
2. Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
3. Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
4. Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical sciences, Tehran, Iran.
5. Health Research Institute, Thalassemia and Hemoglobinopathies Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
6. Integrative Oncology Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran.
7. Department of Biomedical Sciences, University of Antwerp, Belgium.
8. Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular- Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.

Submmited 13 March 2019; Accepted 20 May 2019; Published 20 June 2019

Various mesenchymal stem cells as easily accessible and multipotent cells can share different essential signaling pathways related to their stemness ability. Understanding the mechanism of stemness ability can be useful for controlling the stem cells for regenerative medicine targets. In this context, OMICs studies can analyze the mechanism of different stem cell properties or stemness ability via a broad range of current high-throughput techniques. This field is fundamentally directed toward the analysis of whole genome (genomics), mRNAs (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in biological samples. According to several studies, metabolomics is more effective than other OMICs for various system biology concerns. Metabolomics can elucidate the biological mechanisms of various mesenchymal stem cell function by measuring their metabolites such as their secretome components. Analyzing the metabolic alteration of mesenchymal stem cells can be useful to promote their regenerative medicine application.

Key words: Mesenchymal stem cells, metabolic pathways, metabolomics, systems biology

*Corresponding author: Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. Email: barjmand@sina.tums.ac.ir .

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

Two main properties of stem cells are including prolonged self- renewal and multi-potent differentiation capacity which make them ideal candidate for cell therapy and regenerative medicine (1-5). Related to these properties, stem cells share several essential genes and signaling pathways (i.e. Hedgehog, Wnt, Notch, phosphatidylinositol 3-kinase/ phosphatase, and nuclear factor-κB signaling pathways) as stemness ability (6-8). In other word, stem cells can preserve their lineage, interaction with the environment, and cross-talk with adjacent cells to keep a balance between repose, proliferation, and restoration, through stemness ability (9-11). However, understanding the mechanism of stemness ability is challenging (9). According to several studies, stable, safe, and more accessible stem cells are considered as an excellent choice for regenerative medicine. In this context, mesenchymal stem cells (MSCs) (as easily accessible, self-renewable, and multipotent cells with few consideration ethics) have significant efficacy in regenerative medicine. (12-26). Furthermore, recent development in OMICs approaches (technologies for understanding the whole activity of cells, tissues, and organs at the molecular level) specifically metabolomics approaches (extensive analysis of metabolites in cells, tissues, and organs) can increase our understanding about the self-renewal and differentiation mechanisms. On the other hand, analysis of chemical alterations related to natural processes of living cells including growth, environmental adaptation, and differentiation can be provided by metabolomics methods (27-29).

OMICs - based stem cell monitoring

Multi- OMICs approaches including genomics, epigenomics, transcriptomics, proteomics, and metabolomics are functional methods to study stem cell biology and its therapeutic application (Fig.1) (30-32).

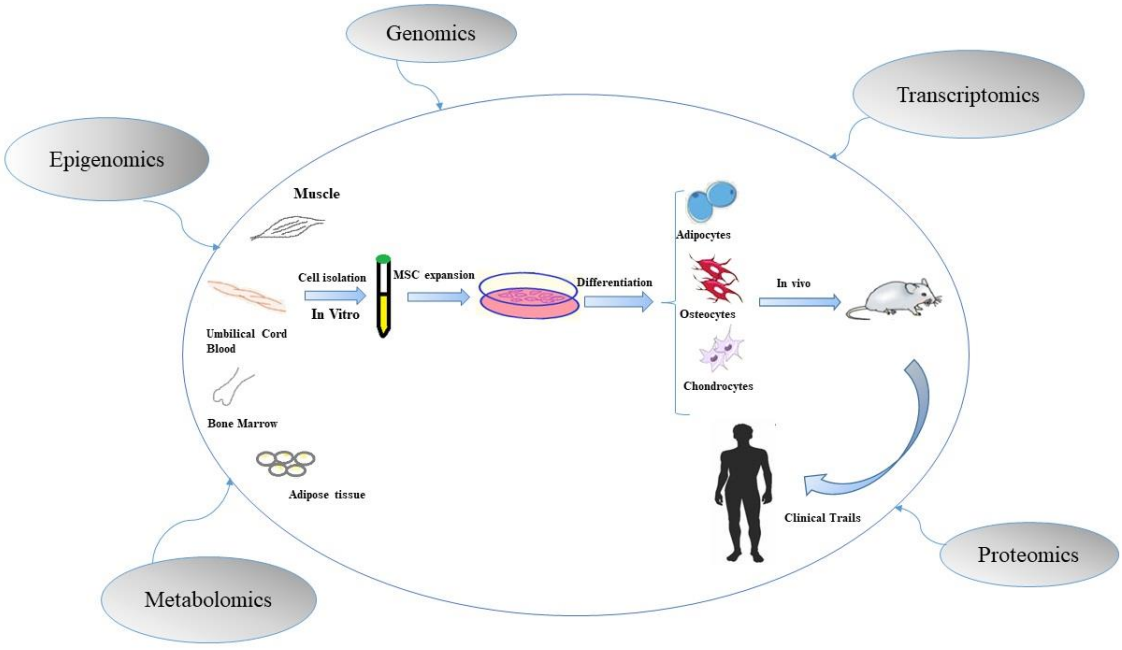

Fig. 1. Based stem cell monitoring. Multi- OMICs approaches are functional methods to study stem cell biology and its therapeutic application through evaluation of molecular mechanisms of stem cells properties and quantification of cellular products (33).

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

At first, human genome project has led to the advancement of genome sequencing and study on DNA by analysis of single nucleotide polymorphisms (SNPs), variation copies, and mutations (34-36). Nowadays, genomics as the most mature approache of OMICs and next generation sequencing (NGS) as the latest technology in this field are used for high-throughput detection and cost effective analysis of biological data (37-40). On the other hand, epigenetic modifications (e.g. methylation and histone acetylation) have an important role in differentiation and development of stem cells (41, 42). The study of heritable modifications (not sequence changes) of DNA is called epigenomics (43, 44). Additionally, qualitative and quantitative transcriptomics can facilitate the investigation of RNAs in stem cells, via molecular and cellular methods such as micro-array and RNA-sequencing (45, 46). It also has a vital role in analyzing key genes and pathways that participate in self-renewal, proliferation, and differentiation of stem cells (47-49). Some transcription factors (related to non-coding RNAs) such as octamer-binding transcription factor 4 (OCT 4) and NANOG can regulate pluripotency feature of stem cells (50, 51). Proteomics tries to evaluate the qualitative and quantitative changes in proteins and identify new markers in stem cell development stages (52, 53). Finally, metabolomics measures and demonstrates the products of metabolism such as amino-acids and fatty-acids. In this respect, metabolomics is an accurate approach to recognize metabolite biomarkers in biological samples (54, 55). Although, application of OMICs, especially metabolomics, for monitoring of stem cell in researches and therapies is in its infancy period, it can be useful to understand different features of cell-based therapy (1, 56).

Stem cells metabolomics

Because of the self-renewal and differentiation properties of stem cells, they can be applied for regenerative medicine, drug screening, toxicity testing, and evaluation of disease phenotypes (57-59). Although they are metabolically inactive population in quiescent state, their metabolic activity increases during differentiation (60). Stem cells niche can preserve them in a quiescent state to maintain their self-renewal ability (61, 62). In other words, morphogens and growth factors in the niche of stem cells can change the regulation of stem cells through numerous metabolic pathways (1, 63, 64). Moreover, molecular mechanisms can regulate differentiation and reprogramming, and also they can control the energy of metabolism in stem cells throughout glycolytic or oxidative phosphorylation (OXPHOS) reactions (1, 65, 66). In other words, changes in glycolysis and OXPHOS have impact on differentiation or reprogramming of stem cells (66-68). Glycolysis and OXPHOS changes can alter the metabolite levels and reduction–oxidation (redox) state (69-71). Subsequently, hypoxia, glycolysis and redox states can affect the homeostasis and regeneration of stem cells (67, 72, 73). For instance, hypoxia has a key role in maintaining undifferentiated state of stem cells by reducing redox state (74-76). For preparing a balance between self-renewal and differentiation ability, the role of redox state can be important (77, 78). Moreover, the increase of reactive oxygen species (ROS) can promote cell differentiation (74, 79). Herein, understanding the mechanism of stem cells (e.g. MSCs) function is momentous for *in vitro* and *in vivo* studies and also the stem cells application in cell therapy.

Metabolomics- based comparison of mesenchymal stem cells

MSCs as multi-potent stem cells can be extracted from different sources. Their intrinsic properties have drawn the attention for developing more comprehensive studies (13, 14). Moreover, realizing the biological mechanisms of their function can be helpful for developing stem cell researches. Accordingly, metabolomics as a

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

valuable tool for stem cell monitoring can clarify the biological mechanisms of MSCs function through assaying metabolites. Metabolites of MSCs are involved in metabolic or signaling pathways (80-82). Metabolic pathways produce vital signals for the self-renewal, differentiation and other properties of MSCs. On the other hand, undifferentiated state and differentiated state of MSCs can be distinguished via their metabolic profile. Accordingly, in undifferentiated state, mitochondrial OXPHOS is maintained at a low level, while the glycolytic function is maintained at a high level (81, 83). Additionally, in the early phase of MSCs differentiation, down-regulation of some pluripotent genes, up-regulation of terminal genes, and changing the subsets of metabolic enzymes can redirect the new fate of cells. Furthermore, in normoxic states, the proliferation and colony-forming abilities of MSCs are considerably increased (84, 85). In other words, hypoxic condition restricts MSC proliferation to maintain long-term self-renewal capacity. Generally, metabolomics can analyze the rapid kinetics and dynamics of metabolic reactions in different MSCs (86-88). Different types of MSCs share various properties due to their gene expression profile. Additionally, MSCs from various sources have also various secretome and metabolic profile (89, 90).

Metabolomics analysis of mesenchymal stem cells secretome

MSCs have demonstrated a pivotal and therapeutic impact on several diseases by producing a broad spectrum of autocrine and paracrine secretion factors (secretome) (15, 81, 91). The characterization of the MSCs secretome can elucidate their activation mechanism (92). Accordingly, metabolomics analyses can decipher the mechanism of secretome component functions (93). MSCs conditioned media (MSCs-CM) and extracellular vesicles (EVs) are two main MSC-sourced secretome.

Metabolomics study of mesenchymal stem cells conditioned media

MSCs-CM encompasses multiple growth factors (GFs), metabolites, and cytokines. It can be prepared through 4 steps including isolation and characterization of cells, culture of cells in a proper culture medium, cell expansion, and CM collection (94, 95). Additionally, it has been shown that MSCs-CM can improve various pathophysiology hallmarks of diseases e.g. lung injury, skin wound, Alzheimer's disease, and Parkinson's disease. For instance, there are some anti-inflammatory cytokines in MSC-CM (i.e. ciliary neurotrophic factor (CNTF), transforming growth factor 1 (TGF1), neurotrophin 3 (NT-3) factor, interleukin (IL) 13, IL18 binding protein (IL18BP), IL10, IL17E, IL27 or IL1 receptor antagonist (IL1RA)), and also some pro-inflammatory cytokines (including IL1b, IL6, IL8, and IL9) (95, 96). The equilibrium between these two types of cytokines can mediate the anti-inflammatory impact of MSC-CM. On the other hand, MSC-CM has anti-apoptotic activity via reducing the pro-apoptotic factors and increasing the expression of pro-angiogenic factors. Metabolomics can support quantification of MSC-CM metabolites by different targeted and non-targeted methods (91).

Metabolomics profiling of mesenchymal stem cells derived extracellular vesicles

EVs including exosomes and micro -vesicles can be secreted by cells which have an important role in intercellular signaling pathways (15, 97). It has been confirmed that MSC-EVs specifically MSCs-derived exosomes (MSC-Exo) can imitate their origin MSCs therapeutic effects in improvement of different disorders. MSC-EVs carry lipids, genetic materials (mRNA and non-coding RNA), and proteins. Moreover, they can be characterized by some surface markers such as CD29, CD73, CD44, and CD105. On the other hand, it is remarkable that MSCs- EVs from different MSC sources have also different

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

composition (98). Namely, menstrual fluid derived MSCs -Exo has greater neurite outgrowth response than bone marrow (BM), chorion, and umbilical cord-derived MSCs. Metabolomics techniques can be used to analyze the mechanism of different MSC-EVs activity based on their different metabolic profile (99).

Analytical techniques in metabolomics analysis

Metabolomics can assay the metabolite compositions of cells and biological fluids through various targeted and non- targeted techniques (100, 101). A broad range of analytical methods containing capillary electrophoresis (CE) (the separation method in which metabolites are separated based on their migration in the electrical field of the capillary tube), gas chromatography (GC) (a method for separating volatile matters), ultra-performance liquid chromatography (UPLC) (as a modern liquid chromatography method can be used for particles less than 2 µl in diameter), and high performance or high-pressure liquid chromatography (HPLC) (the highly advanced form of column chromatography which pumps the sample of metabolites in mobile phase at high

Table 1. Advantages and disadvantages of metabolomics techniques.

Method	Advantages	Disadvantages	References
NMR	- Simple sample preparation -Excellent reproducibility -Quantify a wide-range of organic compounds in the micro-molar range	-Low sensitivity compared with MS methods - Suitable for quantification of metabolites present in relatively high concentration	(102, 103)
GC-MS	- High separation efficiency - The oldest and a robust tool for qualitative metabolic profiling	-Non-volatile matrices require additional preparation - Some gases are challenging (CO2, N2, O2, Ar, CO, H2O)	(104, 105)
LC-MS	- High separation efficiency - No derivatization is needed for the analysis of polar or high molecular weight metabolites - Quick analysis of small samples	- Ion suppression	(103, 106)
CE-MS	-Suitable for the separation of polar and charged compounds - Powerful for charged metabolites -High-analyte resolution – providing information mainly on polar or ionic compounds -Short analysis time -Very small sample requirement	- Poor concentration sensitivity	(107, 108)
HPLC-MS	-Robustness -Ease of use - Good selectivity -Adjustable sensitivity	-Lack of efficiency due to low diffusion coefficients in liquid phase	(109, 110)
UPLC-MS	-Powerful technique in biomolecular research - Covers a number of polar metabolites and enlarges the number of detected analytes -Better efficiency with speedy analysis	Less time life of columns	(107, 111)

CE: capillary electrophoresis; GC: gas chromatography; HPLC: high performance liquid chromatography; LC: liquid chromatography; MS: mass spectrometry; NMR: nuclear magnetic resonance; UPLC: ultra-performance liquid chromatography.

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

pressure within a column or the stationary phase) linked to high-throughput techniques including nuclear magnetic resonance (NMR) (a spectroscopic procedure to follow local strong stationary magnetic fields around atomic nuclei which is for absorbing very high-frequency radio waves) and mass spectrometry (MS) (an analytical manner to ionizing chemical samples to identity unknown composites and chemical features of different molecules based on their mass-to-charge ratio) can be used for separation, examination, and quantification of the cellular metabolites composition as metabolomics approaches (107, 112-114). Each of the metabolomics approaches has some advantages and disadvantages (Table 1).

Conclusion and future perspectives

Metabolomics is an impressive research area, which can be used for screening the metabolic modifications during the stem cells reprogramming, proliferation, and differentiation (56, 115). Indeed, screening the metabolic modifications of stem cells (e.g. MSCs) can facilitate their application for regenerative medicine purposes via increasing the man control over *in vitro* manipulation of stem cells including tissue-specific stem cells activation, and promote stem cells for migration to the side of tissue injury. Based on researches, some important metabolic elements can be used to dedifferentiate stem cells toward organ-specific somatic cells (116). Accordingly, in the coming future it seems that the application of generated knowledge on metabolic key methods can be useful for therapeutic targets without the necessity of genetic manipulation. On the other hand, combination of metabolomics technology with other technologies (i.e. genomics, proteomics, structural biology and imaging) can increase its performance to identify novel biological pathways in mechanism of stem cell function, and also to identify disease mechanism (39, 117). Additionally, progress in the development of metabolite databases and *in silico* fragmentation tools can pave the way for large-scale metabolomics analysis (118, 119).

Acknowledgement

The authors would like to thank Dr. Mohsen Khorshidi and Shokouh Salimi for their considerable assistance.

Conflict of interest

Authors declare no conflict of interest.

References

1. Shyh-Chang N, Ng HH. The metabolic programming of stem cells. Genes Dev 2017;31:336-46.

2. Biehl JK, Russell B. Introduction to stem cell therapy. J Cardiovasc Nurs 2009;24:98-103; quiz 4-5.

3. Rahim S, Rahim F, Shirbandi K, et al. Sports Injuries: Diagnosis, Prevention, Stem Cell Therapy, and Medical Sport Strategy. Adv Exp Med Biol 2018.

4. Goodarzi P, Falahzadeh K, Aghayan H, et al. Therapeutic abortion and ectopic pregnancy: alternative sources for fetal stem cell research and therapy in Iran as an Islamic country. Cell Tissue Bank 2019;20:11-24.

5. Rahim F, Arjmand B, Shirbandi K, et al. Stem cell therapy for patients with diabetes: a systematic review and meta-analysis of metabolomics-based risks and benefits. Stem Cell Investig 2018;5:40.

6. Matsui WH. Cancer stem cell signaling pathways. Medicine (Baltimore) 2016;95:S8-S19.

7. Nwabo Kamdje AH, Takam Kamga P, Tagne Simo R, et al. Developmental pathways associated with cancer metastasis: Notch, Wnt, and Hedgehog. Cancer Biol Med 2017;14:109-20.

8. McCubrey JA, Rakus D, Gizak A. Effects of mutations in Wnt/β-catenin, hedgehog, Notch and PI3K pathways on GSK-3 activity—Diverse effects on cell growth, metabolism and cancer. Biochim Biophys Acta Mol Cell Res 2016;1863:2942-76.

9. Aponte PM, Caicedo A. Stemness in Cancer: Stem Cells, Cancer Stem Cells, and Their Microenvironment. Stem Cells Int 2017;2017:5619472.

10. Plaks V, Kong N, Werb Z. The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? Cell Stem Cell 2015;16:225-38.

11. Chosa N, Ishisaki A. Two novel mechanisms for

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

maintenance of stemness in mesenchymal stem cells: SCRG1/BST1 axis and cell-cell adhesion through N-cadherin. Jpn Dent Sci Rev 2018;54:37-44.

12. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells - current trends and future prospective. Biosci Rep 2015;35.

13. Schafer R, Spohn G, Baer PC. Mesenchymal Stem/Stromal Cells in Regenerative Medicine: Can Preconditioning Strategies Improve Therapeutic Efficacy? Transfus Med Hemother 2016;43:256-67.

14. Goodarzi P, Larijani B, Alavi-Moghadam S, et al. Mesenchymal Stem Cells-Derived Exosomes for Wound Regeneration. Adv Exp Med Biol 2018;1119:119-31.

15. Frese L, Dijkman PE, Hoerstrup SP. Adipose Tissue-Derived Stem Cells in Regenerative Medicine. Transfus Med Hemother 2016;43:268-74.

16. Payab M, Goodarzi P, Foroughi Heravani N, et al. Stem Cell and Obesity: Current State and Future Perspective. Adv Exp Med Biol 2018;1089:1-22.

17. Goodarzi P, Alavi-Moghadam S, Sarvari M, et al. Adipose Tissue-Derived Stromal Cells for Wound Healing. Adv Exp Med Biol 2018;1119:133-49.

18. Derakhshanrad N, Saberi H, Tayebi Meybodi K, et al. Case Report: Combination Therapy with Mesenchymal Stem Cells and Granulocyte-Colony Stimulating Factor in a Case of Spinal Cord Injury. Basic Clin Neurosci 2015;6:299-305.

19. Larijani B, Aghayan H, Goodarzi P. Clinical Grade Human Adipose Tissue-Derived Mesenchymal Stem Cell Banking. Acta Med Iran 2015;53:540-6.

20. Shirian S, Ebrahimi-Barough S, Saberi H, et al. Comparison of Capability of Human Bone Marrow Mesenchymal Stem Cells and Endometrial Stem Cells to Differentiate into Motor Neurons on Electrospun Poly(epsilon-caprolactone) Scaffold. Mol Neurobiol 2016;53:5278-87.

21. Goodarzi P, Aghayan HR, Larijani B, et al. Stem cell-based approach for the treatment of Parkinson's disease. Med J Islam Repub Iran 2015;29:168.

22. Aghayan HR, Goodarzi P, Arjmand B. GMP-compliant human adipose tissue-derived mesenchymal stem cells for cellular therapy. Methods Mol Biol 2015;1283:93-107.

23. Larijani B, Aghayan HR, Goodarzi P, et al. GMP-grade human fetal liver-derived mesenchymal stem cells for clinical transplantation. Methods Mol Biol 2015;1283:123-36.

24. Arjmand B, Aghayan HR. Cell manufacturing for clinical applications. Stem Cells 2014;32:2557-8.

25. Goodarzi P, Falahzadeh K, Nematizadeh M, et al. Tissue Engineered Skin Substitutes. Adv Exp Med Biol 2018;1107: 143-88.

26. Larijani B, Arjmand B, Ahmadbeigi N, et al. A simple and cost-effective method for isolation and expansion of human fetal pancreas derived mesenchymal stem cells. Arch Iran Med 2015;18:770-5.

27. Panopoulos AD, Yanes O, Ruiz S, et al. The metabolome of induced pluripotent stem cells reveals metabolic changes occurring in somatic cell reprogramming. Cell Res 2012;22: 168-77.

28. Peng B, Li H, Peng XX. Functional metabolomics: from biomarker discovery to metabolome reprogramming. Protein Cell 2015;6:628-37.

29. Wu J, Izpisua Belmonte JC. Stem Cells: A Renaissance in Human Biology Research. Cell 2016;165:1572-85.

30. Singh H. Multi-omics approach to stem cell studies. Minerva Biotecno 2017;29:169-73.

31. Suravajhala P, Kogelman LJA, Kadarmideen HN. Multi-omic data integration and analysis using systems genomics approaches: methods and applications in animal production, health and welfare. Genet Select Evol 2016;48:38.

32. Winkler J, Sotiriadou I, Chen S. The potential of embryonic stem cells combined with-omics technologies as model systems for toxicology. Curr Med Chem 2009;16:4814-27.

33. Naidoo N, Pawitan Y, Soong R, et al. Human genetics and genomics a decade after the release of the draft sequence of the human genome. Hum Genomics 2011;5:577-622.

34. Simonti CN, Capra JA. The evolution of the human genome. Curr Opin Genet Dev 2015;35:9-15.

35. Anderson MW, Schrijver I. Next generation DNA sequencing and the future of genomic medicine. Genes (Basel) 2010;1:38-69.

36. Churko JM, Mantalas GL, Snyder MP, et al. Overview of high throughput sequencing technologies to elucidate molecular pathways in cardiovascular diseases. Circ Res 2013;112: 1613-23.

37. Ohashi H, Hasegawa M, Wakimoto K, et al. Next-generation technologies for multiomics approaches including interactome sequencing. Biomed Res Int 2015;2015:104209.

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

38. Chaitankar V, Karakulah G, Ratnapriya R, et al. Next generation sequencing technology and genomewide data analysis: Perspectives for retinal research. Prog Retin Eye Res 2016;55:1-31.

39. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol 2017;18:83.

40. Podobinska M, Szablowska-Gadomska I, Augustyniak J, et al. Epigenetic Modulation of Stem Cells in Neurodevelopment: The Role of Methylation and Acetylation. Front Cell Neurosci 2017;11:23.

41. Boland MJ, Nazor KL, Loring JF. Epigenetic regulation of pluripotency and differentiation. Circ Res 2014;115:311-24.

42. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation 2011;123:2145-56.

43. Trerotola M, Relli V, Simeone P, et al. Epigenetic inheritance and the missing heritability. Hum Genomics 2015;9:17.

44. Roson-Burgo B, Sanchez-Guijo F, Del Canizo C, et al. Transcriptomic portrait of human Mesenchymal Stromal/Stem Cells isolated from bone marrow and placenta. BMC Genomics 2014;15:910.

45. Miura S, Himaki T, Takahashi J, et al. THE ROLE OF TRANSCRIPTOMICS: PHYSIOLOGICAL EQUIVALENCE BASED ON GENE EXPRESSION PROFILES. Reviews in Agricultural Science 2017;5:21-35.

46. Yeo JC, Ng HH. Transcriptomic analysis of pluripotent stem cells: insights into health and disease. Genome Med 2011;3:68.

47. Churko JM, Lee J, Ameen M, et al. Transcriptomic and epigenomic differences in human induced pluripotent stem cells generated from six reprogramming methods. Nat Biomed Eng 2017;1:826-37.

48. Chin CJ, Li S, Corselli M, et al. Transcriptionally and Functionally Distinct Mesenchymal Subpopulations Are Generated from Human Pluripotent Stem Cells. Stem Cell Reports 2018;10:436-46.

49. Huo JS, Zambidis ET. Pivots of pluripotency: the roles of non-coding RNA in regulating embryonic and induced pluripotent stem cells. Biochim Biophys Acta 2013;1830: 2385-94.

50. Sakamoto N, Honma R, Sekino Y, et al. Non-coding RNAs are promising targets for stem cell-based cancer therapy. Noncoding RNA Res 2017;2:83-7.

51. van Hoof D, Krijgsveld J, Mummery C. Proteomic analysis of stem cell differentiation and early development. Cold Spring Harb Perspect Biol 2012;4.

52. Pripuzova NS, Getie-Kebtie M, Grunseich C, et al. Development of a protein marker panel for characterization of human induced pluripotent stem cells (hiPSCs) using global quantitative proteome analysis. Stem Cell Res 2015;14:323-38.

53. Johnson CH, Ivanisevic J, Siuzdak G. Metabolomics: beyond biomarkers and towards mechanisms. Nat Rev Mol Cell Biol 2016;17:451-9.

54. Deidda M, Piras C, Bassareo PP. Metabolomics, a promising approach to translational research in cardiology. IJC Metabolic & Endocrine 2015;9:31-8.

55. Bhute VJ, Bao X, Palecek SP. Advances in Applications of Metabolomics in Pluripotent Stem Cell Research. Curr Opin Chem Eng 2017;15:36-43.

56. Peffers MJ, Collins J, Fang Y, et al. Age-related changes in mesenchymal stem cells identified using a multi-omics approach. Eur Cell Mater 2016;31:136-59.

57. Mahla RS. Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. Int J Cell Biol 2016;2016:6940283.

58. Singh VK, Kalsan M, Kumar N, et al. Induced pluripotent stem cells: applications in regenerative medicine, disease modeling, and drug discovery. Front Cell Dev Biol 2015;3:2.

59. Ilic D, Polak JM. Stem cells in regenerative medicine: introduction. Br Med Bull 2011;98:117-26.

60. Rafalski VA, Mancini E, Brunet A. Energy metabolism and energy-sensing pathways in mammalian embryonic and adult stem cell fate. J Cell Sci 2012;125:5597-608.

61. Li L, Bhatia R. Stem cell quiescence. Clin Cancer Res 2011;17:4936-41.

62. Mendelson A, Frenette PS. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. Nat Med 2014;20:833-46.

63. Ferraro F, Celso CL, Scadden D. Adult stem cels and their niches. Adv Exp Med Biol 2010;695:155-68.

64. Reinwald Y, Bratt J, El Haj A. Pluripotent stem cells and their dynamic niche2016.

65. Shyh-Chang N, Daley GQ, Cantley LC. Stem cell metabolism in tissue development and aging. Development

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

2013;140:2535-47.

66. Mathieu J, Ruohola-Baker H. Metabolic remodeling during the loss and acquisition of pluripotency. Development 2017;144:541-51.

67. Burgess RJ, Agathocleous M, Morrison SJ. Metabolic regulation of stem cell function. J Intern Med 2014;276:12-24.

68. Varum S, Rodrigues AS, Moura MB, et al. Energy metabolism in human pluripotent stem cells and their differentiated counterparts. PLoS One 2011;6:e20914.

69. Zhang J, Nuebel E, Daley GQ, et al. Metabolic regulation in pluripotent stem cells during reprogramming and self-renewal. Cell Stem Cell 2012;11:589-95.

70. Ryall JG, Cliff T, Dalton S, et al. Metabolic Reprogramming of Stem Cell Epigenetics. Cell Stem Cell 2015;17:651-62.

71. Perales-Clemente E, Folmes CD, Terzic A. Metabolic regulation of redox status in stem cells. Antioxid Redox Signal 2014;21:1648-59.

72. Pala F, Di Girolamo D, Mella S, et al. Distinct metabolic states govern skeletal muscle stem cell fates during prenatal and postnatal myogenesis. J Cell Sci 2018;131.

73. Bigarella CL, Liang R, Ghaffari S. Stem cells and the impact of ROS signaling. Development 2014;141:4206-18.

74. Yun Z, Lin Q. Hypoxia and regulation of cancer cell stemness. Adv Exp Med Biol 2014;772:41-53.

75. Sart S, Song L, Li Y. Controlling Redox Status for Stem Cell Survival, Expansion, and Differentiation. Oxid Med Cell Longev 2015;2015:14 pages.

76. Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell 2010;7:150-61.

77. Iqbal MA, Eftekharpour E. Regulatory role of redox balance in determination of neural precursor cell fate. Stem Cells Int 2017;2017:13 pages.

78. Wang K, Zhang T, Dong Q, et al. Redox homeostasis: the linchpin in stem cell self-renewal and differentiation. Cell Death Dis 2013;4:e537.

79. Ji AR, Ku SY, Cho MS, et al. Reactive oxygen species enhance differentiation of human embryonic stem cells into mesendodermal lineage. Exp Mol Med 2010;42:175-86.

80. Klontzas ME, Vernardis SI, Heliotis M, et al. Metabolomics Analysis of the Osteogenic Differentiation of Umbilical Cord Blood Mesenchymal Stem Cells Reveals Differential Sensitivity to Osteogenic Agents. Stem Cells Dev 2017;26:723-33.

81. Ivanova G, Pereira T, Caseiro AR. Metabolomic and Proteomic Analysis of the Mesenchymal Stem Cells' Secretome. Metabolomics-Fundamentals and Applications: InTech; 2016.

82. Lee SJ, Yi T, Ahn SH, et al. Comparative study on metabolite level in tissue-specific human mesenchymal stem cells by an ultra-performance liquid chromatography quadrupole time of flight mass spectrometry. Anal Chim Acta 2018;1024:112-22.

83. Ito K, Ito K. Metabolism and the Control of Cell Fate Decisions and Stem Cell Renewal. Annu Rev Cell Dev Biol 2016;32:399-409.

84. Hu C, Fan L, Cen P, et al. Energy Metabolism Plays a Critical Role in Stem Cell Maintenance and Differentiation. Int J Mol Sci 2016;17:253.

85. Boyette LB, Creasey OA, Guzik L, et al. Human bone marrow-derived mesenchymal stem cells display enhanced clonogenicity but impaired differentiation with hypoxic preconditioning. Stem Cells Transl Med 2014;3:241-54.

86. Ito K, Suda T. Metabolic requirements for the maintenance of self-renewing stem cells. Nat Rev Mol Cell Biol 2014;15: 243-56.

87. Fujisawa K, Takami T, Okada S, et al. Analysis of Metabolomic Changes in Mesenchymal Stem Cells on Treatment with Desferrioxamine as a Hypoxia Mimetic Compared with Hypoxic Conditions. Stem Cells 2018;36:1226-36.

88. Pattappa G, Heywood HK, de Bruijn JD, et al. The metabolism of human mesenchymal stem cells during proliferation and differentiation. J Cell Physiol 2011;226: 2562-70.

89. Phelps J, Sanati-Nezhad A, Ungrin M. Bioprocessing of Mesenchymal Stem Cells and Their Derivatives: Toward Cell-Free Therapeutics. Stem cells int 2018;2018:23 pages.

90. Flower T, Pulsipher V, Moreno A. A new tool in regenerative medicine: mesenchymal stem cell secretome. J Stem Cell Res Ther 2015;1:1-3.

91. Vizoso FJ, Eiro N, Cid S, et al. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. Int J Mol Sci 2017;18.

92. Cunningham CJ, Redondo-Castro E, Allan SM. The

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

therapeutic potential of the mesenchymal stem cell secretome in ischaemic stroke. J Cereb Blood Flow Metab 2018;38:1276-92.

93. Mukherjee P, Mani S. Methodologies to decipher the cell secretome. Biochim Biophys Acta 2013;1834:2226-32.

94. Park CW, Kim KS, Bae S, et al. Cytokine secretion profiling of human mesenchymal stem cells by antibody array. Int J Stem Cells 2009;2:59-68.

95. Hwang JH, Shim SS, Seok OS, et al. Comparison of cytokine expression in mesenchymal stem cells from human placenta, cord blood, and bone marrow. J Korean Med Sci 2009;24: 547-54.

96. Kwon HM, Hur SM, Park KY, et al. Multiple paracrine factors secreted by mesenchymal stem cells contribute to angiogenesis. Vascul Pharmacol 2014;63:19-28.

97. Boilard E. Extracellular vesicles and their content in bioactive lipid mediators: more than a sack of microRNA. J Lipid Res 2018;59:2037-46.

98. Li Y, Cheng Q, Hu G, et al. Extracellular vesicles in mesenchymal stromal cells: A novel therapeutic strategy for stroke. Exp Ther Med 2018;15:4067-79.

99. Rani S, Ryan AE, Griffin MD, et al. Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. Mol Ther 2015;23:812-23.

100. Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. Circulation 2012;126:1110-20.

101. Zhang A, Sun H, Wang P, et al. Modern analytical techniques in metabolomics analysis. Analyst 2012;137: 293-300.

102. Xiao JF, Zhou B, Ressom HW. Metabolite identification and quantitation in LC-MS/MS-based metabolomics. Trends Analyt Chem 2012;32:1-14.

103. Klein MS, Shearer J. Metabolomics and type 2 diabetes: translating basic research into clinical application. J Diabetes Res 2016;2016:10 pages.

104. Iwasaki Y, Sawada T, Hatayama K, et al. Separation technique for the determination of highly polar metabolites in biological samples. Metabolites 2012;2:496-515.

105. Zhang A, Sun H, Xu H, et al. Cell metabolomics. OMICS 2013;17:495-501.

106. Dunn WB, Broadhurst DI, Atherton HJ, et al. Systems level studies of mammalian metabolomes: the roles of mass spectrometry and nuclear magnetic resonance spectroscopy. Chem Soc Rev 2011;40:387-426.

107. Preet A, Karve TM, Rizk N. Metabolomics: approaches and applications to diabetes research J Diabetes Metab 2012;6:S:6.

108. Stanczyk FZ, Clarke NJ. Advantages and challenges of mass spectrometry assays for steroid hormones. J Steroid Biochem Mol Biol 2010;121:491-5.

109. Lu J, Xie G, Jia W, et al. Metabolomics in human type 2 diabetes research. Front Med 2013;7:4-13.

110. Scalbert A, Brennan L, Fiehn O, et al. Mass-spectrometry-based metabolomics: limitations and recommendations for future progress with particular focus on nutrition research. Metabolomics 2009;5:435-58.

111. Ramautar R, Mayboroda OA, Somsen GW, et al. CE-MS for metabolomics: Developments and applications in the period 2008-2010. Electrophoresis 2011;32:52-65.

112. Kushnir MM, Rockwood AL, Bergquist J. Liquid chromatography-tandem mass spectrometry applications in endocrinology. Mass Spectrom Rev 2010;29:480-502.

113. Pang B, Zhu Y, Lu L. The Applications and Features of Liquid Chromatography-Mass Spectrometry in the Analysis of Traditional Chinese Medicine. Evid Based Complement Alternat Med 2016;2016:7 pages.

114. Plumb R, Castro-Perez J, Granger J, et al. Ultra-performance liquid chromatography coupled to quadrupole-orthogonal time-of-flight mass spectrometry. Rapid Commun Mass Spectrom 2004;18:2331-7.

115. Meissen JK, Yuen BT, Kind T, et al. Induced pluripotent stem cells show metabolomic differences to embryonic stem cells in polyunsaturated phosphatidylcholines and primary metabolism. PLoS One 2012;7:e46770.

116. Gaspar JA, Doss MX, Hengstler JG, et al. Unique metabolic features of stem cells, cardiomyocytes, and their progenitors. Circ Res 2014;114:1346-60.

117. Ramalingam A, Kudapa H, Pazhamala LT, et al. Proteomics and Metabolomics: Two Emerging Areas for Legume Improvement. Front Plant Sci 2015;6:1116.

118. Fukushima A, Kusano M. Recent progress in the development of metabolome databases for plant systems

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]

biology. Front Plant Sci 2013;4:73.

119. Wolf S, Schmidt S, Muller-Hannemann M, et al. In silico fragmentation for computer assisted identification of metabolite mass spectra. BMC Bioinformatics 2010;11:148.

[Downloaded from ijmcmed.org on 2026-11-15]

[DOI: 10.22088/IJMCM.BUMS.8.2.30]