76486_Auto_EditedC.docx

Metabolic-epigenetic nexus in regulation of stem cell fate

Liu Y *et al*. Metabolic-epigenetic nexus effect

Yi Liu, Di-Xin Cui, Yue Pan, Si-Han Yu, Li-Wei Zheng, Mian Wan

Abstract

Stem cell fate determination is one of the central questions in stem cell biology, and although its regulation has been studied at genomic and proteomic levels, a variety of biological activities in cells occur at the metabolic level. Metabolomics studies have established the metabolome during stem cell differentiation and have revealed the role of metabolites in stem cell fate determination. While metabolism is considered to play a biological regulatory role as an energy source, recent studies have suggested the nexus between metabolism and epigenetics because several metabolites function as cofactors and substrates in epigenetic mechanisms, including histone modification, DNA methylation, and microRNAs. Additionally, the epigenetic modification is sensitive to the dynamic metabolites and consequently leads to changes in transcription. The nexus between metabolism and epigenetics proposes a novel stem-cell-based therapeutic strategy through manipulating metabolites. In the present review, we summarize the possible nexus between metabolic and epigenetic regulation in stem cell fate determination, and discuss the potential preventive and therapeutic strategies *via* targeting metabolites.

Key Words: Metabolism; Epigenetic regulation; Stem cell fate; Nexus effect

Liu Y, Cui DX, Pan Y, Yu SH, Zheng LW, Wan M. Metabolic-epigenetic nexus in regulation of stem cell fate. *World J Stem Cells* 2022; In press

Core Tip: Stem cell fate can be regulated by metabolites. Recent studies have suggested that there is a nexus between metabolism and epigenetics, as several metabolites could function as cofactors and substrates in epigenetic mechanisms. We review many basic and preclinical studies, and the results support this view. This finding may provide a clue to further studies on the co-effects of metabolism and epigenetics in cell fate determination.

INTRODUCTION

Stem cells are specialized cells with a capacity for prolonged self-renewal and production of various lineage cells, which contribute to the development, maintenance and repair of organs, such as teeth, hair follicles, and liver. These long-lived cells produce proliferating progenitors that differentiate into functional cells. Disorder of this procedure results in hyperplasia, hypoplasia or dysfunction of the organs[1]. How such cell fate determination is regulated is one of the central questions in stem cell biology. High-throughput sequencing has been conducted to establish gene expression profiles of both embryonic and adult stem cells, which helps address the crucial genes in stem cell fate regulation[2]. Epigenetic mechanisms, including histone modification, DNA methylation, and microRNAs (miRNAs), have uncovered the post-transcriptional regulation associated with stem cell fate[3]. Parallel proteomics studies have expanded our understanding of stem cell biology through constructing protein expression profiles of various stem cell populations. Despite these findings, the molecular network that regulates stem cell fate, maintaining pluripotency or initiating differentiation, is not completely understood due to the expression differences between mRNA and protein, the inconsistency between protein expression and its function, or the discordance between gene expression and cellular phenotype[4].

Although genomics and proteomics discuss the biological events at the gene and protein levels, respectively, several biological activities in cells occur at the metabolic level, including cell signaling, energy transfer, and intercellular communication[5]. To establish the metabolome, the collection of all metabolites at a specific time, metabolomics has been developed as one of the important components in systems biology. Metabolomics is considered to be a prospective approach in various areas of researches, such as development, pathology, diagnosis, and environmental science, since it elaborates what happens in cells[6]. To address what occurs during regulation of stem cell fate determination, metabolomic research has been conducted to construct metabolic profiles of embryonic stem cells and differentiated neurons and cardiomyocytes in mice. Stem cells are characterized by highly unsaturated metabolites

that regulate cell differentiation through oxidative reactions, suggesting the vital role of metabolism in stem cell fate determination. Metabolism is considered to function as a major energy source during the process[5,7,8]. Recent studies have demonstrated that lipid metabolism provided 90% of acetyl-CoA in histone acetylation. S-adenosylmethionine (SAM), one of the methionine metabolism metabolites, functions as a methyl donor in histone as well as DNA methylation[9]. Additionally, the epigenetic modification could be sensitive to the dynamic change in the metabolites, leading to changes in transcription. These findings provide compelling evidence that establishes the nexus between metabolism and epigenetics and propose a novel stem-cell-based therapeutic strategy through manipulating metabolites[10-12].

In the present review, we summarize the nexus between metabolic and epigenetic regulation in stem cell fate determination, along with potential preventive and therapeutic strategies targeting metabolites (Figures 1 and 2).

LIPID METABOLISM

Lipids, crucial in maintaining cellular homeostasis, is attached to epigenetic reprogramming of homeostasis[13]. Acetyl-CoA from lipid metabolism could promote histone acetylation and drive cellular growth. Hence, acetyl-CoA is a crucial indicator for cell growth and development. Furthermore, acetyl-CoA reduces the production of b-hydroxybutyrate, an inhibitor of histone deacetylases (HDACs), which as antiproliferative and prodifferentiative properties[14]. The relation between lipid metabolism and epigenetic modification of gene expression in different stem cells has been reported by several studies[15].

Lipid metabolism contributes 90% of acetyl. Chromatin structure opening occurs when histone acetylation is present, activating stem cell transcription[16]. This suggests that lipid availability regulates the pluripotency of stem cells and promotes cell differentiation[17]. Itokazu group's research on the importance of gangliosides in neural stem cells (NSCs) found that when the cellular histone deacetylase activity was inhibited by fatty acids, the levels of AcH3 and AcH4 on the *GM2/GD2S* gene increased,

promoting neuronal differentiation of NSCs[18]. Ardah *et al*[19] and Boddeke *et al*[20] also showed that the increase level of saturated fatty acids promoted NSC differentiation into neurons. Murray *et al*[21] reported that butyrate promoted myogenic differentiation of satellite cells.

Cornacchia *et al*[22] showed that the level of H3K27Ac, H3K9Ac and H4K8Ac was elevated by activation of histone acetylation in human pluripotent stem cells, while histone deacetylases, SIRT1 and HDAC1 are limited. Similar evidence has also been reported in animal studies[23,24]. The levels of H3K27ac decreased in the presence of low fatty acid metabolism in the gonads, leading to gene expression of male differentiation-specific signal inhibition[25].

Acetyl-CoA production can be regulated by acetyl-CoA carboxylase a, a rate-limiting enzyme whose activation limits the production of acetyl-CoA, thus promoting stem cell pluripotency. This is a traditional pathway in human as well as mouse embryonic stem cells (ESCs)[26,27].

These results show that lipid metabolism affects stem cell differentiation through histone acetylation modification.

AMINO ACID METABOLISM

Amino acids are one of the most fundamental substrates in cells, and are essential for metabolism of proteins, lipids and nucleotides. Previous reports have demonstrated that amino acid metabolism affects maintenance of stem cell pluripotency. In this review, we highlight the amino acids that influence stem cells critically.

Glutamine

Glutamine is the most abundant amino acid in metabolism, and is especially active in synthesis of nucleotides and fatty acids[28,29]. Glutamine changes α-ketoglutarate (α-KG) through deamination[30], which is a critical substrate for modification of proteins and DNA by demethylases. The mechanism is that α-KG acts as a substrate for Jumonji-C and Tet, which regulate demethylase interaction with histone and DNA, respectively.

Demethylases are essential for stem cell pluripotency acquisition and maintenance. Many studies have highlighted the role of glutamine metabolism in the maintenance and differentiation of stem cells.

DNA methylation correlates with the repression of expression. α-KG positively regulates demethylation of DNA and promotes stem cell differentiation[31,32], and is key to the determination of stem cells fate as an appropriate balance between H3K9me2 acquisition and H3K27me3 depletion. Tischler *et al*[33], Xing *et al*[34] and Zylicz *et al*[35] came to similar conclusions in experiment on mouse primordial germ cell–like cells (PGCLCs). Okabe *et al*[36] have reported that histone H3K9me3 demethylation induced by an increase in α-KG activates transcription, leading to steatoblast cellular differentiation. Glutamine also regulates fetal oocyte differentiation through DNA demethylation enzyme TET1[37].

As DNA demethylation can lead to higher levels of 5-hydroxymethylcytosine, several recent studies have reported that α-KG fluctuations may influence ESC differentiation[38]. The self-renewal of ESCs decreases with deficiency of glutamine, but can recover with α-KG supplementation[39]. Hepatic stellate cell (HSC) and effector T cell differentiation is also promoted by α-KG. A surprising finding is that α-KG can suppress tumor initiation and influence progression. These effects are inhibited by succinate and fumarate, providing a possible therapy for cancer[40].

Singh *et al*[41] have suggested that α-KG induces cell death, with degradation of hypoxia-inducible facor-1α and suppression of histone H3 (Lys 27) acetylation. The exact mechanism of histone acetylation regulated by α-KG still needs to be explored. Morris *et al*[42] has shown that α-KG is an effector of *p53*-mediated tumor suppression, whose accumulation in *p53*-deficient tumors can drive tumor cell differentiation and inhibit malignant progression. Ascorbate has a positive effect on HSC differentiation and suppresses leukemogenesis[43].

All these studies above highlight the importance of glutamine in cell fate determination.

Methionine

Methionine is an essential amino acid that plays an irreplaceable role in the synthesis of SAM. Methionine in the normal diet promotes production of SAM, which serves as a methyl donor for methyltransferases of histones and DNA[44]. The fluctuation of methionine and SAM levels regulates H3K4me3 formation and maintains the undifferentiated state of human ESCs/induced pluripotent stem cells (iPSCs)[45]. Kosti *et al*[46] have reported that limited methionine levels are associated with neuronal differentiation, along with reduction of H3K27me3. Tang *et al*[47] have also provided evidence that reduced conversion of methionine to SAM leads to reduced ESC pluripotency. Zhang *et al*[48] have also found similar evidence that SAM plays an important role in the differentiation of B cells into plasmablasts, and SAM deficiency is accompanied by induction of H3K27me3. The theory may be an attractive option for improving therapeutic effectiveness in patients with systemic lupus erythematosus.

Fluctuation in the methionine cycle is related to cancer epigenetics. The increase in H3K4me3 and H3K27me3 Levels in cells treated with methionine in cancer stem cells parallels the increase in SAM to some extent[49,50]. This may provide a new therapy for cancer[51].

Taken together, these findings show that methionine has an important influence on stem cell fates.

Proline

Proline is a nonessential amino acid derived from glutamine metabolism. Pyrroline-5-carboxylate (P5C) is an intermediate product of both proline biosynthesis and catabolism. P5C is converted to proline by P5C reductase (Pycr1). Emerging evidence indicates that L-proline influences the epigenetic landscape of stem cells by regulating histones and DNA methylation[52,53]. L-Proline regulates H3K9 methylation and activates reprogramming of stem cells. Supplementation with L-proline increases DNA 5-methylcytosine and reduces of 5-hydroxy-methylcytosine, which promotes DNA methylation. It has recently emerged that hypermethylation may lead to α-KG

depletion, limiting the activity of TETs and JMJs, and resulting in increased DNA and histone methylation .A study on mouse embryonic stem cell has shown that L-proline influences the balance between self-renewal and differentiation[54]. Proline availability increases DNA and histone methylation, and is an essential procedure in embryonic-stem-to-mesenchymal like transition[55].

Proline is one of the most important amino acids in stem cell fate determination because of its epigenetic effects.

Glycine

Glycine takes part in one-carbon metabolism as a methyl group provider through the glycine cleavage system[56]. The glycine cleavage system is a multienzyme complex consisting of four individual components: glycine decarboxylase, amino methyltransferase, glycine cleavage system protein H, and dihydrolipoamide dehydrogenase[57]. It has been revealed that glycine influences stem cell pluripotency by controlling the synthesis of SAM, thus promoting H3K4me3 modification, and open euchromatin[58]. This process is present in human and mouse PSCs[59].

NUCLEOTIDE METABOLISM

We focus on metabolism of noncoding RNA. Noncoding RNA is RNA that does not encode a protein. ncRNA is transcribed from the genome and exerts its effects at the RNA level. Global ncRNA abundance influences cell fate determination and differentiation, and is important when embryonic development and its dysregulation causes cancer[60-62].

There are reports that lnc13728 may positively regulate expression of ZBED3 to promote the adipo-genic differentiation of human adipose-derived mesenchymal stem cells[63]. lncRNA has effects on hematopoietic cells in hematopoiesis regulation and the early stage of cell fate determination. Wu *et al* have reported that, in hematopoietic stem cells and in differentiated lineage progenitors, lncRNA expression is given priority[64].

Griffiths and his colleagues have demonstrated that miR-181a inhibition activates the early latent neurogenic gene to restore CA1 neurons, providing a positive clinical outcome in survivors of forebrain ischemia[65]. Zhang *et al*[66] have shown that miR-124 inhibits pancreatic progenitor cell proliferation to maintain a quiescent state, thus determining the fate of pancreatic progenitor cells. In cancer cells, miRNA might be a preferential pathway in cell reprograming. It has been reported that GLUT1, GLUT3 and GLUT4 are overexpressed in most cancers. miR-122 regulates lipid levels in liver. miR-185 and miR-342 inhibit migration and invasion of prostate cancer cells, which may be a therapeutic option for prostate cancer[63]. He *et al*[67] have shown that miR-146a from exosomes has an effect on β-cell dedifferentiation, which may provide a new therapy for type 2 diabetes[68]. High expression of miR-130a can increase osteogenic differentiation of bone marrow mesenchymal stem cells, which could be a potential therapy for age-related bone loss[69,70]. Huang *et al*[71] have reported that miR-330-5p negatively regulates differentiation of mesenchymal stem cells.

In summary, ncRNA plays an essential role in stem cell fate determination and could act as a breakthrough point in disease therapy. However, we still have a long way to go to understand the whole regulatory network of ncRNA.

GLUCOSE METABOLISM

Glucose and oxygen are important regulatory elements that help direct stem cell fate. In the undifferentiated state, stem cells, and their artificially reprogrammed equivalent iPSCs, are characterized by limited oxidative capacity and active anaerobic glycolysis. The importance of optimizing glucose metabolism during nuclear reprogramming by epigenetic regulation has been demonstrated in several studies.

Glycolysis

Glycolysis is defined as a cytosolic redox reaction that transform a single glucose molecule into two pyruvate molecules accompanied by generation of two net ATP and two reduced NADH molecules. Although glycolysis is not as energetically efficient as

complete oxidation, this pathway can occur in the absence of oxygen and enables a fast rate of ATP production, which may also be the reason why some highly proliferating cell types typically utilize glycolysis.

High glycolytic flux may be frequently observed in various stem cell populations and is critical for the acquisition and maintenance of cell pluripotency[72]. Li *et al*[73] have shown that Glis1 can directly bind to and open chromatin structure at glycolysis-related genes to promote glycolysis. Higher glycolytic flux subsequently upregulates cellular acetyl-CoA and lactate levels, leading to increased acetylation of H3K27 and pluripotency gene loci.

Glycolytic flux can be influenced by several factors, including epigenetic regulators and environmental conditions. For example, NAD-dependent histone deacetylase SIRT6 has been proved to act as a key regulator of glucose homeostasis, and its absence favors the metabolic profile of anaerobic glycolysis, which may activate gene reprogramming and pluripotency maintenance[74]. The epigenetic modifications are essential for the cell fate decisions in NSCs as well. High glucose levels increase H3K14 acetylation level, which can lead to premature neurogenetic differentiation of NSCs, which probably provides a promising target for intervention in fetal neurodevelopment deficits[75]. Protein glycosylation is one of the most diverse and complicated co- and post-translational modifications, and can regulate self-renewal, pluripotency, and differentiation of stem cells through epigenetic mechanisms by histone modification and DNA methylation[76]. Glycolytic flux can also be regulated by oxygen. Glycolysis increases at 5% oxygen, acetylation of H3K9 and H3K27 is elevated, while H3K27 trimethylation is downregulated, leading to a more open chromatin structure and altered fate of human PSCs[77,78].

In summary, glycolysis is the dominant metabolic phenotype that controls stem cell fate.

Glucose oxidative phosphorylation

Glucose oxidative phosphorylation is another critical pathway for maintaining bioenergetic homeostasis as a bridge between the tricarboxylic acid (TCA) cycle and ATP synthesis. Oxidative phosphorylation is a more efficient pathway for ATP production compared to glycolysis, producing 36 ATP molecules per glucose. Oxidative phosphorylation promotes stem cell differentiation. Uittenbogaard *et al*[79] have provided evidence that enhancing oxidative phosphorylation can trigger neuronal differentiation by generating H3K27ac. Oxidative phosphorylation also mediates hematopoiesis stem cell differentiation toward definitive hematopoiesis through actyl-CoA metabolism[80].

Several TCA-cycle-related metabolic intermediates like NADH, FADH, fumarate and succinate are reported to contribute to epigenetic regulation of transcription and be connected with stem cell fate.

NADH: NAD+ is a coenzyme that serves as a co-substrate for Sirtuins, an HDAC family, and catalyzes deacetylation of histone lysine; a crucial protein post-translational modification[81-83].

NAD/NADH ratio can dictate the fate and function of different cell types. Increased NAD+ production is required for cell differentiation[84]. BMAL1 regulates primary myoblast proliferation and differentiation through increasing cytosolic NAD+. Reduced NAD+ level prevents the differentiation of preadipocytes[85]. Okabe *et al*[36] have confirmed that high NAD+ levels upregulate the TCA cycle, increasing α-KG and contributing to histone H3K9 demethylation and transcriptional activation. Zhu *et al*[85] have demonstrated that increasing cytosolic NAD levels can restore hypoxic cell proliferation and myofiber formation in Bmal1-deficient myoblasts, influencing oxygen-dependent myoblast cell fate. The effect of NAD/NADH ratio on stem cell fate is caused by generation of L-2-hydroxyglutaric acid; an analog of α-KG that regulates histone and DNA methylation by competitive inhibition of JHDMs and TETs. There are reports that increased NAD+ levels may delay aging-related phenotypes, which may provide new therapeutic option for type 2 diabetes and heart failure[86,87]. Besides,

NAD^{+} is a cosubstrate of Sirtuins, potentially regulating T cells, and could provide a therapeutic option for immune-related diseases[88].

In summary, NAD^{+} plays a key role in a diverse array of biological processes.

FADH: FAD, the oxidized form of FADH2, is a cofactor of LSD1, and plays a pivotal role during early embryonic development and differentiation of ESCs and cancer stem cells[89-92]. LSD1 catalyzes the demethylation of mono- and dimethylated K4 or K9 on histone H3 *via* the FAD-dependent enzymatic oxidation[93]. Recent studies have found that LSD1 inhibition can enhance death in rhabdomyosarcoma cells[94]. Decreased expression of LSD1 is involved in the programmed oocyte death by autophagy in perinatal mice through promotion of H3K4me2 expression[95]. FAD also regulates NSC proliferation through modulation of histone methylation by affecting the action of LSD1. In addition, LSD1 is highly expressed in a few aggressive cancer types and is closely related with differentiation, proliferation, migration and invasion of cancer cells and poor prognosis.

Succinate: Succinate accumulation can decrease α-KG/succinate ratio, leading to inhibition of TET and JHDM enzymes and delayed differentiation of primed human PSCs. This effect can be reversed when the α-KG/succinate ratio increases[32,86]. Accumulation of succinate, resulting in genetic and epigenetic changes like histone hypermethylation, may lead to transformation of normal cells to cancerous cells[96,97]. Wong *et al*'s study in colorectal cancer cells showed that promoting accumulation of succinate may upregulate DNA methylation and stem cell features[98]. AA6 is a novel compound succinic acid, identified as an inhibitor of α-KG dehydrogenase, which can increase the αKG level in diabetic human cardiac mesenchymal cells and in the heart of high-fat diet, leading to DNA demethylation, and has beneficial effects of cardiac mesenchymal stem cells (CMSCs) protection in diabetes[99].

Fumarate: Fumarate is reported to inhibit α-KG-dependent dioxygenases involved in DNA and histone demethylation. Laukka *et al*[100] have shown that fumarate downregulates global 5-hydroxymethylcytosine levels in neuroblastoma cells *via* TET inhibition. Furthermore, Sharda *et al*[101] have reported that fumarate promotes monomer-to-dimer transition of malic enzyme 2 to enhance mitobiogenesis, linking metabolism to mitobiogenesis. Aberrant accumulation of fumarate may mediate epigenetic reprogramming. Some studies have reported the link between fumarate accumulation, epigenetic changes, and tumorigenesis. Accumulation of fumarate, inhibiting Tet-mediated demethylation, induces epithelial-to-mesenchymal transition; a phenotypic switch associated with cancer initiation, invasion and metastasis[102]. This implies that fumarate accumulation contributes to the aggressive features tumors[103].

Pentose phosphate pathway

The pentose phosphate pathway (PPP) is another glucose metabolism pathway, divided into oxidative and nonoxidative arms, respectively producing NADH and ribose-5-phosphate and/or xylulose-5-phosphate that influence the regulation of transcription[104]. NADPH production in the pathway is involved in folate metabolism[105]. Previous studies have reported that regulation of the PPP results in iPSC reprogramming[106]. The PPP actively provides energy and metabolic intermediates for proliferation and pluripotency in cancer cells, ESCs and iPSCs[107,108]. Intracellular pH increase selectively activates catalysis, enhancing PPP flux, leading to nucleotide upregulation, increased $NADPH/NADP^+$ ratio, and cell proliferation[109].

It remains to be elucidated whether PPP is linked to stem cell epigenetic remodeling.

OTHER POTENTIAL INFLUENTIAL FACTORS

Structure

The structure of scaffolds can affect stem cell metabolism. Three-dimensional graphene foam has better properties than two-dimensional foam for NSC differentiation. However, the possible mechanism needs to be explored[110].

Micronutrients

Vitamin C: Vitamin C is a crucial micronutrient that may be involved in stem cell pluripotency by activating H3K36 and H3K9 demethylases through JmjC function[111]. A study using human PGCLCs also indicated the pathway[112,113]. Micronutrients influence stem cells specification.

Folic acid: Folic acid is first metabolized to dihydrofolate and then to tetrahydrofolate, taking part in DNA synthesis, influencing DNA and histone methylation[105]. Several studies have elucidated the role of folate metabolism in regulating of the epigenetic landscape of stem cells[114,115]. Li *et al*[116] have shown that folic acid deficiency in NSCs decreases cell proliferative capacity but increases apoptosis. Kasulanati *et al*[117] in a study of ESCs have provided more evidence for the effect of folic acid on PSC pluripotency. Pei *et al*[118] in a study of mouse ESCs have demonstrated that under folate deficiency conditions, H2AK119ub1 increases, and expression of neural tube closure-associated genes decreases. This suggests a possible mechanism for neural tube defects. Xie *et al*[119] have shown that folate inhibition can activate histone modification of H3K4me1 transcription, suggesting that epigenetic regulation varies for different histone modifications.

Crosslinking: Horitani *et al*[120] have reported that glucose along with triglyceride increases metabolic stress spikes in mice, resulting in demethylation of H3K27me3, and expression of senescence-like phenotypes in bone marrow stem/progenitor cells. This could provide a therapeutic method for patients with cardiovascular disease and type 2 diabetes.

CONCLUSION

This review summarizes the recent studies about the metabolic–epigenetic nexus and provides compelling evidence that metabolism regulates stem cell fate determination

through [15] epigenetic mechanisms, such as histone acetylation, histone methylation and DNA methylation, in a variety of physical and pathological phenomena. The latest studies have also suggested that potential manipulation of metabolites holds great promise in developing novel preventive, diagnostic and therapeutic strategies for a variety of diseases, which still requires further study prior to application in clinic settings.

There are still some essential questions. For example, what is the outcome of the regulation of metabolism on the epigenetic and transcriptional procedures of stem cells. The interplay of metabolism and epigenetics also brings out the complexity in environmental exposures studies, as the method of cell metabolism and potential transgenerational inheritance has been changed[15,121].

However, there were still some limitations. Most studies have attached importance to the level of enzymatic activity in cells, and we must accept that there is a difference between the measured and actual values[15]. All research was conducted under experimental and not physiological conditions, and it is not hard to conclude that there might be some variation.

In summary, when it comes to the mechanism of stem cell fate determination, there is indeed interplay between metabolism and epigenetics. We need more accurate data acquisition and more realistic simulation as well as more specific mechanisms. The development of new technologies make it easier to measure cellular metabolic status, and the accumulation of past studies support our further exploration in this field.

76486_Auto_EditedC.docx

PRIMARY SOURCES

| 1 | www.ncbi.nlm.nih.gov
Internet | 81 words — 2% |

| 2 | Muhammad Abid Sheikh, Bright Starling Emerald, Suraiya Anjum Ansari. "Stem cell fate determination through protein O-GlcNAcylation", Journal of Biological Chemistry, 2021
Crossref | 46 words — 1% |

| 3 | Ram Prosad Chakrabarty, Navdeep S. Chandel. "Mitochondria as Signaling Organelles Control Mammalian Stem Cell Fate", Cell Stem Cell, 2021
Crossref | 43 words — 1% |

| 4 | www.jove.com
Internet | 41 words — 1% |

| 5 | Marco Sciacovelli, Emanuel Gonçalves, Timothy Isaac Johnson, Vincent Roberto Zecchini et al. "Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition", Nature, 2016
Crossref | 35 words — 1% |

| 6 | www.science.gov
Internet | 33 words — 1% |

| 7 | H CHANG. "Microarray Analysis of Stem Cells and Differentiation", Essentials of Stem Cell Biology, 2009
Crossref | 28 words — 1% |

8   Jenna E. AbuSalim, Kazutoshi Yamamoto, Natsuko Miura, Burchelle Blackman et al. " Simple Esterification of [1- C]-Alpha-Ketoglutarate Enhances Membrane Permeability and Allows for Noninvasive Tracing of Glutamate and Glutamine Production ", ACS Chemical Biology, 2021
Crossref

22 words — 1%

9   Aliaa A Alamoudi, Amina Alnoury, Hoda Gad. "miRNA in tumour metabolism and why could it be the preferred pathway for energy reprograming", Briefings in Functional Genomics, 2018
Crossref

21 words — 1%

10   H. Ümit Kaniskan, Michael L. Martini, Jian Jin. "Inhibitors of Protein Methyltransferases and Demethylases", Chemical Reviews, 2017
Crossref

19 words — < 1%

11   Xiao Chen, Bing Shao, Chengmin Yu, Qunmei Yao, Peibin Ma, Haijiao Li, Bin Li, Chengye Sun. "Energy disorders caused by mitochondrial dysfunction contribute to α-amatoxin-induced liver function damage and liver failure", Toxicology Letters, 2021
Crossref

18 words — < 1%

12   www.sciencedirect.com
Internet

18 words — < 1%

13   Yohei Hayashi, Yasuhisa Matsui. "Metabolic Control of Germline Formation and Differentiation in Mammals", Sexual Development, 2022
Crossref

16 words — < 1%

14   www.frontiersin.org
Internet

12 words — < 1%

15 www.perkinelmer.com
Internet
12 words — < 1%

16 Eduardo J. Patriarca, Federica Cermola, Cristina D'Aniello, Annalisa Fico et al. "The Multifaceted Roles of Proline in Cell Behavior", Frontiers in Cell and Developmental Biology, 2021
Crossref
10 words — < 1%

17 Pei Zhu, Noah X. Hamlish, Abhishek Vijay Thakkar, Adam W.T. Steffeck et al. " BMAL1 drives muscle repair through control of hypoxic NAD regeneration in satellite cells ", Genes & Development, 2022
Crossref
10 words — < 1%

18 Rosalinda Madonna, Aniko Görbe, Peter Ferdinandy, Raffaele De Caterina. "Glucose Metabolism, Hyperosmotic Stress, and Reprogramming of Somatic Cells", Molecular Biotechnology, 2013
Crossref
10 words — < 1%

19 cmbl.biomedcentral.com
Internet
10 words — < 1%

20 Takayoshi Suzuki, Naoki Miyata. "Lysine Demethylases Inhibitors", Journal of Medicinal Chemistry, 2011
Crossref
9 words — < 1%

21 "Regenerative Medicine: Laboratory to Clinic", Springer Science and Business Media LLC, 2017
Crossref
8 words — < 1%

22 Eduardo K. Moioli. "Inhibition of osteogenic differentiation of human mesenchymal stem cells", Wound Repair and Regeneration, 5/2007
Crossref
8 words — < 1%

23   JAMES M. PHANG. "The Regulatory Functions of Proline and Pyrroline-5-carboxylic Acid", Elsevier BV, 1985
Crossref

8 words — < 1%

24   Yukihiro Itoh, Daisuke Ogasawara, Yosuke Ota, Tamio Mizukami, Takayoshi Suzuki. "SYNTHESIS, LSD1 INHIBITORY ACTIVITY, AND LSD1 BINDING MODEL OF OPTICALLY PURE LYSINE-PCPA CONJUGATES", Computational and Structural Biotechnology Journal, 2014
Crossref

8 words — < 1%

25   lib.smu.edu.cn
Internet

8 words — < 1%

26   Zhenwu Zhang, Wenjun Zhai, Jie Liang, Zhenbao Chen, Mingjun Ma, Yicheng Zhao, Yang Liang, Xuyan Li, Chun‐Bo Teng. "Mutual inhibitions between epidermal growth factor receptor signaling and miR‐124a control pancreatic progenitor proliferation", Journal of Cellular Physiology, 2018
Crossref

7 words — < 1%

EXCLUDE QUOTES   OFF   EXCLUDE SOURCES   OFF

EXCLUDE BIBLIOGRAPHY   OFF   EXCLUDE MATCHES   OFF