Ataxia Telangiectasia Mutated (ATM) Control

Subjects: Others

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Control of excessive oxidative stress is vital within cells to maintain cellular and genome integrity. Damage to the genome is particularly detrimental to host organisms and cells have evolved complex pathways to detect and coordinate response to and repair of DNA damage. But even with successful DNA damage repair, activation of the DNA damage response (DDR) can modulate inflammatory responses directly and through epigenetic mechanisms. Studies indicate that many pathophysiological states that are characterized by elevated oxidative stress are also associated with upregulation of the DNA damage response (DDR).

ataxia telangiectasia mutated (ATM) | DNA damage response | innate immune response | oxidative stress | epigenetic regulation | p53 | sepsis

1. Introduction

It is well known that low basal levels of reactive oxygen and nitrogen species (ROS and RNS, respectively, or RONS) play crucial signaling roles within cells under normal physiological conditions. The major ROS involved in signaling include the superoxide radical (O2 −•), hydrogen peroxide (H 2O 2), formed by reduction of superoxide via superoxide dismutase (SOD) and spontaneous dismutation of superoxide, and the hydroxyl radical (HO .) formed by H 2O 2 in the presence of free transition metals. RNS include the nitric oxide (NO) radical and peroxynitrite (ONOO −), the product of a chemical reaction between O2 −• and NO [1]. Controlled subcellular localization and accumulation of oxidants allows for use of these reactive species as signaling molecules [2].

While low physiological levels of RONS are crucial for cell signaling and growth, levels that exceed a critical threshold of antioxidant capacity within the cell can lead to damage of cellular biomolecules including nucleic acids, proteins, and lipids. Recent studies have revealed a concentration-dependent response within the cell to different levels of RONS. Three levels of cellular response to oxidants are identified as (i) eustress at normal physiological conditions (i.e., H 2O 2 concentrations of 1–10 nM), (ii) adaptive stress via redox sensors and effectors such as the Keap1-Nrf2 and JNK-NF-κB transcription factor activation pathways (i.e., H 2O 2 concentrations of 10–100 nM), and (iii) excessive oxidative stress leading to cellular distress and damage to cellular components (i.e., H 2O 2 concentrations > 100 nM) [3]. Thus, under elevations in RONS slightly above physiological levels, adaptive cellular antioxidant signaling pathways are capable of responding to oxidative stress up to a threshold level. However, excessive production and accumulation of RONS occurs and is implicated in a broad host of pathological states including neurodegenerative diseases such as Alzheimer’s [4], Parkinson’s, and Huntington’s diseases [5],

atherosclerosis [6], rheumatoid arthritis [7], ischemia reperfusion injury [8], aging and age-related conditions such as cardiovascular diseases, chronic kidney disease [9], cancer [10], and sepsis [11].

Control of excessive oxidative stress is vital within cells to maintain cellular and genome integrity. Damage to the genome is particularly detrimental to host organisms and cells have evolved complex pathways to detect and coordinate response to and repair of DNA damage. Studies indicate that many pathophysiological states that are characterized by elevated oxidative stress are also associated with upregulation of the DNA damage response (DDR). For example, markers of DDR upregulation are found in patients of inflammatory diseases such as cancer [12][13] and chronic systemic autoimmune diseases [14]. Acute parasitic infection with Trypanosoma cruzi was found to induce phosphorylation of histone H2AX (i.e., γH2AX) [15] , migraine headaches are associated with increased marker of oxidative DNA damage 8-hydroxy-2′-deoxyguanosine (8-OHdG) [16], and patients with sepsis were found to have increased markers of oxidative DNA damage (8-OHdG) levels compared to healthy controls [17]. Certain pathophysiological conditions associated with elevated RONS are also correlated with epigenetic changes to the nuclear chromatin of affected (i.e., oxidative stress) cells. One striking example are the epigenetic changes in macrophages and dendritic cells during acute inflammatory conditions such as sepsis that are responsible for suppression of these cells and hypo-responsiveness upon subsequent infection in sepsis survivors. Lasting changes, as in the latter example, can only occur when epigenetic changes are made to stem cells that replenish the supply of successor cells throughout the lifetime of an individual.

Sepsis is a prime representative inflammatory disease characterized by high oxidative stress through which epigenetic reprogramming of hematopoietic stem cells (HSCs) by pathways putatively upregulated by RONS may be explored. Recent evidence suggests that DDR factors such as ATM, p53, and p21 may be involved in initiating these epigenetic changes. Here we discuss the newly emerging evidence for interplay between the antioxidant response, the DNA damage response, and the epigenetic regulation, in particular of hematopoietic stem cells. Implications from this connectiveness may open new avenues of mechanistic research for a host of different pathologies associated with elevated oxidative stress, including cancer, autoimmune disease, and aging.

2. Physiological Regulation and Response to RONS

Maintenance of the nuclear genome is vital for survival and eukaryotic organisms have evolved an elaborate array of pathways to detect and coordinate repair of various forms of DNA damage [18]. DNA lesions can generally occur through a wide range of sources, including UV irradiation and genotoxic agents, but are primarily the result of endogenously generated RONS under conditions of proinflammatory responses. Different types of DNA damage result in varied repair pathways and include alterations to bases, formation of bulky adducts, mismatched base pairs, crosslinking, loss of a base (also known as AP site), single-strand DNA breaks (SSBs), and double-strand DNA breaks (DSBs).

The canonical function of ATM as a master regulator of the DSB DDR pathway is well-established. In this role, ATM mediates S-phase checkpoint activation in conjunction with initiation of DDR signaling [19]. In most cell types ATM is predominantly localized to the nucleus as an inactive and noncovalent homodimer [20]. Upon detection of DSBs,

human ATM is acetylated at lysine K3016 (in the FATC domain), autophosphorylated at serine S1981, and subsequently monomerized and may also be recruited to sites of DNA damage by the Mre11, Rad50, Nbs1 (MRN) protein complex at the DSB site [21]. Autophosphorylation may not be a requirement for activation in response to DNA damage in non-human species such as mice or Xenopus [22][23][24]. Thus, in response to DSBs, ATM is converted into an active monomer form that phosphorylates an estimated hundreds of substrates that are involved in cell cycle checkpoints, DNA repair, and additional cell responses [19][20][25]. Following response to DNA damage, ATM phosphorylates and activates p53 and Chk2, initiating DNA repair, cell cycle arrest, and other processes. Under such conditions, the phosphorylated ATM forms discrete foci in the nucleus. ATM and Chk2 can both lead to γH2AX, which is a commonly used marker of DSBs. H2AX is phosphorylated at serine S139 by ATM. DSB foci uniquely contain γH2AX, which spreads throughout neighboring chromatin domains over more than 1 Mb on each side, nucleating additional response sites to amplify the repair signal [26][27].

Phosphorylation of p53 at serine Ser20, a downstream effector transcription factor, leads to its activation, translocation to the nucleus, and transcriptional upregulation of genes that regulate the cell cycle, DNA repair, apoptosis, senescence, and angiogenesis, and the ubiquitin ligase MDM2, leading to accumulation of p53 [28]. One of the many downstream targets of activated p53 transcriptional upregulation is p21 Cip1/ Waf1 (p21), a cyclin-dependent kinase inhibitor that primarily inhibits cyclin/cyclin-dependent kinase (CDK) complexes and regulates the G1/S phase cell cycle progression. Upregulation of p21 is one of the key mechanisms through which p53 mediates cell cycle arrest in response to DNA damage detection [29].

Overall, the evidence indicates that RONS play crucial roles in regulation of epigenetic modifications to nuclear DNA through redox mediators, direct utilization as cofactors in chemical modifications on DNA, and through regulation of epigenetically modifying enzyme expression.

3. Pathological States Associated with High Oxidants Result in Epigenetic Changes to Stem Cells

Sepsis is a prime example of a proinflammatory pathological condition characterized by excessive oxidative stress with resultant epigenetic modifications to innate immune cells and hematopoietic stem cells (HSCs). Sepsis is defined as a state of life-threatening organ dysfunction that occurs due to dysregulated and excessive host response to an infection that presents with a wide array of symptoms such as hypoxia, hypotension, hypercoagulation, circulatory failure, tachycardia, high blood lactate levels, metabolic disorders, and multiple organ failure (MOF) [30][31]. Thanks to advances in emergency medical care the number of patients who survive sepsis has risen steeply in recent years. However, a large portion of sepsis survivors face long-term complications including physical, psychological, and cognitive disorders, as well as persistent immunological impairment and immunosuppression that lead to a lifelong increased risk of mortality. The reasons for this increased rate of mortality among sepsis survivors is thought to be due to changes in their innate immune system function, resulting in immune dysregulation and inability to respond adequately to subsequent infection. Dysregulation of the innate immune function in sepsis survivors is termed the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). The mechanisms underlying PICS remain unclear and are the subject of intensive research [32].

Recent findings suggest that the immunosuppression of innate immune cells in sepsis survivors is a form of innate immune memory, which is defined as a functional reprogramming of innate immune cells after a pathogenic encounter leading to either an enhanced (trained) or reduced (tolerant) response to subsequent encounters [33]. Macrophages, along with neutrophils, dendritic cells, and T-helper (TH) cells, are a major component of the immune response to sepsis and are one of the cell types most impacted by immunosuppression due to their critical role in the immune response upon subsequent infection. Phenotypic differences between macrophages from healthy individuals and those from sepsis survivors with impaired immune function (PICS) have been studied extensively. Genes with inducible expression in macrophages under normal physiological conditions that are not inducible in 'tolerant' (Class T) macrophages include genes such as iNOS (NOS2), CD40, IL-6, IL-1β, caspase 12, etc. [34].

Innate immune cells present during the acute phase of sepsis undergo chromatin modifications that alter their cellular function; however, the permanent change seen in immune cells of sepsis survivors for years after the initial insult and well beyond the lifespan of any innate immune cells present at the time is due to changes to the hematopoietic stem cell (HSC) pool that give rise to all successive innate immune cells. Numerous studies indicate that induction of emergency hematopoiesis, the rapid activation and differentiation of HSCs within the bone marrow (BM) environment, and even depletion of HSCs occur during sepsis[1] [35][36][37]. In addition, recent studies provide evidence that during the acute phase of sepsis, epigenetic changes are made to HSC nuclear chromatin [38]. This critically important piece of the emerging picture provides a mechanism for how innate immune cells of sepsis survivors remain permanently suppressed. Changes to gene transcriptional programs within mature innate immune cells during sepsis last only as long as the reprogrammed cells. In contrast, changes to the epigenetic status of HSCs can be imparted to all progeny immune cells.

While it is broadly accepted that RONS are capable of inducing DNA damage and triggering upregulation of the DDR [39], evidence has accumulated that RONS cause DNA damage in innate immune cells specifically during sepsis. In a study of human sepsis patients, the level of oxidative DNA damage, measured by 8-OHdG levels, found that DNA damage was increased in septic patients compared to healthy controls [17]. These increases in DNA damage were suggested to be correlated with increased levels of oxidative stress (i.e., RONS).

4. The Upregulation of the DDR and the Epigenetic Modifications to Stem Cells May Be Causally Linked

ATM has been demonstrated to modulate the activity of several transcription factors (TFs) with known epigenetic regulatory functions such as HIF1α and NFκB, providing a link between ATM and epigenetic regulation. Interestingly, ATM activated by oxidative stress may activate HIF1α through two separate routes: (i) through activation of AKT and mTORC1 and (ii) through direct activation of HIF1α. Interaction of ATM with downstream mTORC1 and HIF1α present myriad routes through which ATM could regulate epigenetic control.

When activated via oxidation and covalent homodimerization, ATM activates AKT, a known key activator of mammalian target of rapamycin (mTOR) complex 1 (mTORC1). The mTORC1 complex is a major regulator of

metabolism, proliferation, growth, autophagy, and anabolic processes within the cell. mTOR is a PIKK and a master regulator of cellular homeostasis [19][40]. One downstream target of mTORC1 is the transcription factor HIF1α. Oxidized ATM activates AKT, thereby increasing translocation of GLUT4 receptors to the plasma membrane and increasing uptake of glucose while upregulating glucose-6-phosphate dehydrogenase (G6PD) and also resulting in activation of HIF1α [41][42]. An alternative and more direct activation of HIF1α by ATM has been described, where ATM that is activated by hypoxic stress directly phosphorylates HIF1α on serine S696 [43]. HIF1α is known to modulate various forms of epigenetic regulation including miRNA expression, histone modification, and chromatin structure [44]. Additionally, HIF1α modulates gene activity of epigenetic regulators histone lysine demethylases (including K-specific demethylases or Jumonji C lysine demethylases) [44]. Activation of this TF, that is tightly associated with epigenetic change, could be one mechanistic pathway through which ATM modulates epigenetic reprograming of innate immune cells and HSCs during sepsis.

Activation of mTORC1 is also known to activate effectors that interact with epigenetic regulators required for modifying chromatin structure and function to control gene expression [45]. For example, mTORC1 signals to downstream epigenetic effects such as regulators of ribosomal gene transcription. mTORC1 can additionally modulate binding of HATs to specific gene promotors, thereby altering gene expression profiles. For example, in yeast mTORC1 promotes binding of the Esa1 HAT to RP gene promotors. Inhibition of mTORC1, such as by rapamycin, also decreases histone H4 acetylation at these promotors by initiating release of Esa1, reducing transcription of the RP gene [46]. mTORC1 inhibition may also increase the activity of specific HDACs, such as Rpd3 in yeast to transcriptionally repress ribosome biogenesis [47].

Protein acetylation has also been demonstrated as an important modulator of NOS2 gene transcription. Binding of NFκB to the NOS2 promoter initiates recruitment of epigenetic modifiers such as HAT enzymes (ex. p300), which acetylate NFκB subunits p65 and p50 and promote NOS2 gene expression. Interestingly, HDAC inhibitors have been shown to suppress induced NOS2 gene transcription through multiple mechanisms including acetylation at inhibitory sites or acetylation of additional subunits (i.e., p52) promoting formation of a complex that cannot bind DNA. Additionally, under conditions of high glucose concentration, Set7 methyltransferase expression is increased resulting in accumulation of H3K4me1 at the RELA gene that encodes the NFκB subunit p65 [48]. Known connections between ATM regulation of the key transcription factor involved in regulating most of the genes that become tolerized in suppressed innate immune cells of sepsis survivors further raises the possibility that ATM is involved in this epigenetic reprogramming.

References

1. Buetler, T.M.; Krauskopf, A.; Ruegg, U.T. Role of Superoxide as a Signaling Molecule. Physiology 2004, 19, 120–123.
2. D’Autréaux, B.; Toledano, M.B. ROS as signalling molecules: Mechanisms that generate specificity in ROS homeostasis. Nat. Rev. Mol. Cell Biol. 2007, 8, 813–824.

3. Moldogazieva, N.T.; Mokhosoev, I.M.; Feldman, N.B.; Lutsenko, S.V. ROS and RNS signalling: Adaptive redox switches through oxidative/nitrosative protein modifications. Free Radic. Res. 2018, 52, 507–543.
4. Behl, C. Oxidative stress in Alzheimer's disease: Implications for prevention and therapy. Subcell. Biochem. 2005, 38, 65–78.
5. Browne, S.E.; Beal, M.F. Oxidative damage in Huntington's disease pathogenesis. Antioxid. Redox Signal. 2006, 8, 2061–2073.
6. Sugamura, K.; Keaney, J.F., Jr. Reactive oxygen species in cardiovascular disease. Free Radic. Biol. Med. 2011, 51, 978–992.
7. Filippin, L.I.; Vercelino, R.; Marroni, N.P.; Xavier, R.M. Redox signalling and the inflammatory response in rheumatoid arthritis. Clin. Exp. Immunol. 2008, 152, 415–422.
8. Jiang, Z.; Duong, T.Q. Methylene blue treatment in experimental ischemic stroke: A mini review. Brain Circ. 2016, 2, 48–53.
9. Liguori, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; Della-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D.; et al. Oxidative stress, aging, and diseases. Clin. Interv. Aging 2018, 13, 757–772.
10. Hayes, J.D.; Dinkova-Kostova, A.T.; Tew, K.D. Oxidative Stress in Cancer. Cancer Cell 2020, 38, 167–197.
11. Prauchner, C.A. Oxidative stress in sepsis: Pathophysiological implications justifying antioxidant co-therapy. Burns 2017, 43, 471–485.
12. Maya-Mendoza, A.; Ostrakova, J.; Kosar, M.; Hall, A.; Duskova, P.; Mistrik, M.; Merchut-Maya, J.M.; Hodny, Z.; Bartkova, J.; Christensen, C.; et al. Myc and Ras oncogenes engage different energy metabolism programs and evoke distinct patterns of oxidative and DNA replication stress. Mol. Oncol. 2015, 9, 601–616.
13. Park, M.T.; Kim, M.J.; Suh, Y.; Kim, R.K.; Kim, H.; Lim, E.J.; Yoo, K.C.; Lee, G.H.; Kim, Y.H.; Hwang, S.G.; et al. Novel signaling axis for ROS generation during K-Ras-induced cellular transformation. Cell Death Differ. 2014, 21, 1185–1197.
14. Souliotis, V.L.; Vlachogiannis, N.I.; Pappa, M.; Argyriou, A.; Ntouros, P.A.; Sfikakis, P.P. DNA Damage Response and Oxidative Stress in Systemic Autoimmunity. Int. J. Mol. Sci. 2020, 21, 55.
15. Florentino, P.T.V.; Mendes, D.; Vitorino, F.N.L.; Martins, D.J.; Cunha, J.P.C.; Mortara, R.A.; Menck, C.F.M. DNA damage and oxidative stress in human cells infected by Trypanosoma cruzi. PLoS Pathog. 2021, 17, e1009502.
16. Geyik, S.; Altunısık, E.; Neyal, A.M.; Taysi, S. Oxidative stress and DNA damage in patients with migraine. J. Headache Pain 2016, 17, 10.

17. Bahar, I.; Elay, G.; Başkol, G.; Sungur, M.; Donmez-Altuntas, H. Increased DNA damage and increased apoptosis and necrosis in patients with severe sepsis and septic shock. J. Crit. Care 2018, 43, 271–275.
18. Van Houten, B.; Santa-Gonzalez, G.A.; Camargo, M. DNA repair after oxidative stress: Current challenges. Curr. Opin. Toxicol. 2018, 7, 9–16.
19. Paull, T.T. Mechanisms of ATM Activation. Annu. Rev. Biochem. 2015, 84, 711–738.
20. Bakkenist, C.J.; Kastan, M.B. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 2003, 421, 499–506.
21. Lee, J.-H.; Paull, T.T. ATM Activation by DNA Double-Strand Breaks through the Mre11-Rad50-Nbs1 Complex. Science 2005, 308, 551–554.
22. Pellegrini, M.; Celeste, A.; Difilippantonio, S.; Guo, R.; Wang, W.; Feigenbaum, L.; Nussenzweig, A. Autophosphorylation at serine 1987 is dispensable for murine Atm activation in vivo. Nature 2006, 443, 222–225.
23. Daniel, J.A.; Pellegrini, M.; Lee, J.-H.; Paull, T.T.; Feigenbaum, L.; Nussenzweig, A. Multiple autophosphorylation sites are dispensable for murine ATM activation in vivo. J. Cell Biol. 2008, 183, 777–783.
24. Dupré, A.; Boyer-Chatenet, L.; Gautier, J. Two-step activation of ATM by DNA and the Mre11–Rad50–Nbs1 complex. Nat. Struct. Mol. Biol. 2006, 13, 451–457.
25. Kozlov, S.V.; Graham, M.E.; Peng, C.; Chen, P.; Robinson, P.J.; Lavin, M.F. Involvement of novel autophosphorylation sites in ATM activation. EMBO J. 2006, 25, 3504–3514.
26. Weintz, G.; Olsen, J.V.; Frühauf, K.; Niedzielska, M.; Amit, I.; Jantsch, J.; Mages, J.; Frech, C.; Dölken, L.; Mann, M.; et al. The phosphoproteome of toll-like receptor-activated macrophages. Mol. Syst. Biol. 2010, 6, 371.
27. Neves-Costa, A.; Moita, L.F. Modulation of inflammation and disease tolerance by DNA damage response pathways. FEBS J. 2017, 284, 680–698.
28. Beyfuss, K.; Hood, D.A. A systematic review of p53 regulation of oxidative stress in skeletal muscle. Redox Rep. 2018, 23, 100–117.
29. He, G.; Siddik, Z.H.; Huang, Z.; Wang, R.; Koomen, J.; Kobayashi, R.; Khokhar, A.R.; Kuang, J. Induction of p21 by p53 following DNA damage inhibits both Cdk4 and Cdk2 activities. Oncogene 2005, 24, 2929–2943.
30. Huang, M.; Cai, S.; Su, J. The Pathogenesis of Sepsis and Potential Therapeutic Targets. Int. J. Mol. Sci. 2019, 20, 5376.

31. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.-D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016, 315, 801–810.
32. Cross, D.; Drury, R.; Hill, J.; Pollard, A.J. Epigenetics in Sepsis: Understanding Its Role in Endothelial Dysfunction, Immunosuppression, and Potential Therapeutics. Front. Immunol. 2019, 10, 1363.
33. Bomans, K.; Schenz, J.; Sztwiertnia, I.; Schaack, D.; Weigand, M.A.; Uhle, F. Sepsis Induces a Long-Lasting State of Trained Immunity in Bone Marrow Monocytes. Front. Immunol. 2018, 9, 2685.
34. Foster, S.L.; Hargreaves, D.C.; Medzhitov, R. Gene-specific control of inflammation by TLR-induced chromatin modifications. Nature 2007, 447, 972–978.
35. Skirecki, T.; Zielińska-Borkowska, U.; Kawiak, J.; Hoser, G. Sepsis modulates the human hematopoietic stem cell compartment in peripheral blood and bone marrow. Crit. Care 2014, 18, P33.
36. Wang, P.; Wang, J.; Li, Y.-H.; Wang, L.; Shang, H.-C.; Wang, J.-X. Phenotypical Changes of Hematopoietic Stem and Progenitor Cells in Sepsis Patients: Correlation with Immune Status? Front. Pharmacol. 2021, 11, 640203.
37. Skirecki, T.; Mikaszewska-Sokolewicz, M.; Godlewska, M.; Dołęgowska, B.; Czubak, J.; Hoser, G.; Kawiak, J.; Zielińska-Borkowska, U. Mobilization of Stem and Progenitor Cells in Septic Shock Patients. Sci. Rep. 2019, 9, 3289.
38. Pinheiro da Silva, F.; Machado, M.C.C. Septic Shock and the Aging Process: A Molecular Comparison. Front. Immunol. 2017, 8, 1389.
39. Nastasi, C.; Mannarino, L.; D'Incalci, M. DNA Damage Response and Immune Defense. Int. J. Mol. Sci. 2020, 21, 7504.
40. Valvezan, A.J.; Manning, B.D. Molecular logic of mTORC1 signalling as a metabolic rheostat. Nat. Metab. 2019, 1, 321–333.
41. Zhang, Y.; Lee, J.-H.; Paull, T.T.; Gehrke, S.; D'Alessandro, A.; Dou, Q.; Gladyshev, V.N.; Schroeder, E.A.; Steyl, S.K.; Christian, B.E.; et al. Mitochondrial redox sensing by the kinase ATM maintains cellular antioxidant capacity. Sci. Signal. 2018, 11, eaaq0702.
42. Khalil, H.; Tummala, H.; Zhelev, N. ATM in focus: A damage sensor and cancer target. BioDiscovery 2012, 1, e8936.
43. Cam, H.; Easton, J.B.; High, A.; Houghton, P.J. mTORC1 Signaling under Hypoxic Conditions Is Controlled by ATM-Dependent Phosphorylation of HIF-1α. Mol. Cell 2010, 40, 509–520.

44. Mimura, I.; Tanaka, T.; Nangaku, M. Novel therapeutic strategy with hypoxia-inducible factors via reversible epigenetic regulation mechanisms in progressive tubulointerstitial fibrosis. Semin Nephrol. 2013, 33, 375–382.
45. Laribee, R.N. Transcriptional and Epigenetic Regulation by the Mechanistic Target of Rapamycin Complex 1 Pathway. J. Mol. Biol. 2018, 430, 4874–4890.
46. Rohde, J.R.; Cardenas, M.E. The tor pathway regulates gene expression by linking nutrient sensing to histone acetylation. Mol. Cell. Biol. 2003, 23, 629–635.
47. Tsang, C.K.; Bertram, P.G.; Ai, W.; Drenan, R.; Zheng, X.F.S. Chromatin-mediated regulation of nucleolar structure and RNA Pol I localization by TOR. EMBO J. 2003, 22, 6045–6056.
48. Handy, D.; Loscalzo, J. Epigenetics and the Regulation of Nitric Oxide. In Nitrite and Nitrate in Human Health and Disease, 2nd ed.; Bryan, N.S., Loscalzo, J., Eds.; Humana Press/Springer Nature: Gewerbestrasse, Switzerland, 2017; pp. 33–52.