

Casual Friday Series

# Short Circuiting Neuropathy

A Biogenetix Clinical Presentation

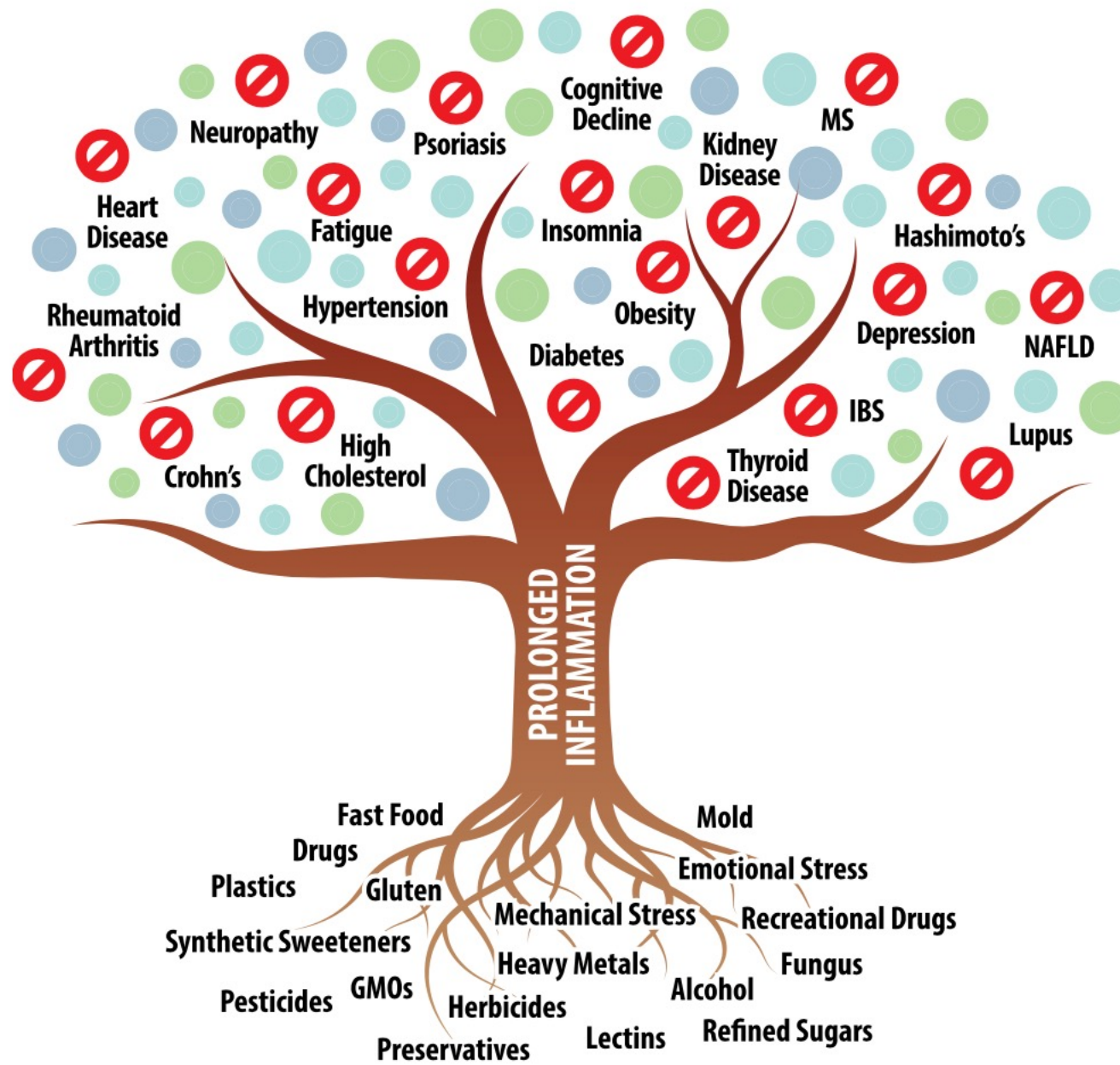
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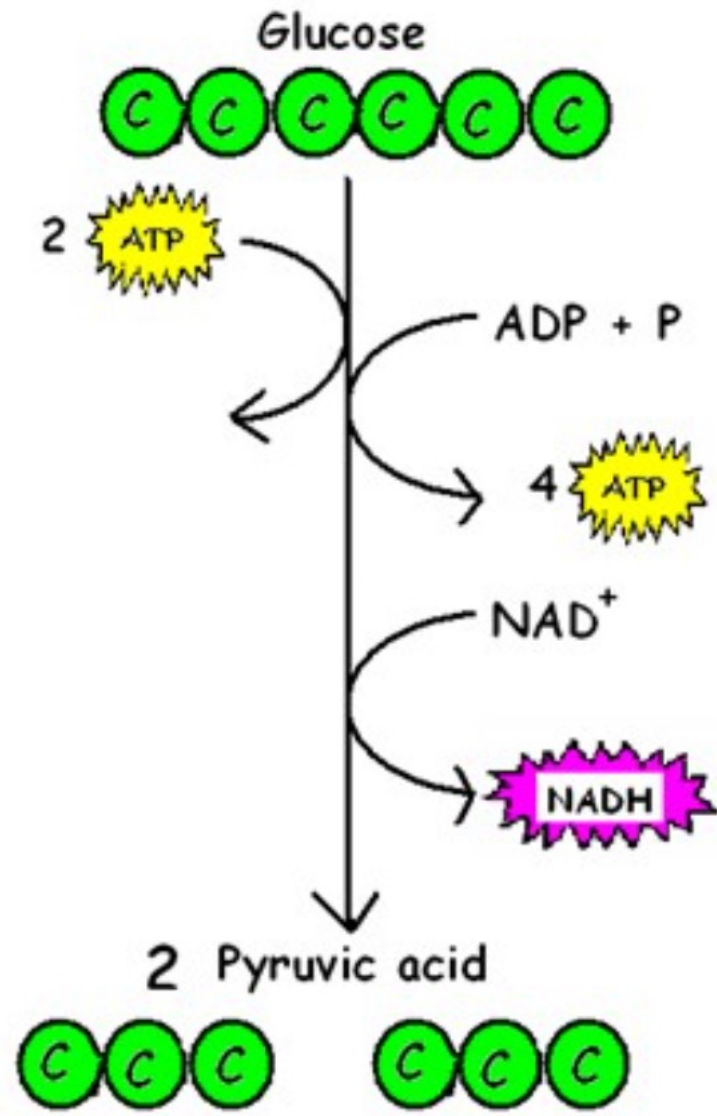


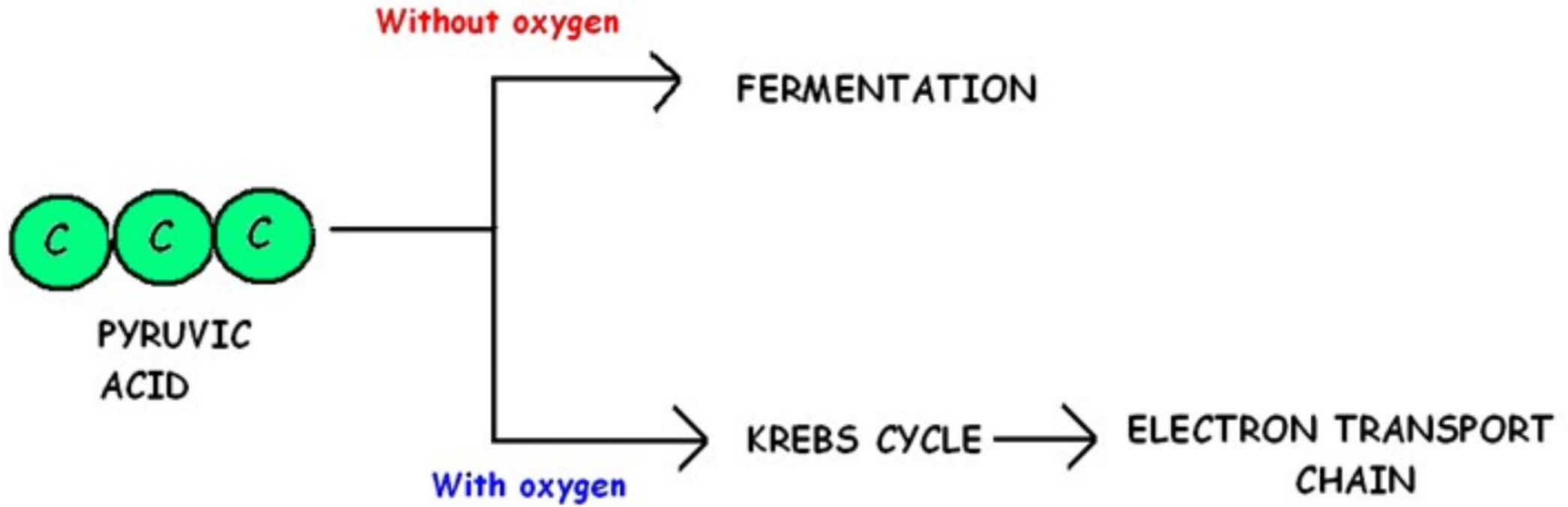
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- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*



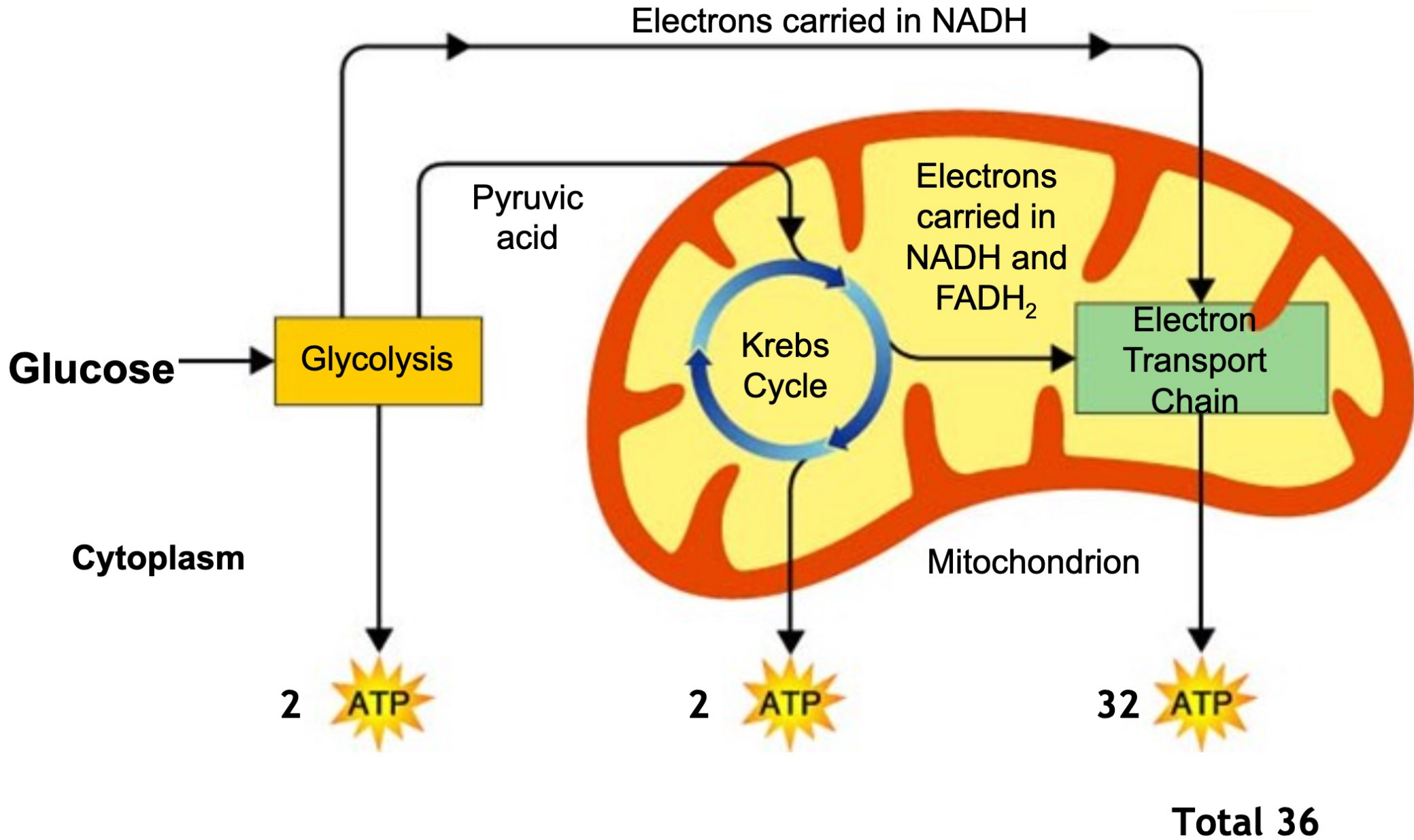


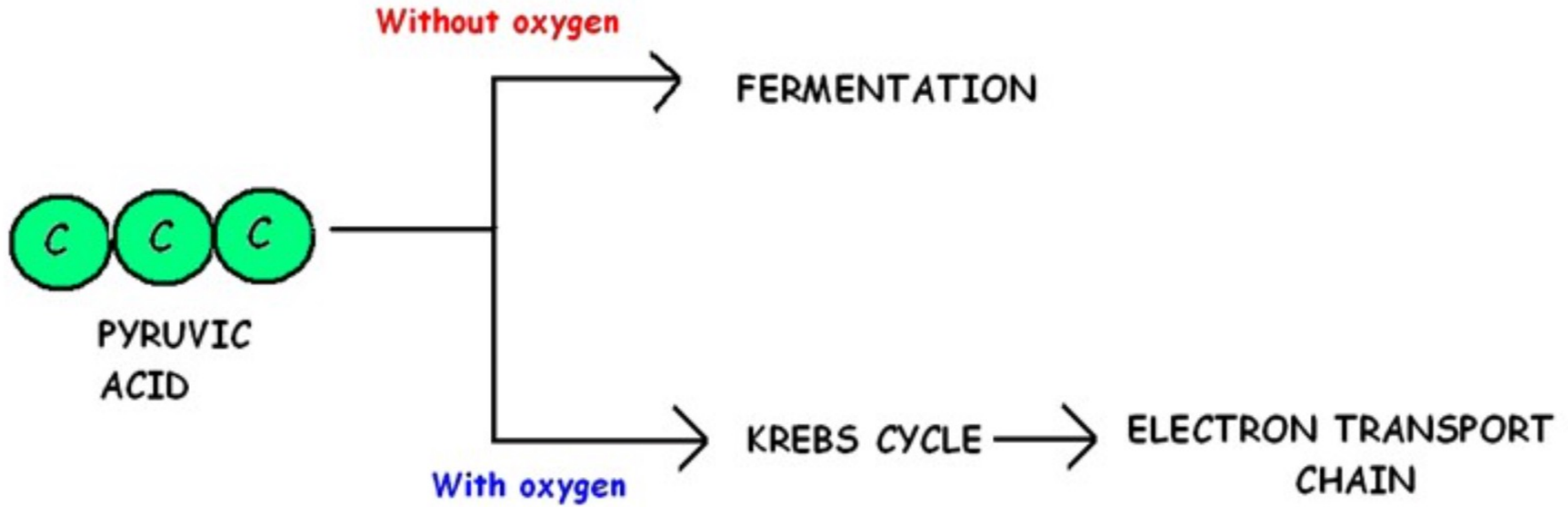






# WITH O<sub>2</sub>





## 2 Types of Fermentation:

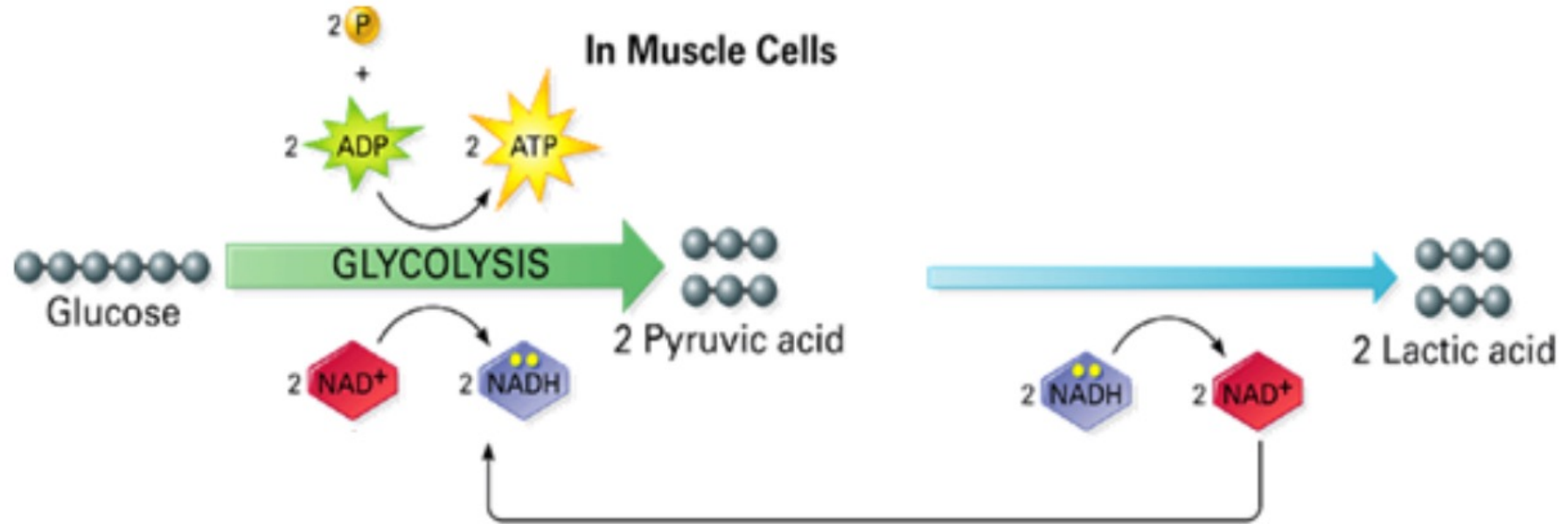
1. Alcoholic

2. Lactic Acid





# WITHOUT O<sub>2</sub>



Fermentation happens in order to generate NAD<sup>+</sup> so cells can keep glycolysis going.



Without oxygen, pyruvic acid build up and all the NAD<sup>+</sup> carriers are saturated/full.

Eventually Glycolysis will STOP.





# Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Diseases by Targeting NAD<sup>+</sup> Metabolism

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## OPEN ACCESS

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NAD<sup>+</sup>, a co-enzyme involved in a great deal of biochemical reactions, has been found to be a network node of diverse biological processes. In mammalian cells, NAD<sup>+</sup> is synthesized, predominantly through NMN, to replenish the consumption by NADase participating in physiologic processes including DNA repair, metabolism, and cell death.

## CD38

The CD38 enzyme and its homolog CD157 were initially described as plasma membrane antigens on thymocytes and T lymphocytes. Their role in NAD<sup>+</sup> consumption have been revealed; that is, CD157/BST-1 could hydrolyze NR (Preugschat et al., 2014) and CD38 hydrolyzes NAD<sup>+</sup> to generate NAM, adenosine diphosphoribose (ADPR), and cyclic ADPR (cADPR). In addition, CD38 also hydrolyzes cADPR (De Flora et al., 2004) and NMN (Grozio et al., 2013).

In mammals, the level of NAD<sup>+</sup> and mitochondrial function decreased partially through regulation of SIRT3 as the expression and activity of CD38 protein increased in various tissues during aging (Camacho-Pereira et al., 2016). Administration of CD38

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CD38 is an enzyme embedded into the membranes of T Lymphocytes. They consume NAD<sup>+</sup>. NAD<sup>+</sup> and mitochondrial function both go down with CD38 activity.





## Sterile Alpha and TIR Motif-Containing 1 (SARM1) Protein

The toll/interleukin-1 receptor (TIR) domain of sterile alpha and TIR motif-containing 1 (SARM1) protein presents NADase activity (Rajman et al., 2018) that is involved in axonal degeneration after axon injury. In response to neuronal injury, the TIR domain of SARM1 cleaves NAD<sup>+</sup> to generate ADP ribose (ADPR) and cyclic ADPR, which may contribute to axonal degeneration (Essuman et al., 2017). Paradoxically, overexpression of enzymes in NAD<sup>+</sup> biosynthesis pathway or supplying NR could inhibit SARM1-induced axon destruction (Gerdt et al., 2015).

In summary, there are many ways of restoring NAD<sup>+</sup> level depletion caused by aging or other diseases, including improving NAMPT expression, providing NAD<sup>+</sup> precursors, or inhibiting NAD<sup>+</sup> consuming enzymatic activities of PARP, CD38, and SARM1. Currently, supplementation with NMN or NR is considered a viable and highly efficient strategy of increasing NAD<sup>+</sup> levels (**Figure 3**).

Toll like receptors, which trigger NFKB and cell mediated inflammation cause breakdown of NAD<sup>+</sup> and further axonal degeneration. Remove NAD<sup>+</sup> and degeneration ensures, specifically within neurons.



[Clin Epigenetics](#). 2016; 8: 61.


Published online 2016 May 25. doi: [10.1186/s13148-016-0224-3](https://doi.org/10.1186/s13148-016-0224-3)

PMCID: PMC4879741

PMID: [27226812](https://pubmed.ncbi.nlm.nih.gov/27226812/)

## Sirtuin functions and modulation: from chemistry to the clinic

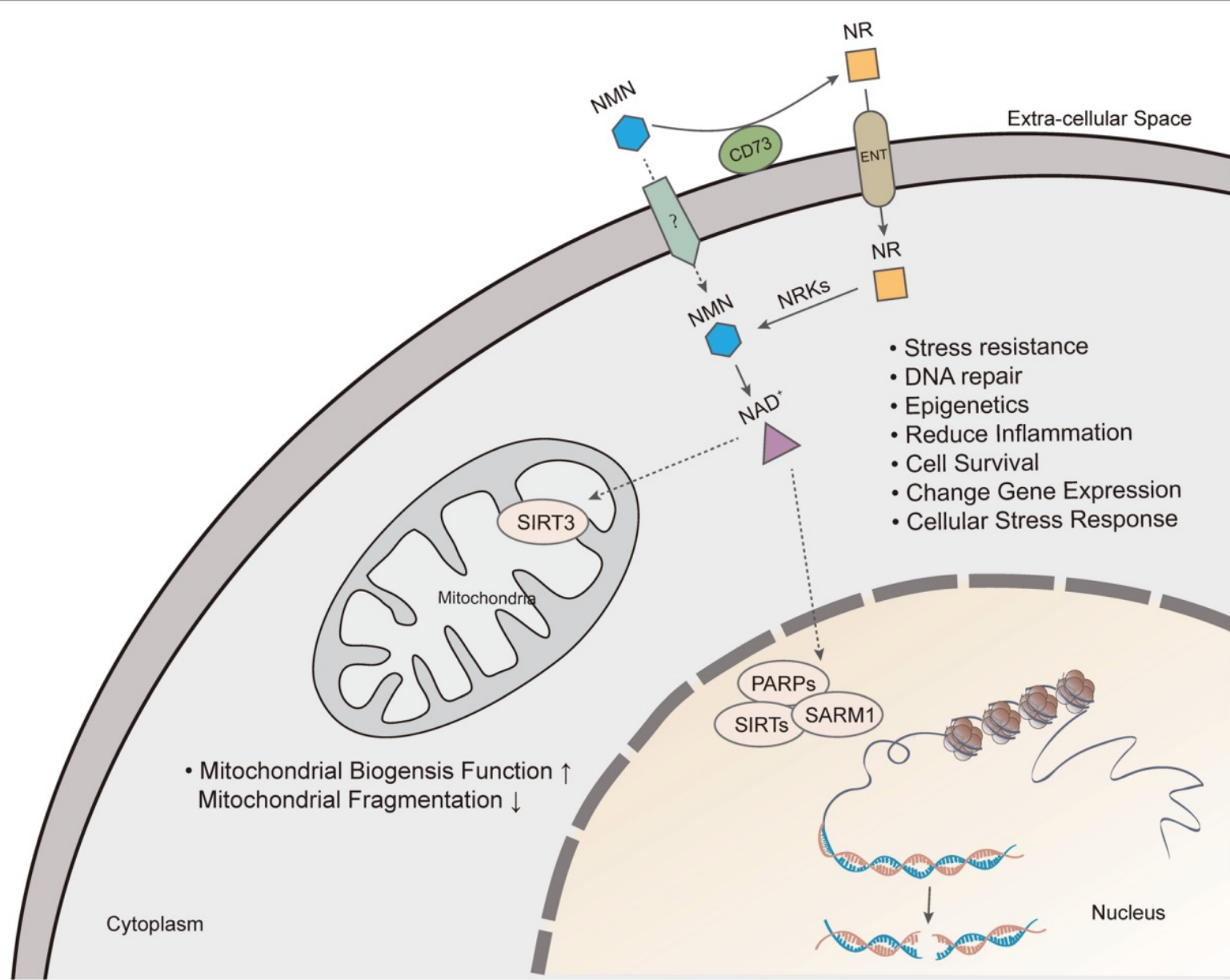
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Sirtuins are NAD<sup>+</sup>-dependent histone deacetylases regulating important metabolic pathways in prokaryotes and eukaryotes and are involved in many biological processes such as cell survival, senescence, proliferation, apoptosis, DNA repair, cell metabolism, and caloric restriction. The seven members of this family of enzymes are considered potential targets for the treatment of human pathologies including neurodegenerative diseases, cardiovascular diseases, and cancer. Furthermore, recent interest focusing on sirtuin modulators as epigenetic players in the regulation of fundamental biological pathways has prompted increased efforts to discover new small molecules able to modify sirtuin activity. Here, we review the role, mechanism of action, and biological function of the seven sirtuins, as well as their inhibitors and activators.







**FIGURE 3** | Nicotinamide mononucleotide exerts pharmacological effects by increasing intracellular NAD<sup>+</sup> levels. Extracellular NMN is cleavage by CD73, which yields NR that is incorporated into cells using equilibrative nucleoside transporters (ENTs). NMN is converted to NAD<sup>+</sup>, which produces beneficial effects on cell, including mitochondrial function, DNA repair, gene expression, anti-inflammation and cell survival.

Obesity and diabetes are inextricably linked. MicroRNAs (miRNAs) are key regulators of metabolism, by which SIRT1 expression is regulated in healthy conditions and metabolic diseases (Lee and Kemper, 2010). In the dietary obese mice, the elevation of hepatic microRNA-34a (miR-34a) inhibited the expression of NAMPT and SIRT1, which was responsible for the decrease in NAD<sup>+</sup> levels and SIRT1 activity (Choi et al., 2013). The reduction of SIRT1 activity resulted in transcriptional responses of decreased fatty acid  $\beta$ -oxidation and increased lipogenesis and inflammation (Choi et al., 2013). Mice overexpressing miR-34a were intraperitoneally injected with NMN (500 mg/kg) for 10 days consecutively, the effects caused by hepatic overexpression of miR-34 were reversed, and glucose tolerance was enhanced (Choi et al., 2013). These results suggested that NMN could be a potential agent for the treatment of obesity-associated T2D involving SIRT1 dysfunction.





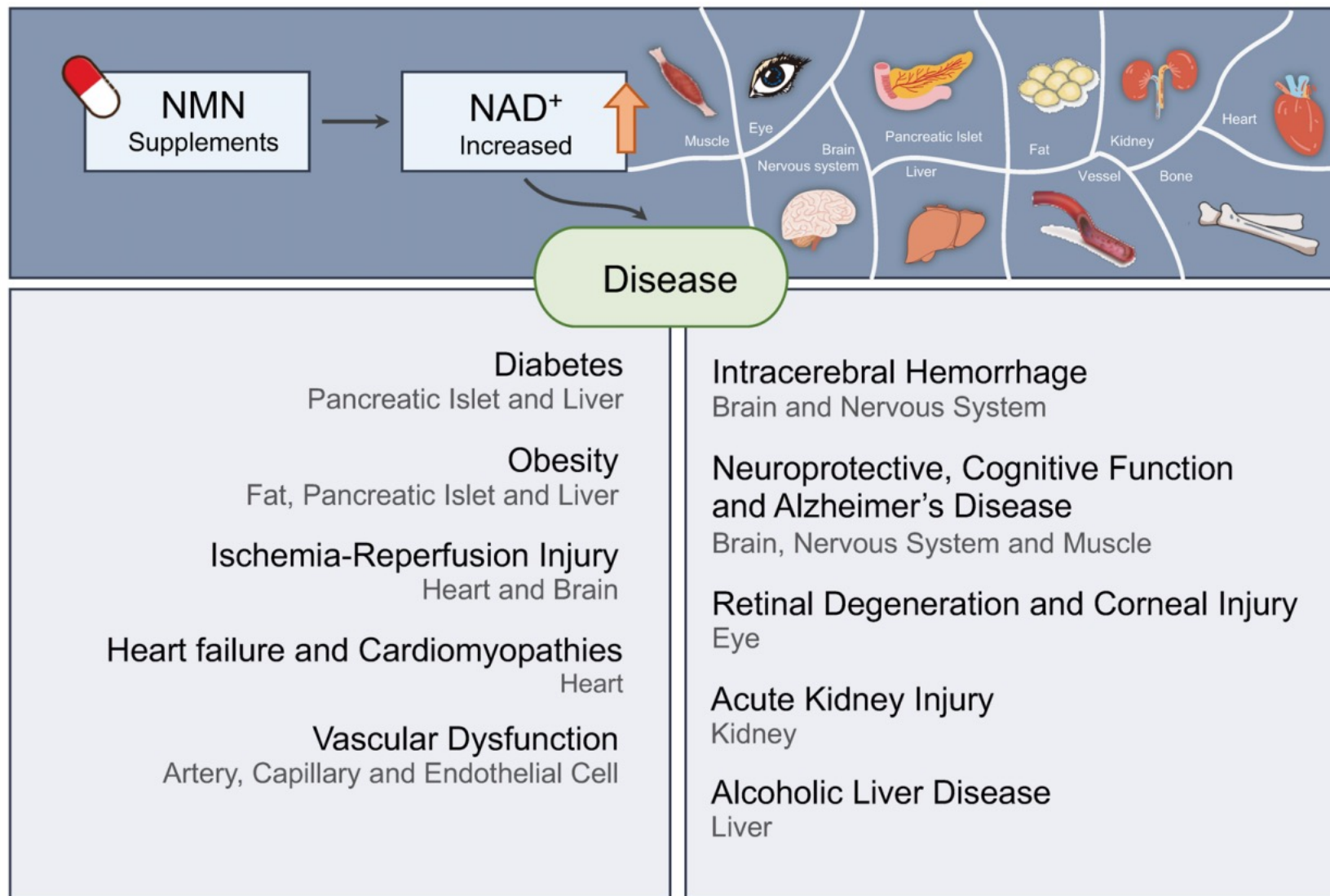
Because of the high intake of dietary sugar, the risk of metabolic syndrome and T2D has been on the increase in humans (Malik et al., 2010). Fructose consumption contributes to the development of pro-inflammatory effect in rodent models, which is involved in the process of insulin resistance and the onset of T2D (Roncal-Jimenez et al., 2011). Fructose-rich diet (FRD) results in T2D-like symptoms, including hyperglycemia, dyslipidemia, and inflammation (Roncal-Jimenez et al., 2011). FRD-fed mice showed an increased expression of IL-1 $\beta$  and TNF- $\alpha$ , which are pro-inflammatory phenotypes. The GSIS and leucine-stimulated insulin secretion (LSIS) were significantly reduced in FRD-fed mice, which was associated with islet dysfunction caused by a decrease of eNAMPT in plasma, whereas the administration of NMN at the dose of 500 mg/kg eliminated the adverse effects of FRD on GSIS and LSIS in mice (Caton et al., 2011).

FRD increased the expression of Inos (induces cellular stress and cell death) and Bax (pro-apoptotic gene) genes and reduced the expression of Pdx1, Glut2, and Gk genes, which are all

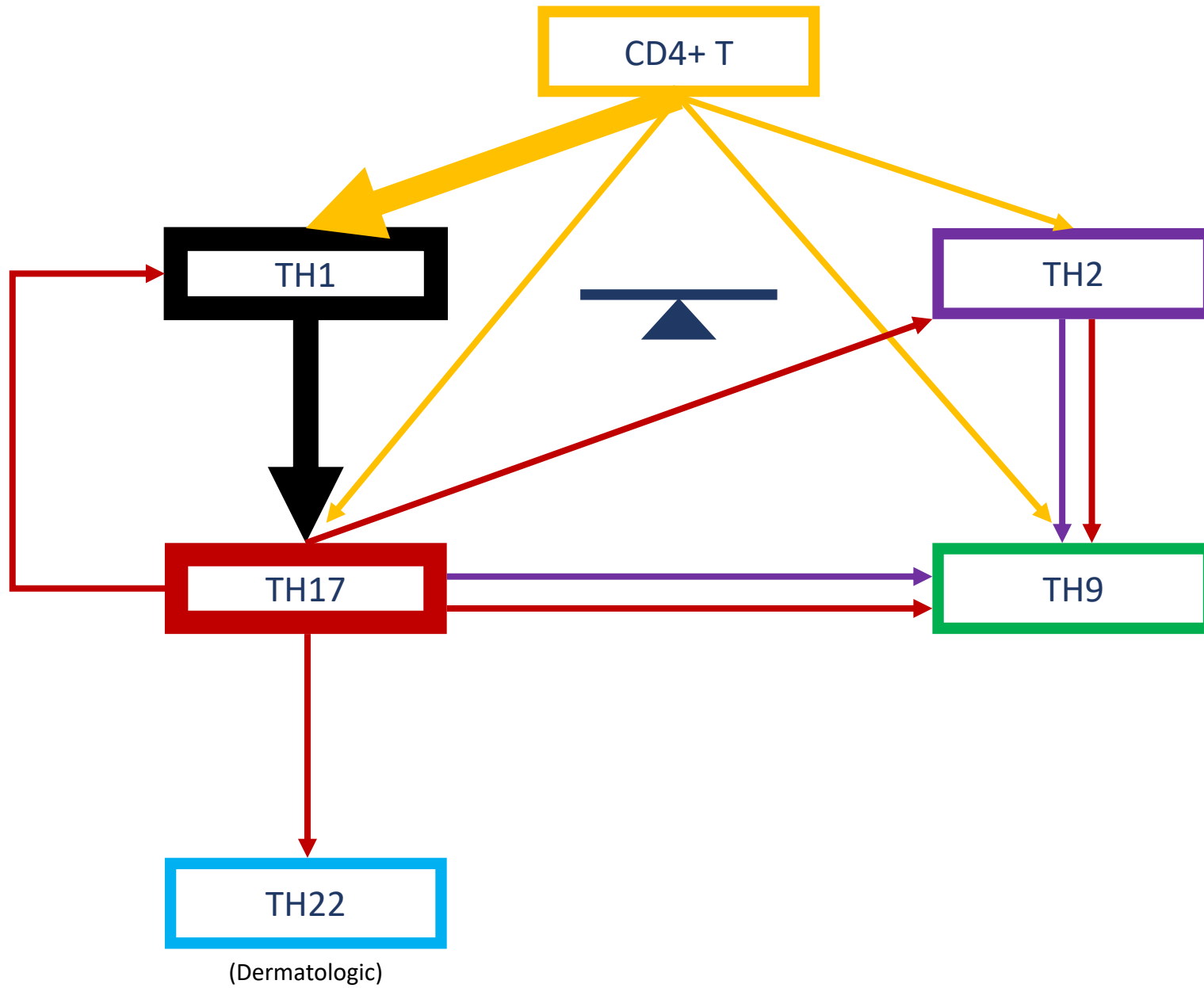
essential for glucose detection and beta-cell differentiation. These changes in gene expression were restored by NMN treatment. Moreover, the decrease in expression of Sirt1 and Sirt3 genes in FDR mice were reversed by NMN treatment. These results suggested that NMN could improve islet function by influencing the expression of genes related to anti-inflammatory, islet beta-cell differentiation, and SIRT1 activation.

Generally, these discoveries demonstrated that NMN could be a promising drug for obese-associated and age-induced T2D through the role it plays in the enhancement of NAD<sup>+</sup> biosynthesis and Sirt1 activity.

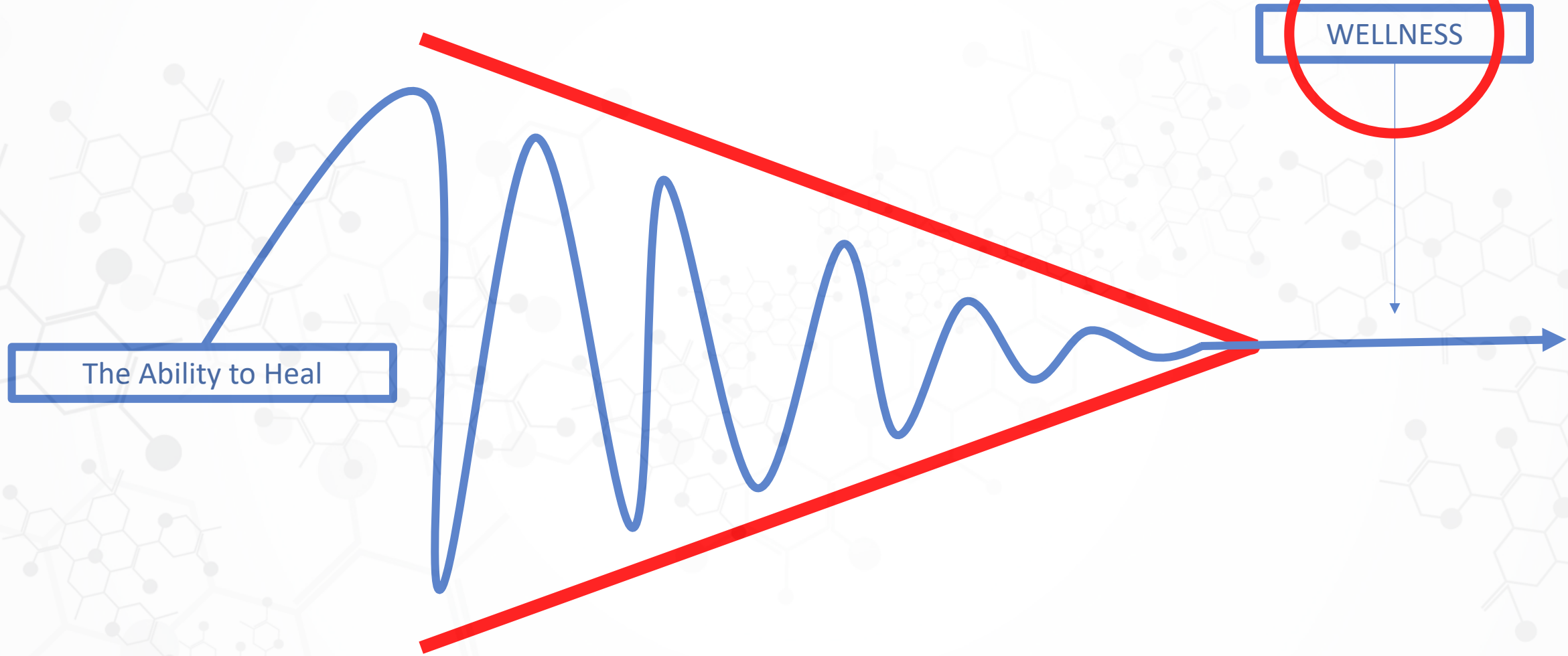




**FIGURE 4 |** Nicotinamide mononucleotide ameliorates various diseases by increasing NAD<sup>+</sup> levels in human. NMN is a promising molecule for therapy of diverse diseases, including diabetes, obesity, ischemia–reperfusion injury, heart failure, Alzheimer’s disease, retinal degeneration, acute kidney injury, and so on.



# Building Protocols



The Ability to Heal

WELLNESS





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