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Editorial-Incorporating the Altered Shikimate Pathway and Mitochondrial Melatonergic Pathways in Type 1 Diabetes Mellitus (T1D) Etiopathogenesis; Implications for Treatment

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Editorial

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Introduction

It had been clear that gut microbiome is correlated with the generation of Type 1 Diabetes Mellitus (T1D) as reviewed by us in the etiopathogenesis of T1D believed to be an autoimmune condition immunotherapy and unsulin independent immunotherapies strategies for the treatment [1-6]. Nevertheless, the precise explanation had been lacking.

Origin of type 1 diabetes mellitus (T1D) takes place from the incapacity of pancreatic βcells to generate enough insulin generally as sequelae of considerable pancreatic βcells damage. T1D gets classified as an immune modulated disease. Nevertheless, the events which guide pancreatic βcells apoptosis still need events to be estimated, causing incapacity of avoidance of continued cellular damage. Changes in the mitochondrial working is definitely the main pathophysiological event reinforcing pancreatic βcells depletion in T1D.Akin to numerous medical disorders ,it has become attractive in T1D,the part of the gut microbiome inclusive of crosstalk of the gut bacteria with the fungal infection Candida albicans. Gut dysbiosis along with gut permeability are intricately correlated with escalated circulating lipopolysaccharide (LPS) and repressed butyrate quantities,which may work in decontrolling immune reactions and systemic mitochondrial working. Here we have reviewed the wider available outcomes of T1D pathophysiology, emphasizing the significance of mitochondrial melatonergic pathways of pancreatic βcells in the guiding of mitochondrial impairment. The repression of mitochondrial melatonin makes pancreatic βcells predisposed to Oxidative stress (OS) and impaired mitophagy; minimally modulated by elimination of melatonin‘s induction of the PTEN induced kinase (PINK1) , thus repressing mitophagy and escalating autoimmune correlated major histocompatibility complex(MHC)-1.The melatonin’s immediate precursor N-acetyl serotonin (NAS), portrays a BDNF simulator through the activation of the BDNF receptor TrkB. Since both full length(TrkB-FL) &truncated(TrkB-T1) possess a substantially robust part in pancreatic βcells working and survival ,NAS, portrays one more perspective of melatonergic pathways germane for pancreatic βcells damage in T1D. Integration of the mitochondrial melatonergic pathways in T1D pathophysiology incorporates broader earlier differing outcomes over pancreatic intercellular events. The repressed *Akkermansia muciniphilia*, Lactobacillus johnsonii, butyrate, and shikimate pathway, inclusive of bacteriophages aid besidespancreatic βcells apoptosis, however further to the bystander activation of CD8+T cells, that enhances effector function and avoids their thymic deselection. The gut microbiome is a significant estimator of the mitochondrial impairment guiding pancreatic βcells elimination and autoimmune actions obtained from cytotoxicCD8+T cells. This possesses considerable future scientific work and treatment repercussions.

Thus recently George Anderson’s group has tried incorporating the aberrations in the shikimate pathway that takes place in case of microbiota like crosstalk of *Akkermansia muciniphilia* with the bacteriophages possessing the capacity of controlling *Akkermansia muciniphilia* quantities [7,8] pointing bacteriophages significantly influences through *Akkermansia muciniphilia* along with the shikimate pathway. Normally shikimate pathway is involved in generation

of aromatic amino acids, apart from tryptophan for phenylalanine,and tyrosine which is essential in microbiota & other gut microbiome for. In humans this symbiont relation is altered with use of glyphosate based herbicides (GBH), which hampers phosphoenol pyruvate (PEP)-binding to enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) thus resulting in death of *Akkermansia muciniphilia* -see ref 10for details. Furthermore they have integrated this abnormal tryptophan metabolism with repression of mitochondrial melatonergic pathway & shikimate pathway in view of melatonin precursor NAS gets formed from tryptophan (5HT) [9,10] (Figures 1&2).

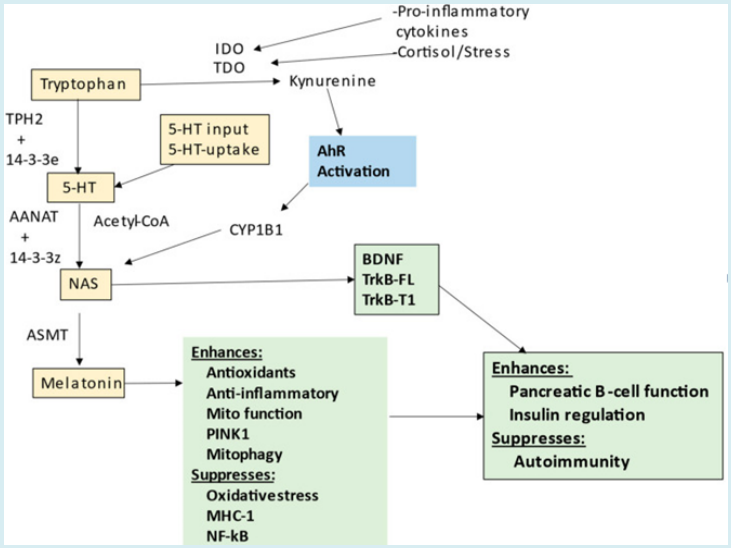

Figure 1: Shows the tryptophan–melatonin pathway (gold shade).

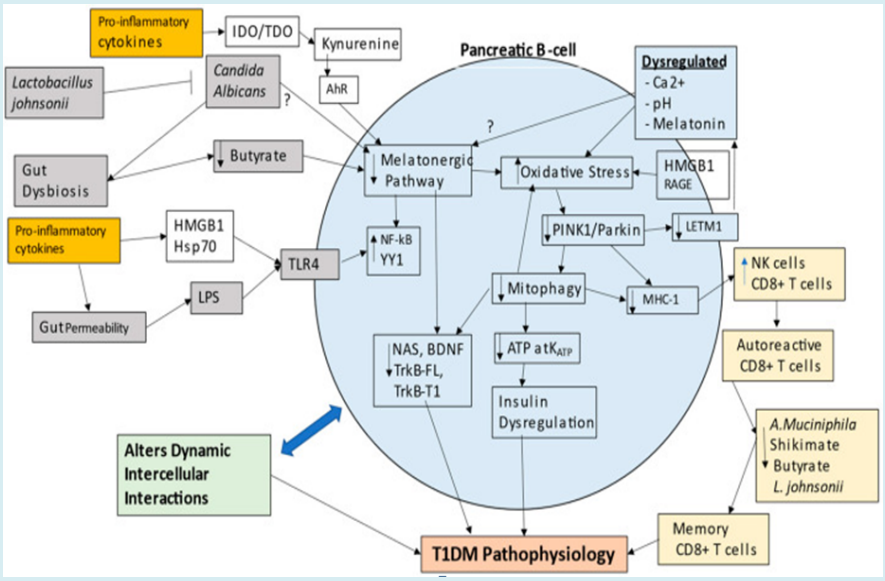

Figure 2: Shows how gut dysbiosis, gut permeability, pro-inflammatory cytokines, and Candida albicans fungal infection act to suppress the mitochondrial melatonergic pathway in pancreatic β-cells.

Tryptophan is converted by tryptophan hydroxylase (TPH2 stabilized by 14-3-3e) to serotonin (5-HT), which is the necessary precursor for the melatonergic pathway. 5-HT can also be provided by neuronal inputs and other cellular sources, including platelets. In the presence of acetyl-CoA, 5-HT is converted by 14-3-3 stabilized AANAT to N-acetylserotonin (NAS), which is then converted to melatonin by AANAT. Under inflammatory conditions, as in T1DM, cytokines increase indoleamine 2, 3-dioxygenase (IDO) and TDO, which converts tryptophan to kynurenine,

suppressing tryptophan levels. Kynurenine also activates the aryl hydrocarbon receptor (AhR), which can increase the NAS/melatonin ratio, as well as suppress available melatonin. NAS increases BDNF and can activate the TrkB receptors. Melatonin has many protective effects as well as suppressing oxidative stress and MHC-1 linked autoimmunity, including in pancreatic B-cells. Abbreviations: 5-HT: serotonin; AANAT: aralkylamine N-acetyltransferase; AhR: aryl hydrocarbon receptor; ASMT: N-acetylserotonin O-methyltransferase; CYP: cytochrome P450; IDO: indoleamine 2,3-dioxygenase; MHC-1 major histocompatibility complex-class 1; NAS: N-acetylserotonin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PINK1: PTEN-induced kinase 1; TDO: tryptophan 2,3-dioxygenase; TrkB-FL: tyrosine receptor kinase B-full length; TrkB-T1: tyrosine receptor kinase B-truncated.

The suppressed capacity to upregulate melatonin prolongs the heightened activation of pro-inflammatory signaling via the transcription factors, NF-κB and YY1, coupled to decreased activation of TrkB-FL and/or TrkB-T1 by NAS and BDNF. A suppressed mitochondrial melatonergic pathway enhances oxidative stress, thereby decreasing PINK1 and its interactions with parkin and LETM1 on the mitochondrial membrane. Decreased PINK1 suppresses mitophagy, coupled to increased MHC-1 that drives 'autoimmune' processes via NK cell and CD8+ T cell attraction. The accompanying decrease in OXPHOS-derived ATP prevent KATP induced insulin, whilst decreased PINK1 attenuates LETM1 phosphorylation, leading to Ca2+ and pH dysregulation, likely accompanied by alterations in how LETM1 interacts with 14-3-3 and/or AANAT in the regulation of the mitochondrial melatonergic pathway. As well as activating TLR4, HMGB1 activates RAGE, thereby further contributing to oxidative stress. Changes in pancreatic β-cell mitochondrial function, including by ROS-driven miRNAs, will change patterned gene induction, with consequent changes in fluxes that mediate pancreatic β-cell interactions with other cells in the pancreatic islet microenvironment, thereby changing the dynamic intercellular interactions occurring. The decrease in shikimate pathway, A. muciniphila, L. johnsonii, and butyrate, contributed to by bacteriophages and enteroviruses, provides 'bystander' activation of autoreactive CD8+ T cells—possibly in Peyer's patches—thereby preventing thymic deselection and driving classical 'autoimmunity'. Abbreviations: AhR: aryl hydrocarbon receptor; BDNF: brain-derived neurotrophic factor; HMGB: high-mobility group box; hsp: heat shock protein; IDO: indoleamine 2,3-dioxygenase; KATP: ATP-activated potassium channel; LETM1: leucine zipper-EF hand-containing transmembrane protein 1; LPS: lipopolysaccharide; MHC-1: major histocompatibility complex-class 1; NAS: N-acetylserotonin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; RAGE: receptor for advanced glycation end-products; NK: natural killer; TDO: tryptophan 2,3-dioxygenase; TrkB-FL: tyrosine kinase receptor B-full length; TrkB-T1: tyrosine kinase receptor B-truncated; YY1: yin yang 1.

Additionally, like we earlier reviewed the association of neurodegenerative and neuropsychiatric diseases, Amyotrophic Lateral sclerosis (ALS) pathoetiology with gut microbiome [9-11]. Moreover George Anderson's group have reasoned out this same abnormal tryptophan metabolism with repression of mitochondrial melatonergic pathway & shikimate pathway in the etiopathogenesis of neuropsychiatric diseases like , Multiple Sclerosis (MS), depression, ALS and tumours like Glioblastoma and other cancers [12-19].

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