Acta Scientific MICROBIOLOGY (ISSN: 2581-3226)

Volume 4 Issue 7 July 2021

Short Communication

Can Targeting Gut Microbiota in Perinatal Events Aid in Prevention of Type 1 Diabetes Development - Influence T1D Genes Crosstalk with Environmental Factors

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1]Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India

[2]Scientific Director, Rotunda-A Centre for Human Reproduction, Mumbai, India

[3]Consultant Neurologist, Swami Satyan and Hospital, Jalandhar, Punjab, India

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Jalandhar, Punjab, India.

Received: April 27, 2021

Published: June 04, 2021

Type 1 diabetes mellitus (T1D) represents a chronic autoimmune disease (AD) resulting from a complex interplay between genetic proneness and Environmental factors(EF). Mostly AD incidence follows a pattern of north-south, with escalated prevalence visualized in countries, such as Finland, Sweden as well as Norway. Gut Microbiota (GM) studies on the implications of extreme climatic environments (like antarctica, time of birth/venue, show impact of extreme cold conditions with no exposure to sunlight thus resulting in Vitamin D deficiency, influence GM composition and immune dysfunction. In case of population from north it is observed that circadian rhythm alterations occur and that have also been illustrated to =>immune dysfunction through a swing in the GM, resulting in AD like T1D [1-5].

EF-For finding the etiopathogenetic ET that initiate the disease origin, longitudinal studies of huge at –risk cohorts got done across a broad geographical area as in Teddy, DABIMMUNE, BABYDIET, ABIS, TRIGR and FINDIA) [5].

Delivery mode

Recent work has queried the earlier work demonstrating that the uterus is devoid of bacteria. Lots of studies demonstrated that DURING intrauterine LIFE, the fetus gets comes in contact with maternal M vial passage across the placenta into the amniotic fluid. Prepartum maternal GM, shift takes place in one direction during first along with third trimester possibly influenced by changes hormonal and immunological milieu at this duration [6], which undergoes reduction at that period. Notably, this shift escalates the butyrate forming taxa that promotes elevated amounts of immunomodulatory Treg cells [6] that decreases chances of maternal rejection of the fetus [7]. Another shift switch in GM occurs just prior to delivery. This switch causes higher variability resulting in reduction of, alpha grp, and greater expression of taxa that induce inflammation. Research on germ free (GF) mice that have been humanized has demonstrated that these changes work as adaptive and promote greater energy transfer among the mother and child. These organisms further promote the proper *anaerobic* spp getting colonized, having dominance in the newborns early life GM. Further alterations occur in the maternal vaginal M immediately prior to delivery. During gestation four main *Lactobacillus* spp get elevated significantly which contribute to stabilization of lactobacilli with reduction in alphadiversity. Those infants that had a vaginal delivery possess a microbiome like vaginal microbiome of the mother while LSCS delivered babies get classically colonized with the species seen on the mothers skin [7]. Variations in the taxa are maximum separate in the 1st 3 months of life. Those having a vaginal delivery possess commensal bacteria like Lactobacillus and Bifidobacterium, whereas LSCS delivered babies are colonized with *Clostridium* spp and *Staphylococcus* spp [7]. Cardwell., *et al.* [8] in 20 separate studies following all adjustments for covariates, maternal T1D incidence, and breastfeeding found still a 20% escalation of T1D initiation in infants that are lower segment caesarean section (LSCS) delivered [8].

Breast feeding [BF]

Verduci., *et al.* [9]. emphasized on promotion of BF for a min of initial 6 months of life and the prevention of early top foods and

no gluten included (prior to age 4 mths) and postponement of cow milk till 12 months of life. These harmful feeding habits create a dysbiotic GM state that can aid in initiation of T1D in infants. Further, they detailed on the probability of adding probiotics, prebiotics and post-biotics in the avoidance of T1D especially in those high risk for T1D (Figure 1) [10].

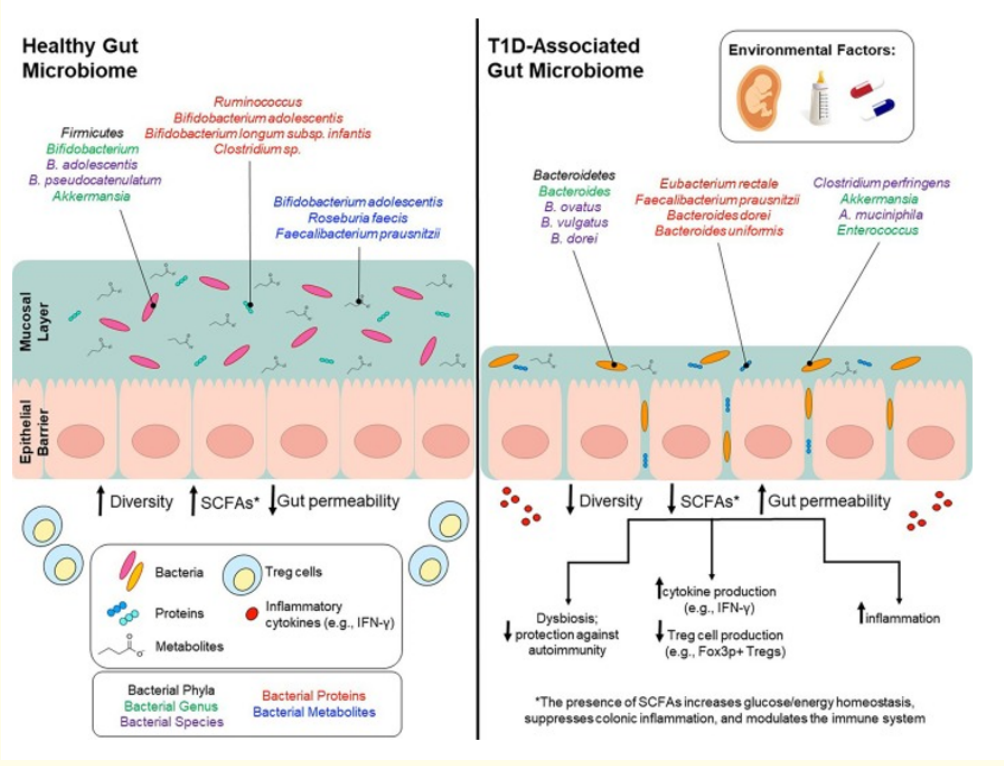

Figure 1: Courtesy ref no-7-Environmental factors modulate gut microbiota and potentially contribute to T1D onset. Environmental factors, such as birth mode, diet early in life, and use of antibiotics can influence gut microbiota composition and can to lead to lower bacterial diversity, decreased SCFA production and increased gut permeability. Bacterial phyla/genus/species that are affected by environmental factors and differ between T1D patients and healthy controls are depicted in the colors black/green/purple, respectively. Bacterial genus/species that have been identified in proteomic analyses and are increased in either T1D patients or healthy controls are shown in red. Bacterial genus/species that have been identified in metabolomics analyses and are increased in either T1D patients or healthy controls are shown in blue.

Role of diet

All studies have shown early life exposure to foreign food antigens, like gluten and bovine insulin might impact β cell auto immunity. As per human experiments found early gluten introduction (prior to age 3 months) to gluten elevates the chances of islet auto immunity which can be mitigated by avoidance of gluten supplementation if child is still being Breast fed.

Cows milk

A meta-analysis that compareda countries T1D incidence rate with its yearly Cows Milk protein intake also sawa positive association with a countries T1D incidence rate with its yearly Cows Milk protein intake.

Antibiotics are usually used for the control of bacterial antigens, that have adverse influence on GM. Antibiotics intake decreases the bacterial diversity markedly, but, several studies have shown that adult GM usually get back to normal posttherapy., Nevertheless A 4day therapy with a mixture of 3 Antibiotics (meropenem, gentamicin and vancomycin) caused 9 bacterial sp getting extinct in adult men 180days. following antibiotics use, besides study causing initial flourish of pathological organisms like - *Enterococcus fae-*

calis and *Fusobacterium nucleatum* and a reduction of BifidobacteriumCalabrese., *et al.* [11]. of T1DM, by affecting permeability of intestine, molecules simulators mimicry, and manipulation of innate and adaptive immune responses. The GM in intestine gets an impact by consumption of kinds of food constituents composition. Some studies have shown that a low fiber intake is correlated with the formation of many inflammatory disease and AD. In this regard, the Mediterranean diet (MD), which is based on high consumption of cereals (preferably as whole grains), legumes like pulses, nuts like almonds, cashew nuts, green leafy vegetables, carrots fruits, with olive oil, in contrast to others and fish, might be protective. Lots of constituents of MD have functional characteristic possessing positive actions on health and good feeling. The preferable habits with regard eating of food are the ones that dictate a lot microbial components of the intestine and the food constituents decide the microbial populations beside their metabolic effects from the early stages of life. Further, metabolic byproducts of food have an impact the immune reaction. The intestine is considered the primary site where food metabolites mediate their effects, through epithelial integrity or mucosal immunity. The epithelial barrier affected aids in of bacterial and/or the diffusion of their break down, constituents such as antigens from food and LPS, from the intestinal lumen to the tissues, which could enhance the stimulation of immune cells, contributing to the pathogenesis of AD, such as T1DM. high amount of fiber consumption and thus of prebiotics with MD aids in the generation of GM that results in good balance of M. With higher dietary fibers consumption, a greater amt of short-SCFAs like butyrate is generated and liberated by anaerobic GM, that facilitates homeostasis of gut, that further aid in generation of tryptophan metabolites and omega-3 FA. greater amt of PUFA and omega-3-FAhelps in achieving a better metabolic regulation for DM Moreover butyrate is necessary in manipulating the immune response by stimulation of differentiation of Treg cells, specifically Fox3p+ Tregs and inhibition of inflammatory cytokines, like IFNγ [11]. Despite animal model studies [AMs] give us a lot of deep insight regards to the particular mode of working, lot of variations inherent to rat/mouse models doesn't allow their use, for human health applications. It is significant to know that scientists have found about 500 variable therapies for prevention/rectification of T1D in NOD mice models, with none of these treatments getting translated into strategies for human T1D therapy. The variations amongst NOD mice model and human results point that we need to consider other AMfor research in T1D besides focus on human studies Further till now maximum approaches have been bacteria centred. Very little virome, proteome and metabolomic studies are there, with no studies on phageome, fungal microbiome and archaeome and meta transcriptome. Further GM composition is that we don't know of any nasal, skin or vaginal microbiota studies in this field of T1D. These signify different mucosal surfaces where M -host Interaction and might aid in the generation of AD like T1D. It is important to understand that no clear cut etiological correlation isolated till now with human disease along withGM. Instead of screening at large scale studies, a better strategy might be tofocus on posit based on specific mechanisms. The significance of microbiota-host interaction in dictating the GM composition, via both dependent on contact and chemically mediated mechanisms modes. Overall, future work needs to look into particular community Crosstalk along with total function to yield better insight of the differing disease causations. Like it was recently posited that existent of microbes that carry an insulin –like peptide might stimulate a, molecular simulation mode in T1D as well as found viral insulitis. Additionally, it was shown how the immunoregulatory phytochemical, indole-3-carbinol (I3C), present in cruciferous vegetables, controlled T1D propagation in NOD mice. Once food gets digested, I3C gets degraded into ligands for the aryl hydrocarbon receptor (AhR), that represents a transcription factor which when on systemic stimulation avoids T1Dgeneration. In NOD mice, food that had I3C-addition resulted in robust AhR stimulation in the small intestine but possessed least systemic AhR action. Once systemic reaction was not evoked, the dietary administration resulted in accelerated insulitis. In support of compartmentalized stimulation of AhR, dietary I3C had no altering action on T helper cell getting differentiated with in lymph nodes that drain spleen or pancreas. Rather, dietary I3C escalated the percentage of $CD4^{+}ROR\gamma t^{+}Foxp3^{-}$ (Th17 cells) in the lamina propria, intraepithelial layer, and Peyer's patches of the small intestine. This immune manipulation in the gut was association with changed intestinal microbiome, with changes in bacterial communities observed in 7 days of I3C administration GM that go t generated belonged to a particular kingdom to anticipate host-microbe crosstalk s that was affected by dietary I3C. Within the phylum Firmicutes, various generator negatively controlled by I3C. I3C-modulated aberrant GM was association with escalation increases in $CD25^{high}$ Th17 cells. Collectively, these results showed that area of AhR stimulation and later crosstalk s with the host microbiome are significant factors in generating AhR-targeted therapies for T1D [12] Giampioli., *et al*. [13] described how probably crosstalk among mothers' phenotype, host FUT2 genetic background and GM composition impact on T1D onset. The study of FUT2-GM crosstalk s may add extra item in the confusing T1D etiology and show novel targets of therapy to halt T1D generation as well as propagation. Dietary intakes, that are the consumption of α- (1, 2)-fucosyl oligosaccharides in formula milk and the

utilization of particular prebiotics and probiotics, could be posited. Further minimal knowledge exists in reference to the EF that can be associated to these alleles. As per current proof pointed that, among those EF, aberrations in the GM might take part in the etiopathology of T1D, that impacts the gut integrity besides aiding in systemic inflammation along with self destruction of the pancreatic β cells. Various studies have isolated changes in GM composition in humans and AM contrasingT1D subjects with controls. Those changes depicted by a greater amounts of Bacteroides along with lesser amounts of the butyrate-generating bacteria like Clostridium clusters IV and XIVa. The mechanistic regarding how aberrant GM in addition to their metabolites interact with the genome and/or the epigenome of the host leading to destructive autoimmunity is still not understood. As T1Dis a disease caused by a lot of factors, getting insight in the crosstalks among various EF like the GM, the genetic and epigenetic components correlated with the early autoantibodies presence can expand insight about the disease pathogenesis. Hence for better understanding into the crosstalk among the gut microbiome, susceptibility genes, epigenetic factors, and the immune system in the pathogenesis of T1D Elhag., *et al.* detailed the mode [14]. Presence of a specific bacterial species like single-SFB) or Bacillus cereus in the female NOD mice procreated under GF conditions enhances the expression of the signature genes in Th17 cells like Il17a, Il17f, Il22, Il1r1, and Il23r which may delay the onset of T1D through regulating the auto-immune response leading to enhanced gut integrity. Moreover, comparative GM evaluation among the NOD mice with and without T1D revealed a significantly> amts of 4 taxa associated with antibiotic-stimulated aberrant GM, like *Enterococcus*, *Blautia*, *Enterobacteriaceae* species, and *A. mucinophila*, these GRPS were shown to be correlated with an exaggerated propagation into T1D (Figure 2) [14]. Thus finally concluding, still lot of work needs to be done with regards to correlation of susceptibility genes, EF and solving the mystery of GM in initiation of T1D. Yet ensuring BF, trying pre/probiotics and diet changes like MD, or FUT2/AhR activation targeting might aid in helping till further insight is gained.

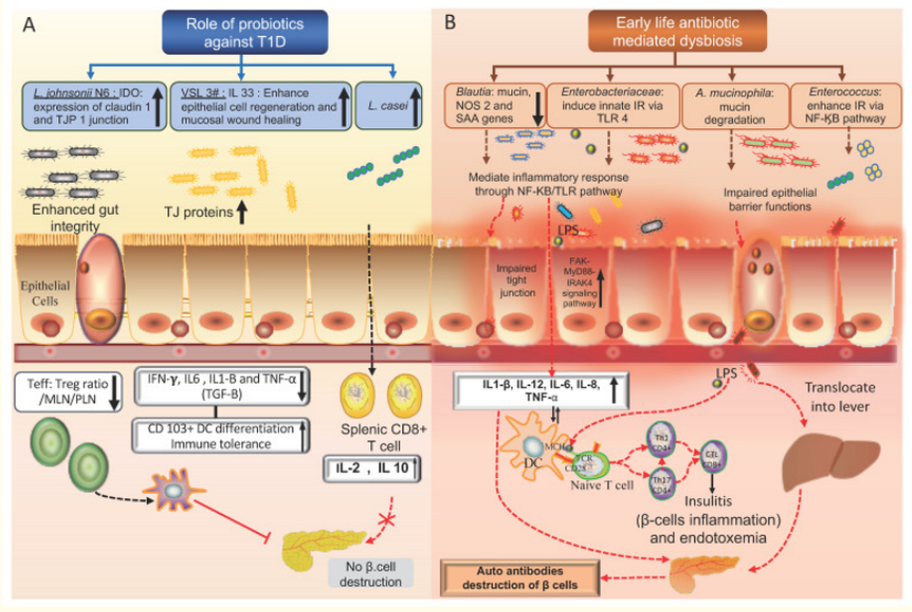

Figure 2: Courtesy ref no-14- Comparison between the opposite effects of probiotics and early-life use of antibiotics in NOD mice. (A) T1D protective effects of probiotic bacteria in NOD mice: *Lactobacillus johnsonii* N6 enhances the expression of INFγ and indolesamine 2,3-dioxygenase enzyme (IDO) which in turn increase the production of claudin-1 tight junction protein that maintains the integrity of the gut epithelium. *Lactobacillus casei* has probiotic properties, lowering the number of the splenic CD8+ cytotoxic T cells and promoting the expression of the anti-inflammatory cytokines (IL2, IL10) leading to increased immune tolerance in the gut. VSL3# probiotic has immune-modulatory functions, enhancing the expression of IL-33 cytokine that is necessary to maintain immune-tolerance in the gut and mesenchymal lymph nodes (MLN). (B) Role of antibiotic mediated dysbiosis in enhancing autoimmunity and pancreatic β-cells destruction in NOD mice: dysbiosis mediated by the use of antibiotics enhances the growth of pathogenic bacteria which promotes the inflammatory response via the TLR pathway which influences the gut permeability leading to metabolic endotoxemia. Endotoxemia stimulates the autoreactive T cells in the pancreatic lymph nodes leading to insulitis and β cell destruction.

Bibliography

1. Kulvinder Kochar Kaur., *et al*. "An Update on Etiopathogenesis and Management of Type 1 Diabetes Mellitus". *Journal of Endocrinology* 1.2 (2017): 1-23.

2. Kulvinder Kochar Kaur., *et al*. "Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review". *Advances in Obesity, Weight Management and Control* 9.1 (2019): 21-28.

3. Kulvinder Kochar Kaur., *et al*. "Attempting Getting Insulin Independent Immunotherapies in Type 1 Diabetes Mellitus (T1D) in the Pre Stage 1 (BeforeIslet Autoantibodies)". *Acta Scientific Paediatrics* 3.6 (2020): 01-04.

4. Kulvinder Kochar Kaur., *et al*. "Path Directed towards a Stage when we almost Cure Type1 Diabetes Mellitus (T1dm) after a Century of Insulin Advent". *EC Diabetes and Metabolic Research* 4.6 (2020): 37-46.

5. Kulvinder Kochar Kaur., *et al*. "Are we any close to unraveling the mechanisms of interactions among Susceptibility genes towards type 1 Diabetes, Gut Microbiota along with Environmental factors –Specifically Early Diet patterns –A Systematic Review?" *Endocrinology and Surgical Endocrinology* 2.1 (2021): 1-20.

6. Walker WA. "The importance of appropriate initial colonization of the intestine in newborn, child, and adult health". *Paediatric Research* 82 (2017): 387-395.

7. Dominguez-Bello MG., *et al*. "Delivery mode shapes the initiation and structure of the initial Microbiata across multiple habitats in the newborn". *Proceedings of the National Academy of Sciences of the United States of America* 107 (2010): 11971-11975.

8. Cardwell CR., *et al*. "Caesarean section is associated with an increased risk of childhood onset- Type 1 diabetes: meta-analysis of observational studies". *Diabetologia* 51 (2008): 726-735.

9. Verduci E., *et al*. "Early nutrition and risk of Type1 Diabetes: the role of Type1 Diabetes". *Frontiers in Nutrition* 7 (2020): 612377.

10. Dedrick S., *et al*. "The role of Gut Microbiota and environmental factors in Type 1 diabetes pathogenesis". *Frontiers in Endocrinology* 11 (2020): 78.

11. Calabrese CM., *et al*. "Gut Microbiota and Type1 Diabetes". *Frontiers in Nutrition* 7 (2020): 617223.

12. Kahalehili HM., *et al*. "Dietary Indole-3-Carbinol Activates AhR in the Gut, Alters Th17-Microbe Interactions, and Exacerbates Insulitis in NOD Mice". *Frontiers in Immunology* 11 (2020): 606441.

13. Giampioli O., *et al*. "Can the FUT2 nonsecretory phenotype associated with Gut Microbiota increase the children susceptibility for Type1 Diabetes? A Minireview". *Frontiers in Nutrition* 7 (2020): 606171.

14. Elhag DA., *et al*. "Exploring the triple interaction between the Host Genome, the Epigenome and the Gut Microbiome in Type1 Diabetes". *International Journal of Molecular Sciences* 22 (2021): 125.

Volume 4 Issue 7 July 2021