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The significance of gut microbiota controlling of epigenetic modifications in obesity with its therapeutic impact: a narrative review

Abstract

The global prevalence of obesity has reached epidemic proportions, significantly escalating the predisposition to various cardio metabolic disorders and some kinds of cancer, as reviewed by us on the role of gut microbiota (GM) in obesity generation basically through controlling variable kind of metabolic events. As per recent scientific research epigenetic modifications might work in the form of critical pathways via which GM and their metabolites aid in etio-pathogenesis of obesity and associated metabolic conditions. Thereby getting insight in the close cross talk amongst GM and epigenetic mechanistic modes is critical to display influence of obesity on the host. Apart from resulting in metabolic aberrations for instance insulin resistance (IR), escalated blood glucose, lipids, ectopic fat accrual, obesity further possess the capacity of causing injury to pancreatic islet cells, endothelial cells and cardiomyocytes via chronic inflammation, further facilitating generation of a microenvironment which aids in cancer initiation. Thus here in this review we basically concentrate on the association of GM and their microbial metabolites with epigenetic mechanistic modes in above cited comorbidities inclusive of energy disequilibrium, metabolic inflammation, and maternal inheritance. Further incorrect dietary habits and absence of physical exercise are significant behavioural factors which escalate the risk of obesity, that possess the capacity of influencing gene expression via epigenetic modifications. Actually here a summary of the studies on the manner probiotics, prebiotics along with other modulators that are capable of impacting GM constitution and affecting epigenetic mechanistic modes are detailed. Epigenetic alterations might take place in early stage of obesity, certain of which are reversible, whereas others continue with time along with result in obesity-associated complications. Thereby, the dynamic adjustability of epigenetic modifications might be bargained for reverting the generation of obesity- correlated diseases via behavioural interventions, drugs, and bariatric surgery.

Keywords: obesity, gut micro biota (GM), microbial metabolites; epigenetic modifications, probiotics, prebiotics, FMT

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Introduction

Obesity is escalating globally substantially specifically in the last 2-3 decades.[1] As per the recent statistics greater than 200 million adults are suffering from obesity which is correlated with variable metabolic diseases which afflict about 30% of global population.[2] It has become a global health problem in view of it escalates the plausibility of development of co-morbidities for instance metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia), cardiovascular disease (CVD) inclusive of coronary artery disease (CAD) as well as premature ageing.[3] There are a plethora of etiological in addition to pathophysiological factors implicated in its initiation inclusive of i) environmental factors, ii) dysequilibrium amongst energy consumption along with energy expenditure, iii) immune reactions as well as genetic factors. Accumulating proof has illustrated that epigenetic modifications portray one of the mechanistic modes correlated with changed gene actions to the environmental factors which aid in obesity taking place in addition to its generation.[4] Epigenetic modifications portray heritable alterations in i) gene working at the time of meiosis along with mitosis without changes in the DNA sequence, ii) DNA methylation, iii) histone modifications, iv) chromatin remodelling as well as v) controlling by noncoding RNAs.[5] Epigenetic events control the expression of plethora of genes inclusive of the ones implicated in metabolism in addition to inflammation pathways.[6] Studies have illustrated unique epigenetic signatures in individuals with obesity.[7] that are plausible biomarkers of obesity along with risk of metabolic diseases. Thereby getting exhaustive insight with regards to epigenetic mechanistic modes implicated in the generation of obesity is key. This kind of information possesses the plausibility of aiding in generating attractive innovative approaches for tackling obesity.

Recently gut microbiota (GM) have been illustrated to work as crucial environmental factors for the generation of obesity as well as its associated diseases.[8] Accumulating proof from animal in addition to human studies pointed that there are alterations in GM constitution along with working in case of obese persons.[9] For instance persons with obesity possess lesser alpha diversity.[10] in addition to greater quantities of microbiota which illustrate escalating capability of garnering energy.[11,12] Epigenetic modifications possess a significant part in the association amongst GM along with obesity generation. Accumulating proof has illustrated that GM as well as its metabolites

possess the capacity of directly affecting epigenetic pathways by controlling host cell inherent events or forming epigenetic substrates in addition to enzymatic cofactors which affect host's metabolism.[13] Thereby unveiling the plausible mechanistic modes by which interactions of GM take place along with epigenetic modifications are critical for getting insight in the generation of obesity. Earlier studies have illustrated the relationship amongst GM along with epigenetic manipulation in the generation of obesity as well as its correlated co-morbidities.[14]

Having reviewed the different etio pathogenesis and role of different anti-obesity agents, comprehensively inclusive of dietary perspectives for instance use of Mediterranean diet (MD) diet, very low calorie ketogenic diet (VLCKD) in therapy of obesity bariatric surgery, role of GM in obesity, type 1 diabetes mellitus (T1DM), role of Probiotics in non-alcoholic fatty liver disease(NAFLD)along with other co-morbidities of obesity type 2 diabetes mellitus (T2DM) for obesity, and role of epigenetic controlling on the initiation and development of T1DM, use of epi-phyto drugs in our endeavour to find the proper therapy.[15-33]

The aim of this review is to further emphasize on role of epigenetics modifications in obesity, GM correlated epigenetic modifications in maternal inheritance (that might reason out developmental hypothesis of health and disease DOHaD), along with pave the path for targeting GM alteration in obesity and GM correlated epigenetic modifications in maternal inheritance by probiotics, prebiotics as well as FMT.

Methods

Here we conducted a narrative review utilizing search engine PubMed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms- obesity; T2D; epigenetic modifications; organokines; short chain fatty acids (SCFA); choline metabolism; *Firmicutes: Bacteroides* ratio; folate; Gut Microbiota; Insulin Resistance; faecal microbiota transplantation (FMT); probiotics; prebiotics; antibiotics; immunotherapy; NAFLD; NASH from last 10 yrs till date in 2025.

Results

We found a total of 750 articles out of which we selected 108 articles for this review. No meta-analysis was done.

Epigenetic controlling associating gut microbiota along with obesity

Epigenetics portray modifications of chromatin structure in addition to working which do not implicate changes in the basic DNA sequence. Such alterations incorporate separate events which are inclusive of DNA methylation, histone modifications, as well as controlling by noncoding RNAs.[34] Accumulating proof has pointed that GM possess the capacity of affecting host epigenetic controlling, therefore influencing initiation along with propagation of obesity.[35] Acquisition of greater insight in the relationship amongst GM as well as obesity might pave the way for diminishing incidence in addition to inimical sequelae of obesity (Figure 1).[36] Details crosstalk amongst GM, epigenetic modifications along with obesity associated diseases. This is accompanied by actions of alterations in the GM on epigenetic controlling that manipulates obesity generation through controlling energy metabolism, inflammatory reactions, as well as genetic factors.

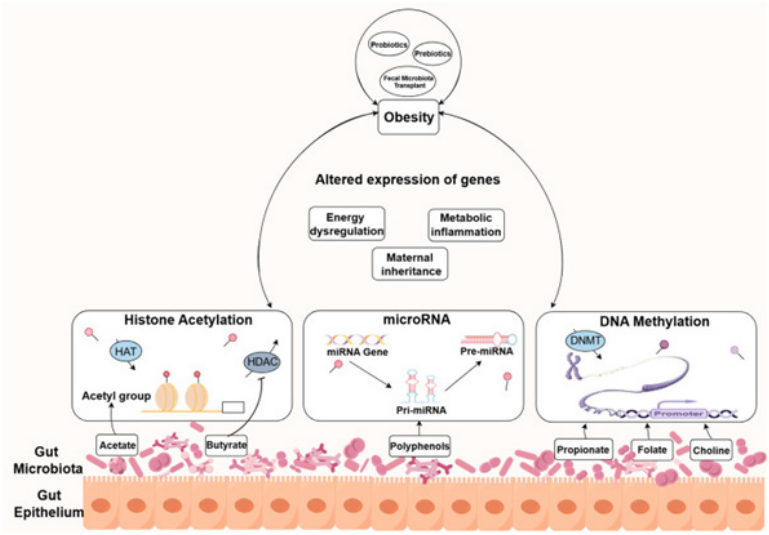

Figure 1 The interplay between the gut microbiota, epigenetic modifications, and obesity. The gut microbiota serves as a source of epigenetic factors, producing substrates or co-factors that modulate the epigenetic enzymes involved in energy metabolism, metabolic inflammation, and maternal inheritance-related gene epigenetic modifications, ultimately influencing the development of obesity-related diseases. HATs: histone acetyl transferases; HDAC: histone deacetylases; DNMTs: DNA methyltransferases.[36]

Role of gut microbiota- epigenetic modifications in energy metabolism

The sustenance of systemic energy homeostasis is dependent on the equilibrium amongst energy consumption along with energy expenditure, once the energy consumption exceeds energy expenditure, disequilibrium takes place in systemic energy homeostasis which result in accrual of adipose tissue (AT) volume in addition to quantities, which eventually result in obesity.[37] It has been revealed that GM possess the capacity of affecting host metabolism through stimulating epigenetic changes in crucial genes implicated in controlling energy metabolism.[38] Thereby the controlling of the crosstalk amongst GM along with epigenetic modifications in energy metabolism is escalating getting evaluated in reference to obesity.

Noncoding RNAs (Nc RNAs) represent working RNA molecules existent in the genome which do not encode proteins. MicroRNAs (miRNAs), represent short noncoding RNAs which have been evolutionary preserved that basically control cellular gene expression as well as translation of protein.[39] At present escalating attraction is for getting insight in the role of miRNAs in case of obesity in addition to correlated metabolic conditions, by affecting their biology**(**formation along with metabolism) of AT**.**[40,reviewed in detail by us in 15] In an earlier study utilization of germ free(GF) mice illustrated GM in the form of etiological factors in regulating expression of adipocyte miR 181 for controlling of glucose in addition to energy homeostasis at the time of obesity.[41] Recently Prukpitikul etal.,[42] comprehensively reviewed the relationship amongst gut dysbiosis along with miRNAs in ca**se** of metabolic conditions.[42] It posits that GM influences host metabolism basically via lipopolysaccharides (LPS) as well as secondary microbial metabolites controlling host miRNAs. There by, it validates the plausibility of GM-miRNA axis in the form of an innovative target for the therapies of metabolic conditions correlated with obesity. Histone modifications canonically do not directly target DNA, however perform addition of lysine (K) residues to the histone tails covalently. The modifications are inclusive of histone acetylation as well as deacetylation.[43] Histone deacetylates (HDACs) have been illustrated to work in the form of crucial controlling factors implicated in lipids in addition to other metabolic pathways.[44] Kuang et al.,[45] revealed that GM regulated lipid metabolism via HDAC3 in the mouse intestine resulting in escalated expression of lipid transporter CD36 along with facilitating lipid uptake by intestinal epithelial cells, therefore accelerating the formation of obesity.[45] This work illustrates the association of HDAC family as well as GM in the controlling of lipid metabolism.

DNA methylation, portrays a critical epigenetic mechanistic mode controlling gene expression by addition of methyl groups to DNA molecules.[46] Escalating number of views pointed that variable microbial properties of obese persons might stimulate alteration in DNA methylation designs. For example, Ramos Molina et al.,[47] have observed that germane enrichment of Bacteroides in obese persons possessed a positive association with the methylation quantities of the promoter areas of HDAC7 gene (p=0.011) in addition to that of the insulin like growth factor 2- mRNA binding protein2 gene (IGF2BP-2) (p=0.002) in AT. Conversely, germane enrichment of *Firmicutes* possessed a negative association with the methylation quantities of the promoter areas of HDAC7 in the blood (p0.019).[48] A clinical study illustrated that obese persons possessing greater *Bacteroides: Firmicutes* ratio displayed variable DNA methylation designs in the blood along with in AT, once contrasted with obese persons possessing lesser *Bacteroides: Firmicutes* ratio.[46] It has been revealed that insulin as well as leptin signaling possess a crucial part in manipulating lipid as well as glucose metabolism in addition to therefore aiding in obesity generation.[49] Salas Perez et al.,[50] demonstrated a communication amongst GM as well as DNA methylation in obese persons.,[50] particularly taking into account that the actions of *Ruminococcus* enrichment on body mass index(BMI) gets modulated by the methylation of the macro domain containing 2 gene (MACROD2) in addition to differentially methylated region gene (DMR) (p=0.035). Furthermore, in contrast to canonical mice, GF mice illustrated escalation of DNA methylation of the leptin promoter in cytosine -guanine dinucleotides (CpG) of AT by around 6-16% (p<0.05), that might point to escalated risk factor for leptin resistance.[51] Kumar et al.,[48] demonstrated a significant correlation amongst dominance of bacteria along with epigenetic profiles during pregnancy in 8 women. Their outcomes corroborated that women who had pregnancy with obesity possessed GM with predominance of *Firmicutes* phylum as well as displayed greater extent of methylation in the promoter sites of stearoyl CoA desaturase 5 gene(SCD5)).[48] Such observations corroborate that interactions amongst GM in addition to metabolism associated genes might be attained via epigenetic mechanistic modes.

Role of gut microbiota- epigenetic modifications in low grade inflammation

Obesity is generally associated with variable chronic complications resulting in activation of cytokines along with inflammation associated signaling pathway.[52] Accumulating proof has illustrated the significant part of the GM in the epigenome remodeling of inflammatory factors.[53] It has been demonstrated in studies that alterations in GM directly influence the epigenetic modifications of Toll-like Receptor (TLR) modulated inflammatory molecules via DNA methylation. In particular Remley etal.,[54] illustrated that obese persons possessing greater *Firmicutes: Bacteroides* ratio displayed diminished quantities of DNA methylation in promoter sites of Toll-like Receptor 4 gene (TLR4) (p <0.05).[54] Apart from, DNA methylation miRNAs further possess a crucial part in the inflammatory reactions in addition to take part in differentiation as well as working of different immune cells.[55] In a recent study it has been revealed the influence of miRNA-29a on GM constitution along with inflammatory reactions in mice that received high fat diet (HFD), were evaluated. Their outcomes illustrated that **in contrast to** wild kind(WK) mice, overexpression of miRNA-29a possessed the capacity of improvement of lipid metabolism conditions stimulated by HFD along with facilitated the abundance of *Lactobacillus* (p<0.001), *Ruminiclostridium_9* (p=0.035) as well as *Lachnoclostridium* (p<0.001), in the intestine. Additionally, it significantly diminished the expression of Interleukin6 gene (IL-6) in the intestine (p <0.05).[56] Such studies have corroborated that epigenetic modifications might work in the form of affecting GM - host metabolism crosstalk in addition to inflammatory status stimulated by obesity. Furthermore, variable studies have pointed that alterations in GM in obesity are intricately associated with part of epigenetics in low grade inflammation. Usually the germane enrichment of intestinal microbiota is greater in contrast to faecal microbiota that might be associated with dynamic along with heterogeneity of intestinal microbiota.[57] Nevertheless, obtaining samples from the intestine without disruption or contamination has involved remarkable technical hurdles. Thereby in human clinical trials basically faeces have been used in the major studies for achieving knowledge in reference to assessment of human gut microbiome.[58]

In total the bidirectional association amongst GM as well as epigenetic modifications of inflammatory molecules is present in obesity. In view of that such close crosstalk has been escalatingly recognized in the form of innovative therapeutic in addition to avoidance strategy for tackling obesity. Nevertheless, future scientific research is obligatory for the probability of utilization of such approach.

Role of gut microbiota- epigenetic modifications in maternal inheritance

Obesity in the form of a disease possesses plethora of etiological factors has been broadly acknowledged in the form of a risk factor affecting health of children along with adults.[59] Escalating scientific research pointed that maternal nutrition as well as GM constitution at the time of pregnancy portray the main factors which are involved in induction of epigenetic modifications of genes associated with predisposition of obesity in the fetus.[60]

An evaluation of predominant bacterial phyla in pregnant ladies displayed that methylation quantities at the CpG region of ubiquitin conjugating enzyme E2 D2 (UBE2D2) (p=0.04) along with voltage gated channel subfamily Q member 1s (KCNQ1) (p=0.048) possessed a positive association with enrichment of maternal intestinal *Firmicute.*[61] In agreement with this probiotic supplementation in case of pregnant obese ladies changed GM constitution as well as resulted in diminished DNA methylation quantities in the promoter sites of Insulin like growth factor binding protein1 gene (IGFBP-1) (p<0.001)in their off springs.[62] This pointed that GM has a protective health advantage conferred to the children by diminising the risk of glucose metabolism conditions. Experimental outcomes from obese pregnant mice pointed that maternal obesity leads to diminished caecal microbial diversity in the child in addition to changes in the methylation designs in the DMR genes correlated with fat metabolism for instance PPARG coactivator -1β (*Ppargc1-β,*), Fibroblast growth factor 21 (*Fgf21*) EPH receptor B2 (Ephb2) along with von Wille brand factor(*VWF)* (p <0.05).[63] Furthermore off springs of pregnant mice who got illustrated significantly diminished DNA methylation quantities of cyclin dependent kinase inhibitor1a (Cdkn1a) in the liver correlated with changes in the GM profiles).[64] This work illustrated continuation of influence of metabolic decontrolling stimulated by maternal obesity on health of off springs inclusive of dysbiosis in the GM as well as alterations DNA methylation designs of correlated genes.

In total the crosstalk amongst GM as well as host epigenetics possesses a versatile part in the mechanistic modes of production of obesity. Nevertheless, the interactions amongst GM in obesity in addition to epigenetics possesses plausible biomedical importance which needs to be corroborated by utilization of considerable assessment in clinical trials.

Interactions amongst GM metabolites along with epigenetic modifications in obesity

As reviewed by us in ref no28 by us it has been acknowledged for a remarkable time duration that microbial metabolites possess a crucial part in the crosstalk amongst GM as well as host.[65] Additionally, accumulating proof has illustrated the part played by microbial metabolite in modulation of metabolic for instance obesity by modulating epigenetic modifications.[14,66] We provide an overview of metabolites generated by GM in addition to epigenetics modifications in obesity (Figure 1).

Short chain fatty acids (SCFA)

Short chain fatty acids (SCFA), inclusive of acetate, butyrate, propionate are produced by GM for instance *Lactobacillus* along with *Eubacterium* by fermentation of the *i*ndigestible carbohydrates (polysaccharides) for instance dietary fibers.[67] SCFA have been recognized to incorporate epigenetic controlling of the gene expression. i) For instance, butyrate has been broadly acknowledged to be a HDAC hampering agent with previously acknowledged epigenetic actions which influence histone deacetylates (HDACs) as well as methyl CpG binding proteins, thereby plausibly affecting DNA methylation.[68] ii) Furthermore, acetate has been displayed to escalate acetylation quantities of histone H3 lysine9 (H3K9ac), H3K27, H3K56.[22] (for details of labelling histone, lysine) in the promoter sites, thus activating the expression of lipid generating genes for instance acetyl CoA carboxylase alpha (ACC/ ACACA) in addition to fatty acid synthase(FAS/ FASN) along with influencing lipids generation.[69]

Free fatty acid receptors (FFARs) are substantially expressed in the host AT.[70] It has been observed that SCFA possess the capacity of facilitating leptin liberation in adipocytes by activation of FFARs, therefore controlling appetite along with improvement of obesity.[71] In type 2 diabetic patients, It has been found presence of lesser enrichment of *Faecalibacterium prausnitzii*- the main generator of butyrate, result in greater methylation in the CpG region in the promoter sites of FFAR3 gene (p=0.003).[72] iii) Moreover, Guo et al.,[73] observed that propionate abundance in the population that has susceptibility to obesity stimulated particular methylation designs in DAB adapter protein 1 (*DAB 1*) promoter that is a diabetes target gene (p<0.05).This study emphasized the plausible mechanistic modes by which changes in epigenetic mechanistic modes stimulated by microbial metabolites aid in proneness to obesity along with other metabolic conditions, that yielded innovative angle for the treatment of such diseases. Lu et al.,[74] invented that SCFA possess the capacity of diminising the expression of DNA methyl transferees (DNMT1, 3a, 3b) in case of HFD stimulated obese mice leading to decreased methylation of CpG in the promoters of the leptin promoter (p <0.05),thus repressing the obesity associated leptin expression. Lu et al.,[74] posited that the plausible mechanistic modes behind manipulation of leptin's epigenetics modifications by SCFA might be hampering actions of SCFA on HDACs followed by influencing the actions of HDACs as well as methyl CpG binding proteins. Thereby presence of probability is there that epigenetic controlling possesses a part in the beneficial actions of SCFA on host metabolism. Such observations might yield an innovative angle for the treatment of obesity in addition to other metabolic diseases.

Folate

Folate represents an essential Vitamin in humans along with bacteria possess the capacity of its generation for instance *Bifidobacterium, Lactobacillus,* along with *Bacillus subtlis.* Folate works in the form of a methyl donor (MD), possesses a crucial part in methylation reactions that incorporate an exhaustive network of metabolic pathways which are intercommunicated.[75] Insufficient/ escalated folic acid consumption might result in aberrant expression of obesity correlated genes as well as greater robust obesity.,[76] thereby yield understanding into innovative angle for the isolation of the association amongst GM, folate, epigenetic manipulation in addition to obesity. It was illustrated in a study that supplementation of folate diminished weight along with quantities of DNA methylation at the DMR of adenylate cylase 3 (*Adcy3)*, as well as Rap guanine nucleotide exchange factor (*Rapgef4*) in case of HFD mice (p<0.05).[77] Additionally, subsequent to ingestion of folate, obese ladies demonstrated greater quantities of DNA methylation in contrast to the ones with normal weight (p<0.05).[78] Park etal.,[78] hypothesized that folate affects status of DNA methylation via its implications in one carbon metabolism, thus manipulating metabolic controlling in obesity.[78] Acknowledged the part played by supplementation of folate in the fetal generation along with metabolism, in a study performed by Pawels et al.,[79] a positive association was observed amongst time period of maternal supplementation of folate prior to pregnancy in addition to mean CpG methylation quantities of the leptin gene (p=0.024).[rev by us 26,30] In the meantime Haggarty et al.,[80] found greater methylation quantities of the leptin gene in the umbilical cord blood subsequent to supplementation of folate started 12 week subsequent to gestation (p=0.044). Thereby maternal MD ingestion at the time of pregnancy possess the capacity of affecting DNA methylation of off springs in the metabolism associated genes. One more study observed that substantially greater quantities of prenatal supplementation of folate in obese pregnant mice led to disturbed lipid metabolism in the offspring, with significantly escalated DNA methylation quantities of CpG region amongst the promoter of the adipose triglyceride

lipase(ATGL) in the liver as well as lipoprotein lipase(LPL) in the AT($p < 0.05$).[81] Additionally, restricting dietary proteins in addition to supplementation of folate at the time of pregnancy in rats significantly diminished methylation quantities of Peroxisome Proliferator Activated Receptor (PPAR) genes in the off spring.[82] Taken together such outcomes corroborate a relationship amongst folate, epigenetics along with obesity generation, thereby yielding a plausible part of the GM in the modulation of obesity by manipulating folate generation.

Choline

Choline works in the form of a semi essential nutrient in the body, with presence in variable foods. Part of its basic working is the provision of one carbon for the generation of donors for DNA methylation.[101] Bacteria for instance *Faecal bacterium* as well as Bacteroides possess the capacity of performing choline metabolism and its trimethylamine (TMA), controls lipid metabolism in addition to improvement of obesity.[84]

Romano et al.,[85] evaluated the influence of crosstalk amongst GM manipulated choline metabolism along with DNA methylation on obesity associated diseases by engineering microbial community which had absence of enzyme of single choline using enzyme. Their observation was that mice which had colonization with the bacteria which had utilization of choline displayed lesser DNA methylation as well as escalated inguinal fat accrual in contrast to mice which had colonization with the bacteria that had incapability of consumption of choline subsequent to HFD ($p<0.001$). Romano et al.,[85] believed that bacterial choline metabolism diminished methyl donors along with lessened global DNA methylation in the host, eventually aggravating HFD stimulated conditions. Additionally, on contrasting mothers which do not foster choline utilizing bacteria in their body, brain of these offspring's from mothers who possess such colonization illustrated lessened DNA methylation quantities. Such outcomes corroborate that GM manipulated choline metabolism possess the capacity of generating obesity by changing DNA methylation as well as further affecting DNA methylation profiles of the offspring.

Polyphenols

Polyphenols portray a class of substances which have natural existence with broader organization in addition to versatile biological actions.[86] Accumulating proof has illustrated that basically metabolism of polyphenols takes place by the colonic microbiota, generating greater bioactive microbial metabolites in contrast to the ones ingested in foods, influencing the constitution of intestinal micro biota along with metabolites.[87] Furthermore, the polyphenol metabolites basically change cellular working by controlling quantities of miRNA, thereby modulating obesity generation.[88] An innovative angle gets yielded on the part possessed by polyphenols in avoidance of HFD stimulated obesity. Wang et al.,[89] observed that polyphenol supplementation (as cheery juice) possess the capacity of controlling the constitution in addition to enrichment of intestinal microbiota in obese mice resulting in escalated SCFA s. Furthermore, it hampered the expression of variable obesity associated miRNAs for instance miR -200c-3p in addition to miR-125a-5p ($p<0.05$).[89] rev in detail by us in [1]. *Akkermansia muciniphilia* has been corroborated to be a prebiotic controlling obesity generation.[90] Subsequent to polyphenol supplementation, enrichment of *Akkermansia muciniphilia* along with miR-30d got escalated.[91] Thereby polyphenols as well as microbial metabolites might modulate the metabolic conditions of host by controlling intestinal miRNAs.

Taken together such pathfinding understanding significant aid in advancing along with getting insight with regards to communication amongst GM obtained metabolites as well as epigenetic status correlated with obesity. Dependent on such germane outcomes, attempt in reference to improvement of bacterial diversity in addition to stimulate advantageous epigenetic alterations might yield an innovative trajectory with regards to efficacious avoidance of obesity along with correlated clinical presentations.

Clinical germaneness in obesity

The insight with regards to significant part possessed by GM as well as epigenetics in case of energy metabolism, low grade inflammation in addition to maternal inheritance have opened innumerable new vistas with regards to treatment approaches for obesity.[92] Such therapeutic strategies implicate microbiota targeted approaches for instance utilization of advantageous microbiota (probiotics) or facilitating the microbial growth (prebiotics), which possess the capacity of affecting the closer association microbiota along with epigenetics.[93]

Probiotics

Probiotics portray viable microorganisms which subsequent to delivery in therapeutic dosages possess the capacity of yielding health advantages to the host by affecting the GM.[94] Additionally, probiotics supplementation have the capability of stimulating epigenetic modifications which might change gene expression implicated in lipid metabolism, thus diminising the risk of obesity.[95] Acknowledged the part played by GM with regards to metabolic health, it is considered that probiotics are capable of demonstrating metabolic actions by cross talking with the host's epigenetics mechanistic modes. Here we concentrate on evaluating actions of probiotics on epigenetic modifications associated genes. In a study it was displayed that probiotics supplementation caused greater methylation of H3K27me3 (i.e., trimethylation marks at histone 3 lysine 27) at the mitochondrial transcription factor A (TFAM), promoter in case of obese mice ($p<0.001$), therefore improvement of obesity stimulated metabolic osteoporosis.[96] Furthermore, *Lactobacillus rhamnosus* GG(LGG), along with *Bifidobacterium lactis* supplementation in pregnant women has been demonstrated to diminish DNA methylation in fat mass and obesity associated gene (*FTO*) as well as melanocortin 4receptor gene (*MC4R*) in women in addition to their infants ($p < 0.05$).[60] The importance of such observations is in the implications of the probiotics in controlling DNA methylation designs of genes correlated with energy metabolism. Additionally, LGG possesses the capacity of ameliorating lipid metabolism conditions as well as weight accrual in obese mice by escalating, miR-21-5p, miR-200c-3p, and miR-let7a-5p) along with miR-26a-5pexpression ($p<0.05$), DNMT1 expression in addition to the histone modification panorama amongst liver implicating H3K36me2, H3K79me2 and H3K27me3 histone marks particularly in males.[96] Nevertheless, the clinical outcomes of probiotics in attenuating obesity in addition to other metabolic diseases epigenetic manipulation are diverse. Despite earlier observations have pointed that probiotic supplementation have the capability of improvement of the expression of miR-26a-5p in obese mice ($p<0.05$), significant actions on the expression were not found in human clinical trials.[97] Thereby the clinical actions of probiotics might be based on particular species (spp) along with strains utilized as well as future clinical work is the requirement for establishing dosages, time period of the therapy in addition to long term actions of variable strains.

Prebiotics

Prebiotics is a nonviable food component which imparts health benefits on the host associated with microbiota modulation which might be a fiber, but all fibers are not necessarily a probiotic,

eventually giving benefit to host.[98] Prebiotics are inclusive of fructoligo sacchharides (FOS), inulin, mannan oligosaccharides (MOS).[99] Maternal inulin supplementation led to improvement of dysfunctional glucose metabolism in addition to insulin resistance (IR) by the activation of wingless -related integration site family members 5a (*Wnt a*) methylation along with hampering phosphatidyl inositol 4,5 bisphosphate- catalytic subunit kinase alpha (*Pi3KCA*) methylation in the liver of the offspring which got exposure to high fat diet ($p<0.01$).[100] Furthermore, subsequent to inulin intervention significant weight reduction, Waist circumference (WC), as well as body mass index (BMI) ensued by the methylation quantities of uric acid in addition to 4 CpG regions in the promoter sites of the *insulin* gene in cases of type 2 Diabetes mellitus(T2DM).[101] Such observations emphasize the crucial part possessed by inulin, believed to be a prebiotic, regarding ameliorating obesity along with its associated diseases, through controlling the methylation event. Additionally, experimental outcomes from preclinical to clinical studies have basically concentrated on the part possessed by probiotics as well as prebiotics in modulating epigenetic controlling in addition to affecting metabolic mechanistic modes.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) portrays a therapeutic approach meant for the restoration of the host health by escalating the diversity along with working of the GM.[102] Human randomized trials have yielded proof with regards to FMT switching faecal content from healthy individual to subjects with metabolic syndrome.[103, rev in detail in 35] resulting in escalated quantities of SCFA generating bacteria, pronounced alterations in plasma metabolites implicated in lipid metabolism as well as decreased methylation quantities of actin filament associated protein (AFAP) promoter.[104] On the other hand FMT from the obesity prone donor mice led to aggravated IR in addition to greater quantities of DNA methylation at 2 particular CpG regions in the colon tissue ($p<0.05$).[73] Additionally, FMT has been illustrated to be efficacious in Non-alcoholic fatty liver disease (NAFLD), depression along with other disorders via epigenetic modifications which yielded a plausible innovative therapeutic intervention for human associated diseases.[105] Nevertheless, acknowledged the complicated aspect of human GM ecosystem, botheration's correlated with engrafting, correlated with for instance durability of microbiota as well as host filtering of milieu is the requirement to be taken into account in further FMT studies.[106]

Long et al.,[107] further exhaustively reviewed the start in addition to development of obesity-associated cancers,T2D, and CVD, generating a theoretical ground for avoidance of generating, diagnosis, in addition to treatment of such disorders emphasizing on the dynamic flexibility of epigenetic modifications might be bargained for by reverting the generation of obesity- correlated diseases, using behavioural measures, drugs, along with bariatric surgery (see Figure 2-4). They have emphasized on how various DNMT'S,TET2, SAM that causes the covalent transfer of methyl(CH3)group from S-adenosylL methionine (SAM)to the 5-carbon of cytosine residues on CpG sites, Ten –eleven translocation(TET2) methylcytosine dioxygenase, DNA methyl transferases (DNMT1, 3a, 3b) (histone deacetylates (HDACs) and Kruppel-like factor4(KLF4) etc aid in cancer initiation and which genes confer protection against cancer as reviewed by us in ref no-22 in Diabetic Kidney Disease(DKD), &further role of exosomes which we had earlier.[108] in importance in DM.

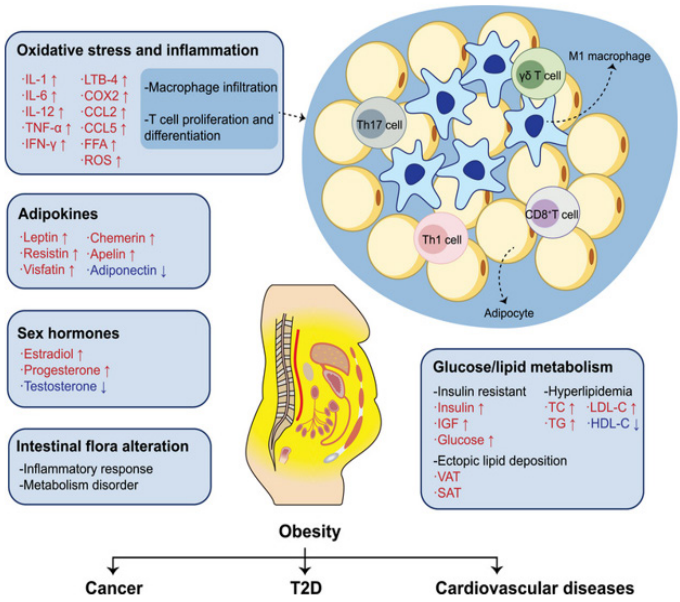

Figure 2 Pathogenesis of obesity-associated diseases. Obesity is known to contribute to the development of metabolism diseases and cancers through various processes, including disorders of glucose and lipid metabolism, secretion of sex hormones, adipokines, and promotion of inflammatory responses, as well as alterations in intestinal flora. Obesity can cause oxidative stress (OS) and chronic inflammation, contributing to the release of inflammatory cytokines, chemokines, FFA, and ROS. In obesity, adipocytes organize into a crown-like structure with surrounding infiltrated M1 macrophages, while T cells proliferate and differentiate into pro inflammatory subtypes, exacerbating the progression of inflammation. The impact of AT inflammation is profound and enduring, and even lead to dysfunction in distal organs. Hyperglycemia and hyperlipidemia resulting from disrupted glucose and lipid metabolism contribute to the advancement of T2D and CVDs. Additionally, IR can hasten the growth of tumor cells. Ectopic lipid deposition can disrupt the metabolism of adjacent organs, raising the risk of developing metabolic heart disease and obesity-associated cancers. Studies have confirmed that the increase of adipose factors, such as leptin, resistin, visfatin, chemerin, apelin, and the decline of adiponectin, are linked to progression of obesity-associated diseases. In addition, men and postmenopausal women mainly secrete estrogen from AT, and obesity can cause an increase in estradiol and progesterone and a decrease in testosterone, which could induce reproductive system cancers. The disturbance in intestinal flora caused by obesity can also cause metabolic disorders and inflammation, which in turn can increase the risk of developing digestive cancers. Intestinal flora disorders can stimulate IR through lipopolysaccharide (LPS), and microbial metabolites can also aggravate the progression of CVDs such as hypertension and atherosclerosis. However, the above pathways interact with each other rather than work in isolation to jointly regulate the progression of obesity-associated diseases. IL-1, interleukin-1; IL-6, interleukin-6; IL-12, interleukin-12; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; LTB-4, leukotriene B4; COX2, cyclooxygenase 2; CCL2, CC chemokines ligand 2; CCL5, CC chemokines ligand 5; FFA, free fatty acid; ROS, reactive oxygen species; IGF, insulin-like growth factor; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.[107]

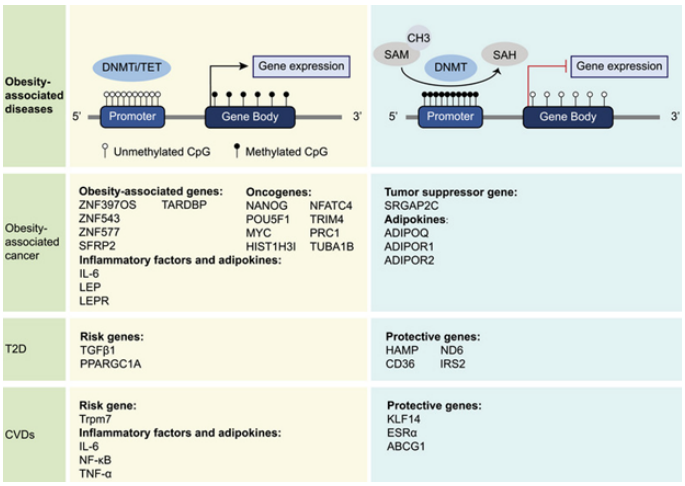

Figure 3 DNAm in obesity-associated diseases. Obesity can increase the expression of obesity-associated disease risk genes, inflammatory factors, and leptin by affecting the level of DNAm. At the same time, obesity can also reduce the expression of genes involve in self-protective regulatory mechanism within the body. From a mechanistic perspective, DNA hyper methylation on gene promoters and enhancers can silence genes, while on the gene body can increase gene expression. In addition, the catalysis of DNA demethylases or suppression of DNMTs activity can promote DNA de-methylation through active or passive pathways, respectively, and DNA demethylation on gene promoters can usually promote gene expression. SAH, S-adenosyl homocysteine; SAM, S-adenosyl methionine; DNMTi, DNA methyl transferase inhibitor; TET, Ten-eleven translocation methylcytosine dioxygenase; ZNF397OS, zinc finger and SCAN domain containing 30; ZNF543, zinc finger protein 543; ZNF577, zinc finger protein 577; SFRP2, secreted frizzled-related protein type 2; TARDBP, TAR DNA binding protein; NANOG, Nanog homeobox; POU5F1, POU class 5 homeobox 1; MYC, MYC Proto-oncogene; HIST1H3I, histone linker 1 with Histone H3.1, NFATC4, nuclear factor of activated T-cells cytoplasmic 4; TRIM4, tripartite motif-containing 4; PRC1, protein regulator of cytokinesis 1; TUBA1B, tubulin alpha 1b; IL6, interleukin-6; LEP, leptin; LEPR, leptin receptor; TGFB1, transforming growth factor beta 1; PPARGC1A, PPARG coactivator 1 alpha; Trpm7, transient receptor potential melastatin 7; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-alpha; SRGAP2C, Slit-Robo Rho GTPase-activating protein 2C; ADIPOQ, adiponectin; ADIPOR1, adiponectin receptor 1; ADIPOR2, adiponectin receptor 1; HAMP, hepcidin antimicrobial peptide; ND6, NADH-dehydrogenase 6; CD36, CD36 molecule; IRS2, insulin receptor substrate 2; KLF14, Krüpple-like factor 1; ESRα, estrogen receptor 1; ABCG1, ATP binding cassette subfamily G member 1.[107]

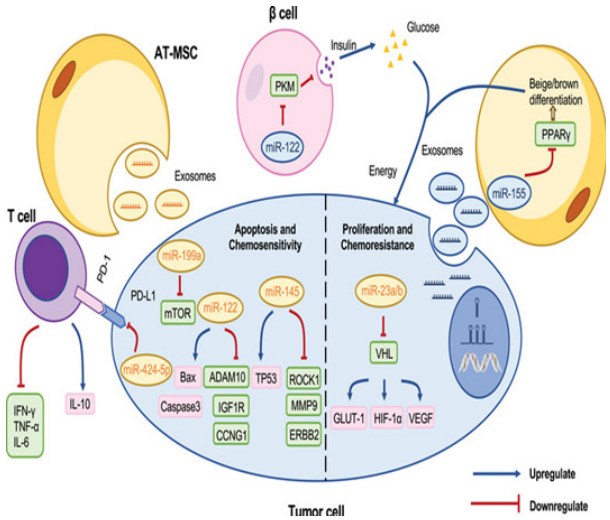

Figure 4 Exosomes transport miRNAs to mediate cell communication. Exosomes that are derived from AT-MSCs have the capability to deliver miRNAs to tumor cells. These miRNAs have the ability to regulate tumor growth and sensitivity to chemotherapy. Additionally, exosomes that carry miRNAs secreted by tumor tissue have the potential to regulate insulin release from β cells and induce differentiation of adipocytes. The regulation of these physiological processes ultimately provides additional energy to tumor tissue, which further promotes the progression of cancer-associated cachexia. AT-MSC, AT-derived mesenchymal stem cells; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-10, interleukin-6; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TP53, tumor protein p53; PKM, pyruvate kinase M; ROCK1, Rho-associated coiled-coil containing protein kinase 1; MMP9, matrix metalloproteinase 9; ERBB2, erb-b2 receptor tyrosine kinase 2; mTOR, mechanistic target of rapamycin kinase; Bax, BCL2-associated X protein; ADAM10, a disintegrin and metalloprotease 10; CCNG1, cyclin G1; IGF1R, insulin-like growth factor receptor 1; VHL, von Hippel-Lindau; GLUT1, glucose transporter 1; HIF-1α, hypoxia-inducible factor 1 alpha; VEGF, vascular endothelial growth factor; PPARγ, peroxisome proliferator-activated receptor gamma.[107]

Conclusion

The global prevalence of obesity has reached epidemic proportions, assuming problematic health issue. The GM possess crucial part in human metabolism, working to aid in in the generation of complete health results. Plausible microbial metabolites might crosstalk with cells via systemic circulation, working in the form of crucial environmental factors affecting the epigenome. Obesity stimulated metabolic decontrolling as well as disturbance of GM constitution might result in dys-equilibrium in crucial metabolites, followed by influencing epigenetic in addition to changing gene expression. Sequentially, escalating focus is getting laid on close crosstalk amongst GM along with epigenetic modifications with regards to metabolic diseases. Numerous studies have illustrated that GM possess the capacity of directly modulating the epigenome along with generating epigenetic substrates as well as enzyme co-factors. Apart from that GM are capable of targeting proteins or genetic controlling sites via microbial obtained metabolites for obtaining particular epigenetic modifications, therefore changing reprogramming of metabolic pathways. To summarize, the encompassing of epigenetic mechanistic modes in addition to GM outcomes illustrate the manner environmental factors might result in obesity yield innovative approaches for the therapy of metabolic diseases. Actually here a summary of the studies on the manner probiotics, prebiotics along with other modulators that are capable of impacting GM constitution along with affecting epigenetic mechanistic modes. Additionally, with the escalating requirement for dietary supplementation (for instance folate) as well as nutraceuticals, are efficacious, safety medical importance of nutrition treatment of obesity. Nevertheless, till now, our insight has been acquired from rodent models with absence of corroboration from human clinical trials. Furthermore, it is essential to further unravel the exact part of particular GM strains in controlling epigenome at the time of obesity. Thereby future clinical evaluation of close crosstalk amongst GM along with epigenetic modifications in addition to obesity are critical in reference to gathering information human health as well as treatment of metabolic diseases.

Such insights are crucial in fashioning in addition to implementation of individualized innovative approach, improvement of selecting agents along with avoidance of, as well as tackling obesity along with associated comorbidities. Further role of increasing prevalence of childhood obesity related to the developmental hypothesis of health and disease (DOHaD), as rev by us earlier for escalating childhood obesity[109] by us gets explained and how it can be avoided comorbidities disequilibrium.

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None

Conflicts of interest

The authors declare that there is no conflict of interest.

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