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Review Article

An update on Targeting Gut Microbiota(GM) for Avoidance of Metabolic dysfunction associated steatohepatitis propagation to Hepatocellular Carcinoma-A Narrative Review.

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Abstract

Metabolic dysfunction associated steatotic liver disease(namely MAFLD) as well as propagation to Hepatocellular carcinoma(HCC), displayed unique molecular along with immune traits .Such properties get impacted by a plethora of factors inclusive of gut microbiome that crosstalk with liver via the 'gut - liver axis'. The bidirectional association amongst gut in addition to its microbiota along with liver possesses a critical part in guiding different liver diseases, with microbial metabolites as well as immune reactions possessing a central part in such events .Here we have attempted to update our earlier work with regards to part of gut microbiota(GM) aiding in generation of Metabolic dysfunction associated steatohepatitis(MASH) as well as propagation to HCC, highlighting the recent advancements in diagnostic in addition to therapeutic interventions with regards to use of faecal microbiota transplantation(FMT), probiotics, prebiotics, synbiotics, antibiotics, along with immunotherapy using a plethora of clinical as well as preclinical studies in avoidance of MASH along with propagation to HCC as well as detailed mechanistic modes of such treatments exhaustively inclusive of methodologiesof administration of FMT as well as their approval by Food and Drug Administration(FDA), just for treatment of recurrent Clostridium difficile infection(CDI) ,with future opportunities for therapeutic interventions in a plethora of diseases like obesity, irritable bowel syndrome (IBS), Parkinson's disease, metabolic syndrome (MetS) type 2 Diabetes mellitus(T2DM), neuropsychiatric disease (NPD) (Autism spectrum disorder (ASD) .More research is needed to overcome the restrictions along with correlated hurdles.

Key Words; gut microbiota(GM) ; avoidance of Metabolic dysfunction associated steatohepatitis(MASH); Hepatocellular carcinoma(HCC); immunomodulatory treatments.

Introduction

The human gut comprises of enrichment as well as variation of microbial population in addition to bacterial variations in the colon has been determined tobe 10^{11}-10^{12}/ml[1]. Over the past few years extensive work has been conducted to understand the critical significanceof trillions of bacteria that are present in the gastrointestinal tract (GIT) along with dynamic interaction among the heterogenous make-up of this large microorganism community along with chances of getting various diseases like obesity, type 2 diabetesmellitus (T2DM) .The molecular strategies implicated are for instance metabolomics, lipidomics, metatranscriptomics along with metagenomic unraveled theinfluence of gut microbial population in variable organs[2]. The changes in the microbial constitution in the gut result in generation of different diseases inclusive of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Coeliac disease,type 2 diabetesmellitus (T2DM), atopy , autoimmune diseases(for instance Ulcerative colitis (UC),lupus, Crohn's disease(CD), Multiple Sclerosis (MS), steatosis in addition to variable carcinomas (oral, gastric, colorectal cancer[3,4,5 rev by us in bile acids cancer& type 1 diabetesmellitus (T1DM)]. Gut microbiota(GM) comprises of variable organisms inclusive of bacteria, viruses along with yeast. *Firmicutes* along with *Bacteroides* portray the pronounced phyla in the GM constitution[6]. Other microbes inclusive of *Actinobacteria, Proteobacteria, Fusobacteria* as well as *Verrumicrobia* are further present . *Firmicutes* phylum basically comprises of 200 separate genera for instance *Lactobacillus, Clostridium* , *Bacillus,Ruminococcus* as well as *Enterococcus* .Of *Firmicutes* phylum *Clostridium* genera is the maximum predominant(95%).Bacteroidetes get constituted by genera for instance *Bacteroides* along with *Prevotella*[7]. In the clinical study it was displayed that the existence of *Ruminococcus obeum* as well as the *Alistepes were* diminished whereas enrichment of Dorea, *Lactobacillus* in addition to *Megasphaera were* observed in Non alcoholic fatty liver disease(NAFLD) patients in contrast to healthy subjects [1,8]. In contrast to NAFLD patients, patients with non alcoholic steatohepapititis(NASH),had greater quantities of *Firmicutes,* however lesser quantities of *Bacteroides* at the phylum level [9]. In the studies it displayed that patients with cirrhosis revealed greater quantities of Enterobacteriaceae as well as *Streptococcus,* however lesser quantities of *Akkermansia.* In the patients with Hepatocellular carcinoma(HCC), quantities of *Bacteroides* along with *Ruminococcus wa*s observed whereas diminished *Bifidobacterium* quantities *were* observed. An inverse association *wa*s observed amongst calprotectin(cellular inflammatory marker) .Faecal microbial variation is clear cut in cirrhosis to early HCC in addition to the existence of *Actinobacteria* phylum *wa*s greater in the early HCC stage. Akin to that *Gemmiger* as well as *parabacteroides wa*s greater in early HCC in contrast to cirrhosis .Conversely, butyrate

generating genera diminished in addition to lipopolysaccharide(LPS) generating genera enrichment occurred in contrast to healthy subjects[10,11]. Escalation of HCC incidence might takes place in view of aberrant escalated *Firmicutes : Bacteroides* ratio occurring in NASH patients[12]. There is existence of proof that alterations in the constitution along with variation of the gut microbiome might result in generation as well as propagation of variable liver diseases. Metabolic impairment associated steatotic liver disease(namely MAFLD) earlier referred to as Non alcoholic fatty liver disease(NAFLD) portray a variety of liver disorders which have the properties of accrual of extra fat in the liver(≥5% hepatic steatosis).The origination of disease spectrum occurs with steatotic liver disease (SLD) which portrays the early stage of accrual of fat in the liver[13]. On propagation of disorder, it might form metabolic MASH earlier referred to as non alcoholic steatohepatitis(NASH) that implicates liver inflammation in addition to injury, plausibly with or without fibrosis. With further advancements of MAFLD stages, MAFLD might further result in generation of cirrhosis, liver failure as well as further liver cancer[14]. Epidemiological proof has demonstrated that NAFLD in addition to its more robust kind NASH has been escalatingly acknowledged to mainly aid in generation of HCC. Dysbiosis in the gut microbiome possess the capacity of disturbing homeostasis, aggravating liver cell by stimulating different kinds of immune modulated reactions. Variable genomic factors disturb the gut-liver axis as well as escalate microbial exposure to the liver[15]. There is existence of proof that microbial metabolites for instance bile acids, trimethylamine in addition to short chain fatty acids (SCFA)etc are involved in the initiation along with propagation of liver diseases[16]. Inappropriate microbial generation in addition to microbial products gaining entry into liver take place via portal vein which might result in hepatic inflammation along with resulting in the generation of propagation of NAFLD to NASH[17]. The GM impacts propagation of NASH to HCC through modulating variable factors for instance i)gut epithelial permeabilityii) endogenous alcohol formation iii) choline metabolism iv) bile acids metabolism as well as liberation of proinflammatory cytokines[18,19]. Earlier we had reviewed different methods of treating NAFLD/ NASH ,concentrated on organokines liberated by AT , liver that are key organs for controlling of lipid metabolism basically organokines (adipokines;hepatokines;myokines;osteokines stellakines),role of GM in MAFLD, NASHand HCC avoidance [20-35].

The aim of this review to detail the significance of GM manipulated impacts on Metabolic dysfunction associated steatohepatitis(MASH) along with HCC. Additionally, it emphasizes on the major diagnostic in addition to therapeutic significance of GM in MASH along with HCCwith updated therapeutic measures (see (Figure1) rev in ref no-36.

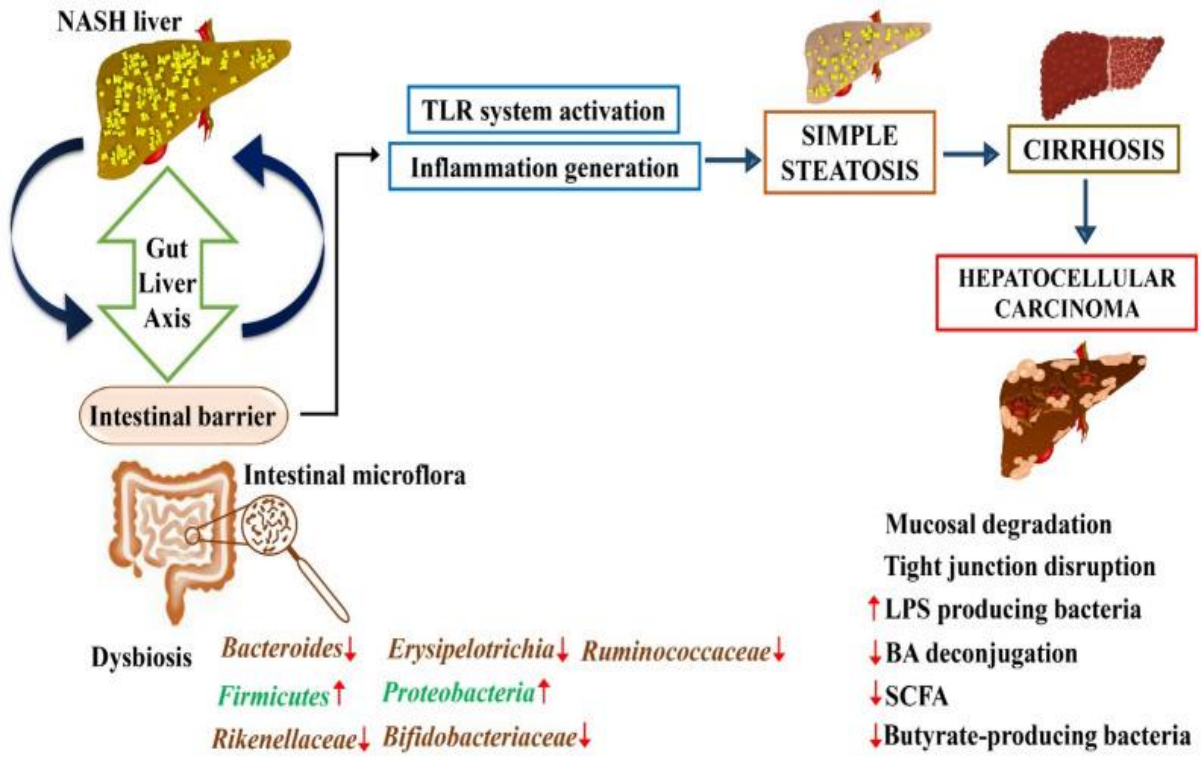

Figure1

Courtesy ref no -36-Progression of liver disease from MASH to hepatocellular carcinoma via gut–liver axis dysregulation. The figure illustrates the pathological progression from MASH to HCC through disruptions in the gut–liver axis. The MASH liver exhibits alterations in the intestinal barrier and gut microbiota, leading to dysbiosis characterized by fluctuations in key bacterial populations. The dysregulated gut microbiota affects the intestinal barrier's integrity, fostering mucosal degradation and tight junction disruption. This breakdown facilitates the systemic infiltration of lipopolysaccharides (LPS) and other bacterial metabolites into the liver through the portal circulation. Increased TLR (Toll-like receptor) activation in the liver induces inflammation, progressing from simple steatosis to cirrhosis and ultimately culminating in hepatocellular carcinoma. Key changes in microbial populations include increased Firmicutes and Proteobacteria, with a decrease in Bacteroides, Erysipelotrichia, Ruminococcaceae, Rikenellaceae, and Bifidobacteriaceae. The figure also notes a decrease in bile acid (BA) deconjugation, short-chain fatty acids (SCFA), and butyrate-producing bacteria, which are critical to maintaining hepatic and intestinal health. Symbols: ↑increase, ↓decrease

Methods

Here we conducted a narrative review utilizing search engine pubmed,google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms NAFLD; NASH; Metabolic impairment associated steatotic liver disease(namely MAFLD) ;organokines; short chain fatty acids (SCFA); MASH; choline metabolism ; *Firmicutes :Bacteroides* ratio ;Fructose; Gut Microbiota; Insulin Resistance; faecal microbiota transplantation(FMT), probiotics; prebiotics; ,antibiotics; immunotherapy;obesity;T2D from last 10 yrs till date in 2024.

Results

We found a total of 750 articles out of which we selected 111 articles for this review. No meta-analysis was done.

Immunomodulatory part of Gut Microbiota(GM) in MAFLD to MASH Propagation

A plethora of clinical as well as preclinical studies have demonstrated that aberrant expression of GM in addition to its metabolites are intricately correlated with liver diseases for instance MAFLD along with MASH, cirrhosis as well as HCC[37,38]. The variations in the GM possess the capacity of promoting the generation of free fatty acids(FFA) in the intestine in addition to escalate permeability of FFA over intestinal region which might result in generation of NAFLD[39]. A plethora of studies pointed that high fat diet(HFD), had the capacity of escalating the quantities of alcohol generating for instance Escherichia genus members of the *Proteobacteria* phylum in the gut which might form acetate as well as acetaldehyde through the oxidation of ethanol in addition to promote the generation of fatty acids along with aid in NAFLD formation[40]. Recent studies pointed that GM gets changed in view of genetic susceptibility in addition to incorrect diet which might influence hepatic carbohydrate as well as lipid metabolism as well as impact the actions of antiinflammatory along with proinflammatory compounds in the liver, that might result in generation of NAFLD propagation to NASH[38]. The ingestion of obesity stimulating diet for instance HFD might disturb gram negative bacteria whose existence is there in the intestinal tract as well as escalate the quantities of LPS which might work in the form of critical controller in generating inflammatory reactions in the liver tissue in addition to generating liver damage through TLR4 signaling along with result in generation of NAFLD as well as its propagation [39]. Additionally, HFD possesses the capacity of after

modulation the enzymes generated by gutmicrobiome,it might work in the form of a catalyst for the transformation of choline to toxic metabolites referred to as dimethylamine along with trimethylamine. Such metabolites might be transformed into trimethylamine-N-oxide (TMAO), in the liver, that generates inflammation in the hepatocytes as well as propagation of NAFLD to NASH[41]. The clinical studies pointed that bacterial overgrowth in the small intestine in view of HFD in addition to genetic factors in case of NAFLD might escalate the risk of NASH generation[42]. Small intestinal bacterial overgrowth(SIBO) pronouncedly impacted propagation to NASH in case of NAFLD subjects.Wiggs etal. [44], performed a contrasting study for the asssessment of existence of SIBO in NASH subjects in addition to healthy controls[43]. They revealed that 50% of NASH subjects displayed SIBO while SIBO was restricted to 22% in healthy controls. Asssessment of average quantities of tumor necrosis factor alpha(TNF-α) got in NASH subjects along with healthy controls which was observed as 14.2 as well as 7.5pg/ml respectively. Quantification of the intestinal bacteria conducted by utilization of glucose hydrogen breath test in addition to quantitative aspirate culture obtained from jejunum(the elimination along with culture of intestinal fluid) with results pointing that low grade SIBO about≥103 CFU/ml in NASH subjects in contrast to controls. Such outcomes demonstrated that NASH subjects possessed the maximum prevalence of SIBO[44].Shanab etal. [46], revealed that an escalated quantities of SIBO in NASH subjects escalates the liberation of Interleukin 8(IL-8) in addition to escalates the expression of TLR4 which promotes the generation along with propagation to NASH [45]. The dysequilibrium amongstTLR further aids in propagation of NAFLD to NASH. Aberrant bacterial deoxy ribonucleic acid(DNA), LPS as well as other endogenous substances possess the capacity of activating the innate immune system through TLR4 in addition to TLR9 which promotes the generation of Kupffer cells along with IL-1β . IL-1β supports the accrual of lipids as well as possesses the capacity of escalating cell demise of hepatocytes with subsequent inflammation in addition to steatosis [46]. Furthermore microbial, pathogen–associated molecular patterns(PAMP) possess the capacity of activating the variable nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing (NLRP) inflammasomes for instance NLRP1, NLRP3, NLRC4(IPAF),AIM2 as well as NLRP6 have the capability of promoting the propagation of NAFLD in addition to development of steatosis [47]. The accumulating proof has demonstrated that TLR4 in addition to microbial obtained LPS are the crucial factors implicated in propagation of cirrhosis[48]. Gut dysbiosis might result in systemic inflammation along with immunoinsufficiency by leading to dysfunctional working of the immune cells for instance Tcells,B cells as well as macrophages etc in addition to result in generation of cirrhosis associated immune dysfunction(CAID). CAID has the capability of facilitating the translocation of bacterial products into the

blood circulating cells along with magnitude of the inflammation[49]. Additionally, gut dysbiosis has the capability of disturbing bacterial flora as well as promoting the LPS/ TLR4 modulated signaling. Gut dysbiosis further might be involved in originating cirrhosis to cancer propagation through escalated liberation of chemokines in addition to chemotaxis of Kupffer cells, that stimulate the profibrinogenic cytokines for instance transforming growth factorβ 1(TGF-β1) [47]. Various inflammatory pathways are responsible for the cirrhosis to HCC propagation stimulated by interactions amongst intestinal bacteria, immune system along with liver. The inflammatory event basically incorporates crosstalk amongst macrophages,Kupffer cells along with PAMP in the liver cells. Macrophages,Kupffer cells along with PAMP possess the capacity of among eliciting nuclear factor-κappa light chain enhancer of activated B cells(NFκB) pathways via binding nucleotide-binding oligomerization domain (NOD) –like receptors in addition to TLRs specifically TLR4 along with TLR9[51]. GM modulated TLR4 signaling pathway takes place as the proinflammatory reactions in the liver as well as facilitates HCC production[52]. The inflammatory chain reactions might evoke escalated liberation in addition to inflammation in liver which in turn result in dysbiosis of microbiota .Such Kupffer cells modulated liberation of proinflammatory cytokines for instance TNF-α, IL-8 , along with IL-1β. Escalated cytokines might evoke lipids accrual as well as hepatocytes apoptosis in addition to leading to steatosis along with inflammation. escalated proinflammatory cytokines in view of aberrant GM controlling were found in practically all the NAFLD in addition to NASH subjects that facilitates the generation along with propagation of NASH viaTLR stimulated pathways[53]. Thereby GM modulated cytokines possess a crucial part in the origination as well as propagation of NAFLD to NASH to HCC[54]. Dysbiosis stimulated by cirrhosis associated with escalated intestinal permeability might stimulate liberation of PAMPs in addition to metabolites modulated by gut microbiome, which result in escalated inflammation, injury along with fat generation in the liver[55]. As per scientific researchers PAMPs start liberation of cytokines, chemokines for instance IL-8 , IL-17 along with IL-1β via TLRs activation precipitating immune cell existence in the liver [56]. Persistent generation of cytokines might result in DNA injury along with Oxidative stress(OS) , therefore leading to starting as well as advancement of HCC[57]. Additionally, generation of microbial metabolites for instance bile acids(BA), trimethylamine, short chain fatty acids (SCFA), PAMPs, lipoteichoic acid (LTA), in addition to branch chain amino acids have been acknowledged to activate hepatic stellate cells(HSCs) through the senescence- associated secretory phenotype(SASP) ,facilitating proliferation of hepatocytes as well as proneness to HCC[58]. Clinical along with preclinical studies have illustrated that BA metabolism further possesses a significant part in propagation of NASH to HCC[59]. Escalated quantities of BA in the liver possess the capacity of stimulating inflammation , hepatocytes DNA injury in addition to

apoptosis; therefore tumorigenesis would take place in the liver [60]. Moreover, dysbiosis in NASH would escalate the enrichment of gram positive microorganisms in the microflora, therefore stimulating HCC via escalated generation of secondary bile acids inclusive of deoxycholic acid (DCA) that limits the activation of liver sinusoidal endothelial cells (LSECs) as well as promotes the repression of C-X-C motif chemokine ligand6(CXCL6), enrollment of natural killer Tcells(NKcells), along with develop tumorigenesis[61]. Furthermore ,secondary bile acids directly stimulate HCC generation NASH by stimulating mammalian target of rapamycin (mTOR) [62]. Guerra-Ruiz etal. [61], illustrated that serum quantities of LPS binding protein (LBP) were significantly escalated in NASH individuals in contrast to healthy patients with simple steatosis .The escalated serum quantities of LBP were associated with aberrant expression of TNF-α in the liver tissue.The escalated quantities of TNF-α possess a critical part in generating HCC[63]. Obesity portrays another risk factor which impacts the alterations in the constitution of microbiota as well as its metabolites for instance LPS in addition to PAMP[64]. The damaged hepatocytes possess the capacity of generating damage –associated molecular patterns(DAMP) that stimulate the inflammatory molecules through TLR in addition to activation of immune cells transition from NAFLD -NASH- HCC[65]. There is presence of proof that gut microbiome possess the capacity of affecting antitumor reactions that might yield an innovative approach for improvement of efficacy of cancer immunotherapy[66]. Accumulating proof has demonstrated that, aberrant characterization of GM might evoke immunorepression by induction of M2(pro tumor)- like tumor associated macrophages(TAM) . Intestinal dysbacteriosis correlated with IL-25 stimulated activation of M2 macrophages possess the capacity of accelerating HCC propagation by liberation of C-X-C motif chemokine ligand 10(CXCL 10), along with accelerate epithelial –mesenchymal transition (EMT) [67]. **V**ariable studies illustrated that GM possessed the capacity of generating oncogenesis in addition to propagation in myeloid derived suppressor cells (MDSC) based way [68]. Aberrant GM modulated dysbiosis further had the capacity of disrupting homeostasis, sequentially facilitating immune modulated hepatocytes damage which further stimulates HCC propagation.Metabolomic in addition to metagenomic studies associated with GM illustrated that GM are capable of leading to Tcell modulated immunrepression through escalating the quantities of regulatory Tcells (Treg) as well as the reduction of quantities of $CD8^+$ T cells inclusive of cytotoxic Tcells [69]. Furthermore, Looetal. [19], illustrated that GM possessed the capacity of generating prostaglandinE2 in addition to cyclooxygenase2(COX2) enzymes that hamper antitumor reactions via prostaglandinE2 receptor4(EP4), therefore facilitating HCC propagation[19]. Expression of various proteins for instance CD68(cluster of differentiation68) is believed tobe a marker macrophages, as well as TLR(TLR2, TLR4, TLR 5, as well as TLR9) possesses a negative part in activation of the innate immune

system. Variable studies illustrated that CD68 is a TAM along with result in the generation along with propagation of NAFLD in addition to NASH to HCC propagation[37]. It further pointed that a leaky gut might lead to overgeneration of GM obtained metabolites affecting the hepatic immune system as well as escalating the HCC risk[70]. (Figure2).

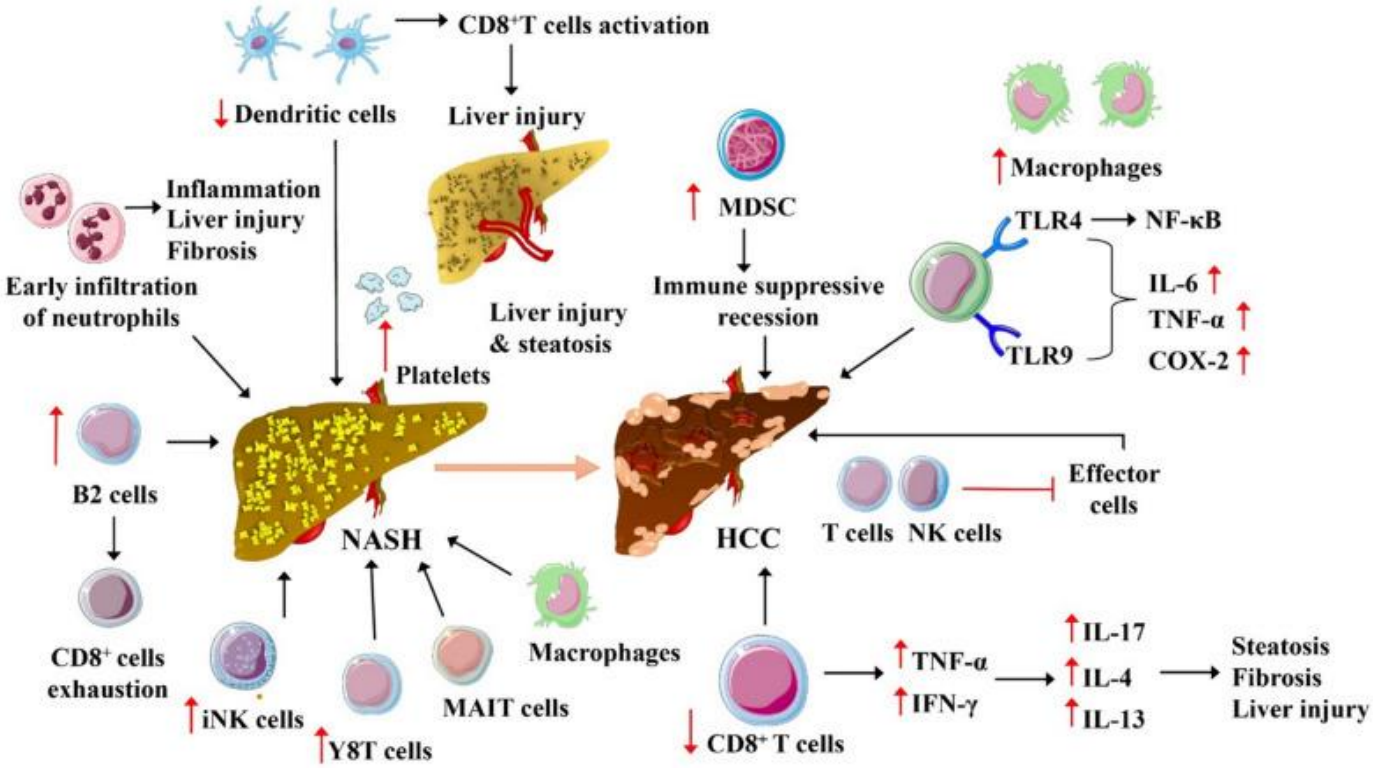

Figure2

Courtesy ref no -36-Potential mechanisms for gut microbiota-associated immune modulation in MASH–HCC progression. This figure illustrates the complex immune interactions and cellular transformations involved in the progression from MASH to HCC. Key features include the early infiltration of neutrophils leading to inflammation, liver injury, and fibrosis, and the role of B2 cells and CD8 + T cells in modulating the immune response. Activation of CD8 + T cells contributes to further liver injury and steatosis, while the presence of myeloid-derived suppressor cells (MDSC) indicates an immune suppressive state facilitating cancer progression. The diagram also highlights the activation of macrophages through toll-like receptors (TLR4 and TLR9) leading to an increase in inflammatory cytokines (IL-6, TNF-α) and COX-2, which are important in the development of HCC. Additionally, the impact of various cytokines such as TNF-α, IFN-γ, IL-17, IL-4,

and IL-13 on the hepatic environment, promoting steatosis, fibrosis, and liver injury, is depicted. Abbreviations and symbols: B2 cells: a type of B cell involved in immune response; CD8 + T cells: cytotoxic T cells which are a part of the immune system that kills cancer cells, virus-infected cells, and other damaged cells; COX-2: cyclooxygenase-2, an enzyme that plays a crucial role in inflammation; HCC: hepatocellular carcinoma; IFN-γ: interferon gamma, a cytokine critical for innate and adaptive immunity; IL-4: interleukin 4, a cytokine involved in the regulation of immune responses; IL-6: interleukin 6, a cytokine involved in inflammation and maturation of B cells; IL-13: interleukin 13, involved in inflammatory responses; IL-17: interleukin 17, a pro-inflammatory cytokine; iNK cells: invariant natural killer T cells, a component of the immune system that recognizes lipid antigens; MAIT cells: mucosal-associated invariant T cells, involved in the mucosal immunity; MDSC: myeloid-derived suppressor cells, regulate immune responses in cancer; NASH: non-alcoholic steatohepatitis

Immunotherapeutic Importance of Manipulating GM in MASH along with HCC

NASH stimulated dysbiosis in GM results in escalated intestinal permeability, therefore escalating exposure to bacterial metabolites, in the liver leading to robust inflammation aiding in HCC[71]. Manipulating GM modulated BA metabolism, actions of TLR, controlling Farsenoid X receptor[FXR] Takeda G protein coupled (GPC) bile acid receptor 5(TGR5) activation, choline metabolism, as well as targeting proinflammatory cytokines has been believed tobe an innovative approach for the therapy of NASH along with NASH linked HCC[19]. Targeting GM agains**t** NASH as well as HCC apparently is a substantially promising strategy, in addition to concurrently possesses no inimical sequelae with considerable safety profile inclusive of faecal microbiota transplantation(FMT), probiotics, prebiotics, synbiotics, antibiotics, along with immunotherapy[12]. The pronounced mechanistic modes by which therapeutically targeted treatment's work are i) regulating T helper cells 17(Th17) cells proliferation that escalate the liberation of interleukin (IL)-17, ii)decreasing quantities of metastasis via diminishing overexpression of vascular endothelial growth factors(VEGF), iii)restricting angiogenesis ,lymphangiogenesis in addition to inflammation [72].iv) Furthermore, changes in the controlling of GM stimulates the generation of SCFA as well as limit the propagation of NASH to HCC. Manipulating GM constitution might result in upregulation of propionate which aid patients in getting over HCC via cyclic 3'5' adenosine mono phosphate(cAMP) quantities based pathway in addition to stimulation of G protein coupled receptor43 (GPR43) [69]. V)Additionally, controlling of GM might have anti HCC actions by escalating the quantities of hepatic CXCL6 + NKTcells along with

escalating the quantities of interferon α (IFN). Concurrently CXCR6+ NKTcells accrual got regulated via the expression of CXCL6 in LSECs that got communicated with microbiome stimulated by primary to secondary BA transformation[74]. Figure3 summarizes variable approaches for **t**argeting gut microbiota faecal microbiota transplantation(FMT), probiotics, prebiotics, synbiotics,antibiotics[rev in ref 75].

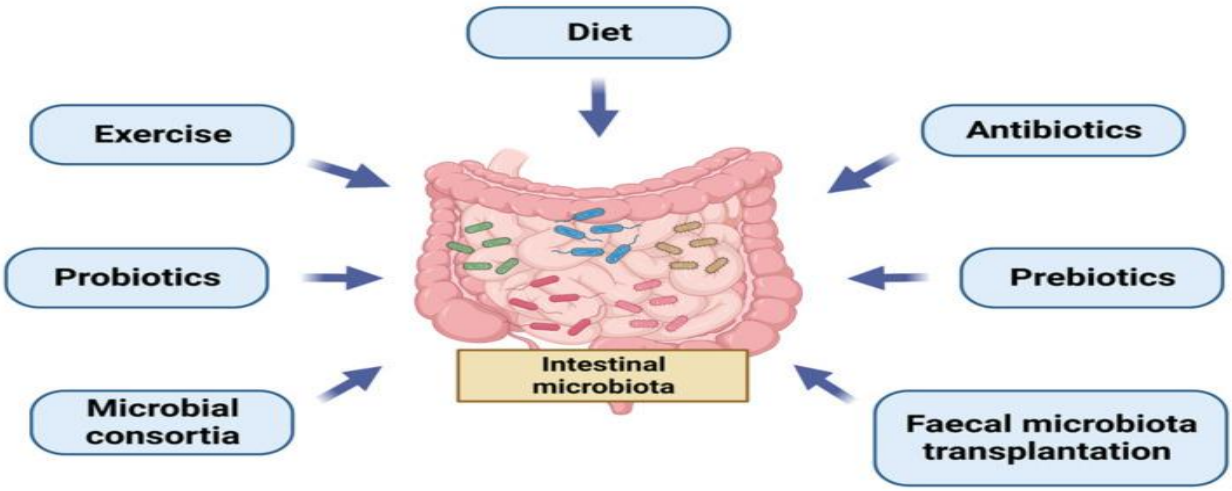

Figure3

Courtesy ref no -75-Different ways to manipulate gut microbiota.

i)Basically probiotics get used for restoration of microbial dysequilibrium[62]. Clinical use of probiotic bacteria illustrated decreasing rates of propagation of NASH as well as decreasing HCC cells spreading by reduction of activation of inflammation modulated by TLR's. PAMP's aid in generating NASH as well as HCC by activation of inflammatory reactions via TLR's. Utilization of probiotic bacteria have illustrated that they are capable of ameliorating liver metastasis by decreasing escalated inflammatory reactions stimulated by TLR's[76].In experimental liver cirrhosis in rats which received treatment with *Lactiplantibacillus plantarius* illustrated decreased TLR4 expression in addition to scanty liver injury. Furthermore, by sterilization of gut along with dysactivation of TLR4 receptor significantly curtailed propagation of HCC by 80% pointed their plausibility in the form of avoidance strategies HCC[77]. Li etal. validated in 2016 , that a combination of probiotics possessed the capacity of decreasing liver fat proinflammatory cytokine for instance interleukin (IL)-17 in case of mouse models .It further pointed that probiotics had the capacity of decreasing liver fat in addition to quantities of aspartate amino transferase (AST) in NASH individuals[78] [NCT00870012,NCT01791959]. The probiotics stimulates the growth of

microbial constitution towards advantageous bacteria inclusive of *Prevotella* as well as *Oscillibacter*. *Prevotella* as well as *Oscillibacter evoke* antiinflammatory metabolites which subsequently decrease Th17 polarization along with escalating the differentiation of regulatory Tcells (Treg) / type 1 regulatory T cells(Tr1) in the gut in addition to generation of antiinflammatory reactions in the cancer cells .Additionally, probiotics are capable of regulating aberrant growth of segmented filamentous bacteria(SFB) which portray bacteria that possess the capacity of liberation of quantities of Th17 in the body. Thereby probiotics delivery diminished quantities of SFB by a considerable magnitude leading to significant decrease in generation of proinflammatory cytokines for instance IL-17. The IL-17A produced by Th17 might promote angiogenesis therefore diminished Th17 along with IL-17 quantities might decrease propagation of HCC . Clinical in addition to preclinical studies have illustrated that probiotics were efficacious against NASH as well as HCC[79]. Moreover ,Helicobacter spp were observed encompassing NASH along with its translocation might be of use in evoking HCC . With that idea, intestinal microbiota profiles might pronouncedly display advantageous actions in HCC patients that got immune checkpoint receptors(ICRs) which pointed that gut microbiota targeted immunotherapy might be advantageous in the treatment of liver cancer [80]. In a double blind, randomized, placebo controlled trial probiotics in cases of Child Pugh A B cirrhosis got performed for the asssessment of anticipative part of gut microbiome in the generation of HCC.As per this specific study, asssessment of part of probiotics towards the existence of endotoxins(LPS) as well as cytokines (TNF-α along with IL-6)in the tumor microenvironment(TME) in addition to further asssessed the expression of TLR4 in the mononuclear cells [NCT038513928] [81].

ii)Prebiotics are a nonviable food component which imparts health benefits on the host associated with microbiota modulation which might be a fiber, that basically are non absorbant oligosaccharide substances which aggravate bacterial growth in addition to sustenance of GM decreasing NASH along with NASH correlated HCC[82]. Dietary polyphenols portray significant prebiotics whose utilization is done currently inclusive of flavonoids which include lignins as well as phenolic acid that have been found in tea, vegetables,fruits,legumes,nuts,red wines. One of maximum significant prebiotic polyphenols is egallic acid which portrays an antioxidant acid which possesses anticancer characteristics. Metabolism of egallic acid take place by microflora whose existence is in the colon generating urolithins whose enrichment is in nuts along with berries[83]. Urolithins possess the capacity of repression of COX2 correlated inflammation in the liver cells[84]. One more polyphenol for instance resveratrol, that is existence in the grapes are capable of diminishing or avoidance of NASH[85] in addition to HCC propagation by breakdown of invasion of

metastasis as well as tumor cell migration in case of liver cancer[86] .Resveratrol works apart from in the form of an immunomodulatory substance by stimulating immune cells which have placement in the TME,or sensitization of tumor cells towards cytotoxic signaling of immune cells[87] .Querceetin represents one more flavonoid which functions in the form of a repressor of nuclear factor-κappa light chain enhancer of activated B cells(NFκB) in the hepatocytes [88]. A prospective cohort study illustrated that escalating the ingestion of tree nuts for instance almonds, hazelnuts, pistachios, macadamias, cashews along with pecans had an association with diminished NASH along with HCC[89]. The combination of pectins in addition to fructoligosacchharides(FOS), raspberry polyphenols over microbial fermentation as well as inflammation manipulation along with asssessment of lipids in the liver was which pointed that FOS in addition to pectins resulted in improvement of raspberry extract against NASH as well as HCC[90]. Furthermore, a study on hepatocytes illustrated that polyphenols extracted from raspberries further regulated immunometabolic signals correlated with obesity generation[91]. Prebiotics supplementation further aid in activation of 5' AMP-activated protein kinase(AMPK) [92]. Astralagus, polysaccharides,grifolan,lentinan as well as krestin(PSK) illustrate anticancer characteristics by controlling actions of immune system in addition to stimulating direct actions against cancer cells [104]. Clinical studies illustrated that omega-3 fatty acids along with eicosapentaenoic acid (EPA),had activity against HCC [NCT04682665].Certain clinical trials further displayed efficacy of prebiotics, along with synbiotics against NASH [NCT02530138, NCT01791959, NCT03184376, NCT03897218].

iii) Additionally, antibiotics utilization might be done to diminish or eliminate changed gut microbial quantities; that aid in limiting inflammatory signals from leaky guts. Various preclinical studies corroborate that separate antibiotics for instance vancomycin, metronidazole, neomycin in addition to ampicillin significantly diminished HCC proliferation[94]. Antibiotic cocktails[(ABX) inclusive of vancomycin, neomycin as well as primaxin generated anti- HCC actions .Such antibiotics possess the capacity of escalating the quantities of hepatic CXCL6 + NKT cells in addition to the quantities of IFNγ along with hampering growth of cancer cells[95]. A phase 2 interventional study asssessment of safety as well as effectiveness of solithromycin against NASH without cirrhosis had been done[NCT02510599]. A randomized interventional clinical trial illustrated the actions of rifaxim on LPS along with associated cytokines in case of NAFLD in addition to NASH [NCT02009592], continuation of antibiotics from β-lactams, tetracycines, fluoroquinolones, sulfonamides, aminoglycosides influence human gut flora. They possess the capacity of modifications in the diversity of GM along with constitution which result in metabolic changes in body

metabolism of SCFA which aid in start along with propagation of NAFLD[106]. Decontrolled metabolism in the body specifically in the metabolism of SCFA might result in obesity, type2 diabetes mellitus(T2DM), as well as metabolic syndrome (MetS). Additionally, studies pointed that persistent antibiotics utilization might result in elimination of gut bacterial diversity along with escalate the predisposition to infection [96]. Persistent antibiotics utilization might escalate the quantities of antibiotics resistant genes in the microbiome. These resistant genes pools might start antibiotics resistance[97]. In such a setting the main botheration is promoting the growth of advantageous microflora, in the meantime diminishing the percentage of microbiota involved in dysbiosis generation for facilitating individuals health. Thereby the generation of innovative antibiotics might be individualized for a person dependent on intestinal along with biochemical personality. Selective antibiotics utilization would diminish the negative influence of antibiotics on human health in view of alterations in gut microbiome[98].

iv)Faecal microbiota transplantation(FMT), represents a medical methodology which has been responsible for switching of a stool sample from a healthy individual to an individual who is diseased [99]. The healthy stool samples constitution is of trillions of advantageous bacteria in the lower intestine , that possess the capacity of mitigating disease . Different studies have displayed that FMT possesses the capacity of restoration of healthy bacteria in the lower intestine that would further aid in stopping Clostridium difficile (C. difficile) from the intestinal region[100,101]. The manner detailed earlier , healthy intestinal tract has considerable quantities of healthy bacteria, nevertheless, in certain situations for instance**,** antibiotics utilization might limit the growth of the bacteria believed to be good, which might be facilitating growth of unhealthy bacteria in the colon. There is predilection for the FMT utilization for the treatment of Clostridium difficile infection(CDI) in addition to cases of IBD[102,103]. Dependent on FMT clinical trials, FMT utilization has further been advocated for irritable bowel syndrome (IBS), Parkinson's disease, metabolic syndrome (MetS) type 2 Diabetes mellitus(T2DM), neuropsychiatric disease (NPD) (Autism spectrum disorder (ASD) [103,104,rev by usin ref 106]. Various methodologies might be used for instance colonoscopy, enema, nasogastric(NG) tube, oral capsules(VOW-ST,SER-109) [107,108].Presently as per recommendations by Food and Drug Administration(FDA), FMT is just recommended for recurrent CDI which does not display response to the canonical antibiotics treatment.Two separate FMT treatments received recommendations by FDA- FDA REBY OTA(faecal microbiota-live -JSLM0 as well as VOWST[109]. Different studies have displayed that FMT is efficacious in 80-90% in avoidance of recurrent CDI subsequent to antibiotics treatment . However there are different long as well as short term inimical

sequelae correlated with FMT[110]. Therefore intense screening of donor in addition to asssessment is warranted with regards to guaranteeing practically negligible inimical sequelae. See Figure4 for FMT details and mechanistic modes .

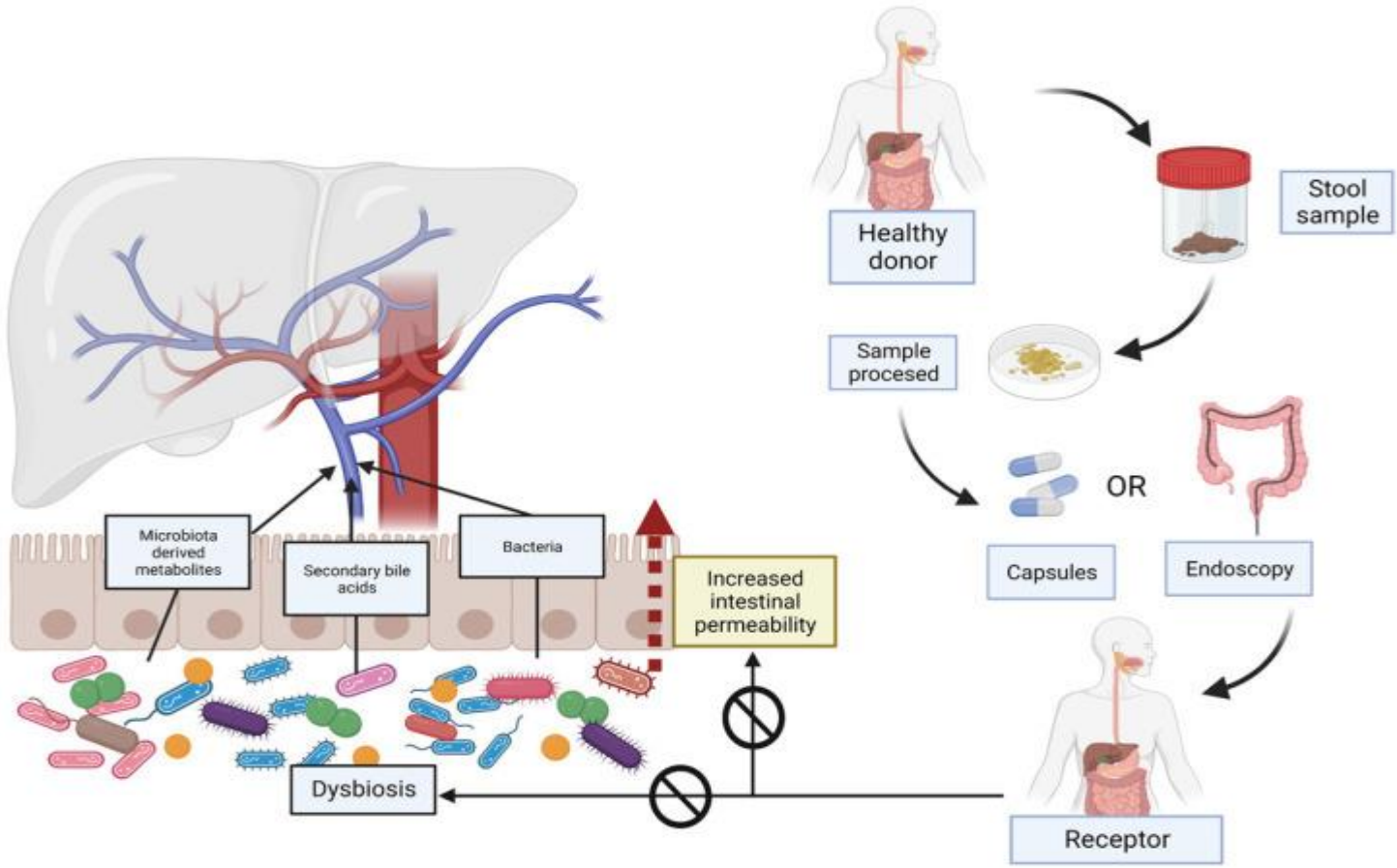

Figure4

Courtesy ref no -75-Non-alcoholic-fatty-liver-disease (NAFLD)-related dysbiosis and increased intestinal permeability and the utility of faecal microbiota transplantation (FMT). The increase in intestinal permeability enables bacteria and their metabolites to reach the liver through the portal system. In FMT, a stool sample is taken from a healthy donor. After processing, it will be administered to the receptor subject with NAFLD. The FMT can be performed in different ways, either orally or by endoscopy or enemas. FMT is intended to reverse existing dysbiosis and restore the intestinal barrier, and consequently improve the severity of the disease.

Restrictions along with Hurdles

Although, we have exhaustively updated part of gut microbiota(GM) in the production of NASH along with propagation its to of HCC ,remarkable restrictions along with hurdles still need to be evaluated.

a) of the maximum detailed studies-most are preclinical- which implicate animal models or in vitro studies-Despite yielding understanding ,they do not possess the capacity of reproducibility of the complicated crosstalk along with environment factors affecting GM in addition to propagation of liver diseases . Thereby -translation of such observations in clinical scenario is problematic in view of human studies have revealed separate outcomes which are more complicated .

b) The gut microbiome is considerably complicated with extensive microbial spp characterization is still to be performed. Such complicated nature ensures botherations implicated in estimation of etiological association amongst microbial alterations as well as disease status .Still there is no insight on the working of plethora of microbial spp amongst the microbiome in addition to their association with host metabolism along with immunity.

c) Existence of significant variations have been observed in GM constitution amongst separate populations in view of dietary, genetics, lifestyle along with antibiotics utilization. Such variations might be influencing replication in addition to application of observations over separate demographic as well as geographical placement grps.

d) Present technologies for evaluation of gut microbiome for instance 16S rRNA sequencing as well as metagenomic sequencing possess restrictions in resolution in addition to precision, therefore might not pick up the entire spectrum of microbial variations or the working capacity of the microbiome. Furthermore , such methodologies are prone for contamination as well as involve remarkable technical hurdles which might influence quality of asssessment in addition to interpreting outcomes obtained.

e) Although manipulation of GM apparently is attractive, therapeutic innovative approach, However, generating efficacious GM dependent therapies is problematic. Problems are inclusive of guaranteeing stability in addition to probiotics survival, ii)unanticipated prebiotics actions on the present gut microflora along with iii) probability of inimical sequelae from spectrum of antibiotics

f) The controlling with regards to microbiota targeted therapies is not completely generated that might interfere with fashioning of clinical trials, approval in addition to marketing accessibility. Furthermore safety issues have to be taken into account, specifically with regards to changes in long term influence on the gut microbiome on immune working as well as proneness to diseases.

g) The crosstalk amongst GM manipulated treatments in addition to existent treatments for NASH along with HCC continue to be uncharted, specifically in lesser resource setting . Such crosstalks might influence effectiveness as well as safety profiles of therapies.

h)The expenditure incurred in generating gut microbiota targeted treatments in addition to methodological needs might restrict their accessibility specifically in lesser resource settings which have considerable NASH along with HCC prevalence.

Conclusions

Thereby GM which is not healthy along with its metabolites result in development of inappropriate immune signaling in the liver , which result in start as well as propagation of variable liver diseases for instance MAFLD ,MASH, in addition to specifically propagation to HCC Probiotics, prebiotics, synbiotics, might be examples of safe, cheap treatment approaches of use against such diseases. Nevertheless, good fashioned in addition to preclinical human studies validate that manipulation of GM evokes immunomodulatory actions in the tumor microenvironment(TME) as well as antitumor reactions. Getting insight in the crucial part possessed by GM might aid in inventing innovative approaches both from diagnostic in addition to avoidance of MASH in addition to its propagation to HCC . Thereby innovative research is needed to target MASH stimulated HCC. Sequencing of genes along with machine learning dependent evaluation of outcomes would aid in isolation of crucial biomarker for the estimation of liver diseases specifically in MASH correlated HCC. In such events greater quantities of laboratory dependent mechanistic modes asssessment as well as clinical trials in considerable details are the requirements for determination of constitution of GM ,which would aid in selecting correct bacterial strains of utility for therapy of cancer. Thereby greater corroboration is required with regards to translation of such present information associated with working role of gut microbiome into diagnostic, prognostic as well as therapeutic approaches in cases afflicted by HCC. Nevertheless, it is validated that GM manipulation has given us a direction for attractive therapeutic approaches for therapy in addition to avoidance of MASH along

with MASH correlated HCC recently Papadopoulos et al. [111], detailed how T cell-mediated adaptive immunity is implicated in the transition from MASH to HCC. Earlier work concentrated on innate immune system alterations nevertheless they displayed significance of adaptive immunity with MASH serving as niche for cancer development,thus greater work is needed to un ravel such association and how GMinfluences it .

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