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AN UPDATE OF USE OF THERAPEUTIC TARGETING OF MACROPHAGES POLARIZATION STATUS IN THE TREATMENT OF OBESITY INDUCED INSULIN RESISTANCE, CHRONIC INFLAMMATION AND TYPE2 DIABETES MELLITUS-A NARRATIVE REVIEW

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ABSTRACT

Aim: There is escalating incidence of obesity in developing along with developed countries, believed tobe a main risk for different metabolic diseases inclusive of type2 Diabetes mellitus (T2D) Non alcoholic fatty liver disease(NAFLD), atherosclerosis besides ischemic cardiovascular disease(CVD). Earlier while in an endeavour to find different medical treatments for obesity, metabolic syndrome(MetS), NAFLD we have tried to concentrate on aetiopathogenesis of obesity, with role of different cytokines, chemokines, natural killer(NK) Cells in obesity, role of macrophages polarization in hepatic and AT, skeletal muscle macrophages. **Methods:** Thus a narrative review was carried out using the pubmed search engine along with Google Scholar, Web of Science, Scopus, MEDLINE, Cochrane library of sciences with the MeSH Terms; chronic low grade inflammation; impaired lipid metabolism; oxidative stress; chronicinflammation; insulin resistance(IR); insulin sensitivity; insulin receptor substrate-1; JNK; IKK/ NFκB ; JAK/STATs; therapeutic interventions from 1980's till November 2022. **Results:** We found a total of 1045 articles including each group out of which we selected 209 articles for this update review regarding association of macrophages polarization status with chronic inflammation and insulin resistance and targets for generation of innovative therapies for treating insulin resistance and T2D. **Conclusions:** Obesity- stimulated chronic low-grade inflammation might result in insulin resistance(IR), It is well acknowledged that macrophages possess a key part in the development of inflammation. Here we detail the molecular modes regarding association of M1 M2paradigm in case of macrophages polarization, low grade tissue inflammation, insulin resistance as well T2D. Furthermore, the part of macrophages in Obesity- stimulated IR is summarized as well as therapeutic drugs**,** recent advancements regarding targeting macrophages for the therapy of T2D is updated. Moreover role of SGLT2 Inhibitors therapeutics has shown to be beneficial regarding macrophages polarization and browning of adipocytes, besides polarized macrophagesalterations in metabolism might aid in generation of markers for these in obesity and T2D.

KEYWORD: Obesity; type2 Diabetes mellitus; macrophages polarization; insulin resistance; chronic Inflammation; molecular modes.

1. INTRODUCTION

There is escalating incidence of obesity in developing along with developed countries.[1] It has been calculated that 57. 8% of the worldwide adult population would be overweight or obese by 2030.[2] Besides implicating adults, there has been sudden surge in obesity in children in the last decades.[3] Obesity significantly influences the physiological functions of the human body. Furthermore, it escalates the risk of numerousmetabolc diseases inclusive of Type2 Diabetes mellitus(T2 DM)in children[4], Non alcoholic fatty liver (NAFL)[5], cardiovascular disease (CVD),[4] atherosclerosis[6], musculoskeletal diseases[7], along with cancer.[8] Besides impacting the quality of life (QOL)of such patients it escalates expenditure.

Of these obesity is intricately correlated with the generation of insulin resistance (IR). Insulin targets different organs like adipose tissue(AT) liver as well as skeletal muscles in obesity at morphological, functional along with molecularlevels.[9] In the form of an etiological factor for T2D[10], IR comprises of a pathological situation in which cells have an incapacity of reaction to insulin stimulation.[18] Obesity results in different alterations in AT inclusive of metabolIc along with endocrine functions like liberation of fatty acids (FA), hormones along with proinflammatory molecules.[12] Lipid accrual in case of skeletal muscles is correlated with IR as well as considerably influences glucose disposal in the skeletal muscles.[13] Regarding liver, IR stimulated by obesity has the properties of dysfunctional capacity of hampering glucose output, which ultimately causes gluconeogenesis.[14] Secondary to escalated glucose quantities, βcells facilitate insulin generation, which results in hyperinsulinemia.[15] Hence IR is in general correlated with hyperglycemia along with hyperinsulinemia.[16], till βcells lose their capacity of sustenance of compensatory escalation of insulin, ultimately causing T2D.[17]

Numerous molecular modes have beenposited amongst obesity, IR, T2D, inclusive of endoplasmic reticulum (ER) stress, Oxidative stress(OS), lipid homeostasis decontrolled treatment, mitochondrial impairment as well as hypoxia[18], however, no clarity regarding the molecular insight exists. Hereour concentration is on the chronic inflammation stimulated by obesity in the form of probable etiological factor for IR.[19] In case of obesity alterations in the polarization status of macrophages in case of AT, liver as well as skeletal muscles were observed[20] along with crosstalk amongst macrophages as well as insulin target organs might impact metabolism along with inflammation.[21]

Earlier we detailed on the part of macrophages polarization status in liver, obesity, dm, different etiopathogentic modes in obesity inclusive of ER stress.[22-41] Here our concentration has been on molecularmodes amongst macrophages, chronic inflammation, IR along with T2D. We detail polarizationstatus, distribution besides accrual of macrophagesin case of insulin target organs, inclusive of AT, liver as well as skeletal muscles along with comprehend the association amongst macrophages as well as IR in addition to therapeutic drugs along with recent advancements regarding targeting macrophages for treatment of T2D.

2. Macrophages Classification

Macrophages represent **a** kind of antigen presenting cell(APC) possessing the capacity of liberation of trophic factors, immune modulators, besides effectors of phagocytosis of pathogens or cell debris along withprocess in addition to present antigen to the cell surface.[42] Variability along with plasticity are emblem of macrophages.[43] 2 kinds of macrophages that have been acknowledged are the canonically activated M1 macrophages, besidesalternately activated M2 macrophages[44], which portray 2 ends of dynamically altering stages of macrophages activation.[45] Induction of activated M1 macrophages is feasible by interferon gamma(IFNγ), Tumor necrosis factor alpha(TNFα) Granulocyte Colony –Stimulating Factor(G-CSF), along with lipopolysaccharides (LPS)[46], whereas, activated M2 macrophages get stimulated by interleukin-4(IL-4) or IL-13.[45] M1 macrophages are implicated in facilitating Th1 reaction having robust microbicidal along with tumoricidal action basically by liberation of proinflammatory cytokines which hamper the proliferation along with injure the adjacent tissue**,** inclusive of TNFα, IL-6, IL-12 besides IL-23, nitric oxide (NO), reactive oxygen species(ROS) along with inducible nitric oxideSynthase (iNOS).[47] M2 macrophages liberate arginase, IL-10, ornithine along with polyamines as well as facilitate Th2 reaction, proliferation, tissue healing, immune tolerance along with tumor propagation.[48] Regarding M2 macrophages 4 kinds of subcategories dependent on the stimuli as well as transcriptional alteration stimulated; oralternatively activated M2 macrophages, activated by IL-4 or IL-13(M2a), type2 macrophages stimulated by immune complexes along with LPS (M2b), deactivated macrophages activated by glucocorticoids, or IL-10(M2c), as well as M2 like macrophages activated by adenines or IL-6(M2d).[49] Oxidative metabolism is utilized by M2 macrophages regarding their functions, while M1 macrophages utilize energy via glycolysis which facilitates generation of proinflammatory cytokine IL-1β or NO.[50]

Furthermore, it has been posited that M1/ M2macrophages Classification is considerably simplistic as macrophages phenotype gets decided by numerous factor**s** which stimulate, hence one can't generalize these restricted subkinds.[43] Newer kinds of macrophages areregularly getting invented. Jaitin et al.[51], observed that a newer kinds of macrophage Trem2+ lipid-associated macrophages (LAM)subkind subsequent to a high fat diet(HFD), that comprises the maximum robust kinds of expanded immune cell subkind of AT macrophages at the time of obesity. Trem2+ LAMs promote the processing in addition to breakdown of lipids by considerable expression of FA transporters Cd36, fatty acids binding proteins 4 along with5(Fabp4, Fabp5), lipoprotein lipase(Lp1) as well as lysosomal acid lipase(Lipa). Moreover, Jaitin et al.[51], further observed that Trem2+ expression is a significant factor in the avoidance of AT impairment, along with metabol**ic** conditions in obesity, besides the elimination of Trem2+ exaggerated white adipose tissue(WAT) hypertrophy in reaction to HFD feeding.[51] Furthermore, Trem2+ macrophages are observed in case of plaque in mice in the early as well as advancements of atherosclerotic lesions.[52] As per a study escalated quantities of Trem2+, Cd9, Spp1 along with cathepsin(Ctsb, Ctsd besidesCtsz) that are correlated with lipid metabol**ic** events

calcification, whereascause downregulation of proinflammatory genes, with further observation of negative associationof Trem2+ macrophages with plaque stabilization.[53]

Rather than fixed M1/ M2macrophages polarization status, Jaitin et al.[51], reflects it as a dynamic event which might be reverted in case of physiological along with pathological situations.[54] Different signaling molecule as well as transcription factorsare implicated in the controlling of macrophages polarizationstatus inclusive of, Peroxisome Proliferator Activated Receptor (PPAR), Kruppel-like factor(KLF), Interferon regulatory factors(IRF's), Signal Transducers and Activators of Transcription(STATs), nuclear factor κB(NFκB) along with Hypoxia inducible factor 1(HIF 1)families. IRF's/ STATs signaling reflects a main pathway regarding modulation of macrophages polarization. IFNγ along with LPS stimulation of IRF's/ STATs signaling causes activation of M1 phenotype through IL-4 or IL-13, whereas, M2 phenotype activation takes place through STATs.[55] Furthermore, it gets impacted by local microenvironment situations like hypoxia[56], besides diseases like obesity, described herein.

Moreover macrophages classification is feasible dependent on their placement along with functionality. Macrophages that are tissue resident are separate from monocyte originating from bone marrow along with circulating in blood.[57] Various tissues possess specific functions of tissue resident macrophages, inclusive of Kupffer cells(KC) in liver, Adipose tissue macrophages(ATM), alveolar macrophages in lung, red pulp as well as marginal zone macrophages in spleen, besides microglia in the brain. Kupffer cells along with ATM's reflect 2 of the main metabo**ic** tissue macrophages.[58] In the case of murine ATM's their propertie**s** have beenwell studied labelling them as F4/80^{+}, CD11b^{+}, CD206^{+}, CD301^{+} cells, whereas in the case of murine ATM's labelling is CD14^{+} /CD16^{-} as well as have expression of markers like CD68, CD163, CD204 along with CD206. It has been well corroborated that human ATM's marginally have expression markers regarding M1/ M2macrophages classification like iNOS along with arginase 1.[59] Moreover, the KC in case of mice canonically have properties of F4/80^{hi}, CD11b^{int}, CD68^{+} cells. In addition to that T cell immunoglobulin mucin domain containing 4(Tim4) along with Ctype lectin domain4 family4 members F(ClecF) have been detailed in the form of surface markers particular to KC.[60] Conversely, murine monocytes which infiltrate the liver possess the propertie**s** of CD11b^{+}, Cx3cr1^{+}, Lys6c^{+}, CCR2. On elimination of KC or damaged/ inflamed tissues monocytes aid significantly in generating liver macrophages pool.[60] In the case of human KCs there is absence of particular markers along with usually recognized by them expressing CD68 along with CD14. In a recently conducted study, numerous studies have illustrated that human KC's further express Macrophage receptor with Collagenous Structures(MARCO), CD163, as well as was Tim4.[61] Lesser insight regarding markers of monocytes in the human liver exist though are inclusive of CCR2, Cx3cr1, SA100A2, as well as CD14.[61]

3. Macrophages along with Obesity Insulin resistance

Macrophages in case of obesity targets organs like adipose tissue(AT) liver as well as skeletal muscles, that are Insulin targets, possess a central part regarding inflammation along with IR.[62] At the time of obese stage infiltration of macrophages takes place in the targets organs get activated to the M1polarization status along with generate numerous proinflammatory cytokines that has a, negative impact on the transmission of insulin signals along with escalate the generation of chronic inflammation along with IR.[63] lymphocyte antigen 6 complex locus C1(Ly -6C).

Adipose tissue(AT) along with ATM's

Adipose tissue(AT) reflects a storage house of FAs at the time of fasting. On the glucose quantities returning to normal subsequent to feeding liberation of free fatty acids (FFA), takes place in the circulation from the AT in the form of an energy resource.[64] They further are the major regions of inflammation in the obese stage, along with further accrual of ATM's is the crucial factor regarding modulating inflammation.[65] In contrast to the subcutaneous AT, visceral adipose tissue(VAT)possesses key part in IR besides the quantities of ATM's in VAT is further greater in contrast to subcutaneous AT.[66] In the case of thinmice ATM pool takes origin from yolk sac progenitors along with renew by themselves with the use of proliferation.[67] Ultimately, replacement of these ATM pool takes place from BM- obtained macrophages probably from monocytes.[68] Regarding thin mice 3 main kinds of ATM's have been detailed. In the case of primitive/early AT, LYYE1^{+} ATM'sare the main populations, that are **i**ntricately correlated with vasculature.[69] Greater examination revealed that 1 or2 CD63^{+} monocyte obtained ATM's subpopulations dependent on differential expression of MHCII, CD11c, along with chemokine X3 –C motif receptor 1(CX3CR1).[51, 70] Clarification does not exist regarding the separationof the2 monocyte obtainedATM's with CD11c expression might be explained by any of these.

In the thin/leanstatus ATM's are usually present in the form of M2macrophages polarization status.[71] Avoidance of the capacity of macrophages from shifting towards M2 status causes exaggerated weight accrual along with impaired glucose tolerance in mice.[72] M2macrophages result in sustenance of insulin sensitivity as well as glucose homeostasis by liberation of IL-10, IL-1 along with catecholamines for controlling lipid metabolism, blockade of inflammation reaction besides escalate insulin sensitivity.[73, 74] Despite, contradictory validation pointed that M2macrophages do not aid towards adipocyte metabolism, or adaptive thermogenesis effect through the generation of catecholamines.[75] Furthermore, validation pointed that

AT possess the capacity of picking up along with breakdown of catecholamines liberated by neurons besides **e**nhancement of this system is feasible by obesity along with ageing, causing a reduction in reaction towards cold stress in addition to starvation.[76]

Of the logos of obesity correlated chronic low grade Inflammation is the accrual of ATM's.[12] Macrophages are implicated in about 10% WAT in case of lean mice along with human in contrast to about 40% in case of obese humans, besides greater than 50% in case of morbidly obese leptin deficient mice.[12,77] Avoidance of accrual of ATM's at the time of obesity can hamper the generation of inflammation besides IR.[78] Earlier in numerous studies, belief was regarding these macrophages getting obtained from peripheral blood mononuclear cells**.** Nevertheless recent studies have illustrated significant escalation of ATM's at the early obesity stages, secondaryto in situ macrophages proliferation in addition to monocytes that are migrating which facilitates accrual of ATM's at the later obesity stages.[79] In case of obese mice, basically macrophages are in M1status possessing the capacity of generation of greater quantities proinflammatory cytokines for impacting the chronic inflammation status. No clarity is present regarding the mode of alterations of macrophages polarization status in obesity, however numerous factors might be present. Lumeng etal.[80], observed that M1 macrophages existent in inflammatory collection of AT originating from circulating monocytes rather than direct transformation of M2 towards M1 polarization status.[80] AT expansion might result in adipocytes hypertrophy along with hyperplasia followed by liberation of signaling molecules like MCP1 along with inflammatory cytokines as well as chemokines that further favour the stimulation of greater quantities of BM- obtained monocytes invading AT followed by differentiation into macrophages.[12,81] Additionally, chronic inflammation stimulated by obesity besides resulting in macrophages accrual causes further avoidance of macrophages elimination.[82]

Furthermore, variations are present regarding the organization of macrophages in AT amongst lean along with obese stages; right through AT equal placement in lean stages whereas in obese stages crown like structures(CLS) macrophages exist in the form of group of cells surrounding adipocytes that are undergoing demise in a ring like structure labelling them as CLS, regarding phagocytosis of the cells along with persistently liberate proinflammatory cytokines.[83] Adipocytes undergoing demise revealed signals of getting engulfed, induction of phagocytic cells migrating towards area of cells demise.[85] Escalation of quantities of CLS, with takes place subsequent to high fat diet(HFD)feeding along with expression of proinflammatory cytokines.[81] Moreover. Hill etal.[70], observed that obese AT possesses unique ATM's populations**,** Ly6C^{+} having ATM's placement exterior to CLS along with are adipogenic. Induction of genes implicated in lipid along with cholesterol biogeneration lymphocyte antigen 6 complex locus C1(Ly -6C) ATM's cause restoration of normal adipose physiology subsequent to adoptive transferring. The lipid -laden CD 9^{+} ATM's with placement amongst the CLS are implicated in the inflammatory signatures of the obese AT,. In case of lean mice adoptive transferring of CD 9^{+} ATM's leads to obesity correlated inflammation.[70] Conversely to CD 9^{-}ATM's, CD 9^{+} ATM's exhibit greater expression quantities of CD16 as well as CD206 along with are possessing the abundance of transcription factor AP1 along with NFκB as well as correlated genes like *Ccl2*, *Il1a*, *Il18* along with *Tnf*.[70] The Trem+LAM get further recalled in the form of major expanded immune cell subset in AT at the time of obesity.[51]

3. 2 Macrophages in Liver along with Kupffer cells (KC's)

Liver represents the biggest gland of human beings with a weight of 1. 5 kg in an adult[84[. Most importantly it regulates metabolism besides modulating various functions that are glycogen storage, synthesis of plasma proteins as well as drug detoxification.[85, 86] In reaction towards postprandial(PP) hyperglycemia**,** liver causes transformation of escalated glucose to glycogen besides in fasting status, maintainance of blood glucose quantities is done via glucose generation.[93] Maximum macrophages possession is by liver as per percentage amongst all of the organs, 20-35%in hepatic non-parenchymal macrophages along with 80-90% of tissue macrophages in host.[87]

Liver is in possessionof 2 main kinds of macrophages, namely Kupffer cells (KC's) as well as monocyte obtained macrophages(Mo MFs]. At the time of obesity KC's are activated towards M1 status, resulting in attraction of inflammatory monocyte in the liver along with facilitation of their differentiation into monocyte obtained macrophages(Mo MFs][88,89], that causes greater percentage of macrophagesin the liver.[90] Mo MFs along with inflammatory activated KC's aid in the obesity stimulated hepatic inflammation along with IR.[91] Mo MFs are considerably lesser in size than KC's in mice[92] besides Mo MFs are 6 times greater regarding HFD feeding in contrast to lean mice, whereas, quantities of KC's is akin amongst the 2 groups.[93] In parallel, KC's along with Mo MFs are necessary, for sustaining homeostasis of liver as well as full body.[94]

Chronic inflammation has been acknowledged to stimulate IR in the liver.[95] KC's possess a main part regarding IR stimulated by HFD feeding via generation of inflammatory modulators inclusive of TNF-α, IL-6, IL-1β, prostaglandins along with ROS which possess a main part in the production of IR.[96,97] Selective elimination of KC's takes place following Intravenous infusion of clodronate without impacting ATM, that is observed to significantly escalate insulin signaling along with hepatic insulin sensitivity regarding HFD. Furthermore, reduction of AT weight without impacting

whole body weight, liver weight or steatosis takes place.[96] Subsequent to treatment with Gdcl3, a hampering agent in particular of KC's, phagocytosis besides other functions of KC's were hampered in addition to **e**nhance glucose tolerance in mice.[97] Additionally, lipid accrual in the liver in view of **e**nhanced FA absorption, escalated generation in liver or reduction of fatty acid oxidation can get utilized for anticipation of T2D[98], besides lipid metabolism stimulated by macrophage- obtained cytokines result in lipotoxicity, which in turn results in liver inflammation along with IR.[99]

3. 3 Muscle along with Macrophages

Muscle mass is a significant pointer of glucose tolerance, since lesser muscle mass is correlated with escalated IR.[100] Escalated quantities of blood glucose subsequent to meals is a stimulator of insulin liberation, that stimulates the skeletal muscle regarding absorption of glucose with about 60% of consumed glucose gets picked up by skeletal muscle.[101] The presentation of IR in **s**keletal muscle is by a reduction in insulin stimulated glucose uptake by skeletal muscle correlated with impairment of insulin signaling**,** glucose transport, oxidative phosphorylation, glycogen generation.[22]

The etiology of IR in skeletal muscle is impairment of insulin signaling along with numerous postreceptor intracellular aberrations, inclusive of dysfunctional glucose transport, glucose phosphorylation, reduction of glycogen oxidation as well as glycogen generation. Macrophages enrolment in the skeletal muscle is further implicated in facilitating IR.[79, 102] In case of skeletal muscle certain phenotypic variations are visualized which possess the capacity of, switching amongst M1 along with M2phenotype in reaction to circulating FFAs, that result in proinflammatory cytokines liberation.[103] Macrophages quantities in skeletal muscles possess a negative along with dynamic association with insulin sensitivity.[103] The quantities of $CD68^+$ in the skeletal muscle of non diabetic obese individuals is escalated in contrast to lean individuals.[103] It has been observed in numerous studies that HFD **e**nhanced the $CD11b^+$, $F4/80^+$, macrophages quantities in muscle in contrast to lean mice.[19, 119] At the time of obesity, muscle macrophages change the inflammatory status of muscle cells by liberating cytokines as well as chemokines.[103] The chronic inflammatory situations result in dysfunctional lipogenesis along with lipolysis in AT which results in **e**nhanced circulating FFA leading to ectopic fat accrual in skeletal muscles.[101,104], along with inflammatory cytokinesliberated by macrophages stimulating lipolysis which results in escalated quantities of lipid metabolism that are associated with skeletal muscles IR[106][rev in 107](fig 1).

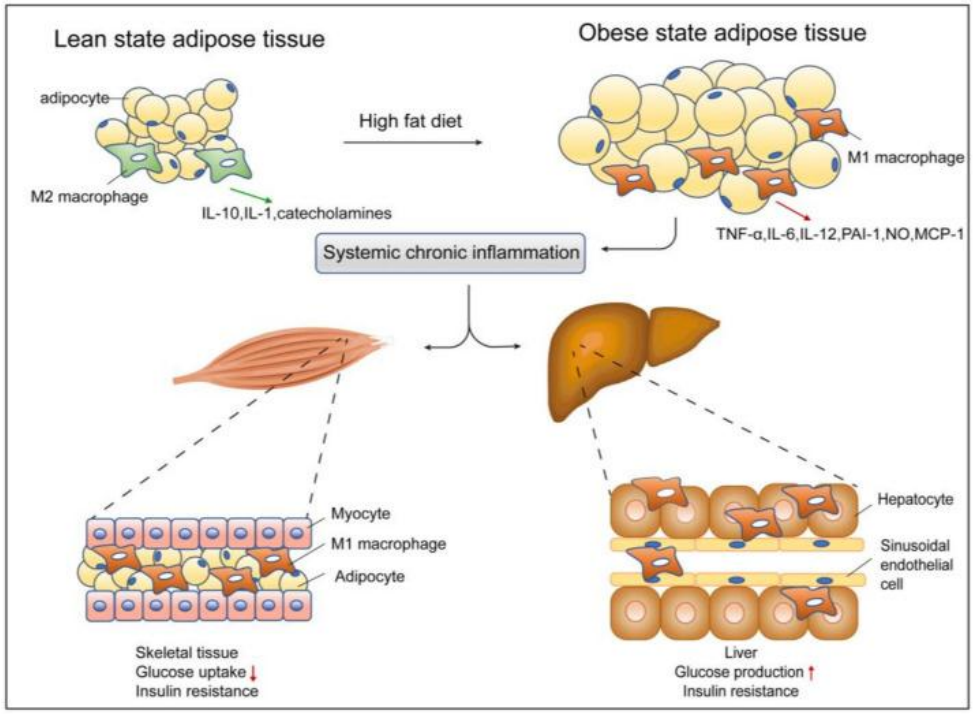

Figure 1: Courtesy ref no-107-Obesity induces macrophage infiltration and insulin resistance in adipose tissue, liver, and skeletal muscle. In the lean state, tissue-resident M2 macrophages in adipose tissue secrete anti-inflammatory factors such as IL-1 and IL-10 to maintain an insulin-sensitive environment. During obesity, increased levels of nutrients result in adipocyte hypertrophy and apoptosis. Proinflammatory mediators result in M2 macrophage polarization into the M1 state, which triggers adipose tissue chronic inflammation. Other metabolic tissues, including skeletal muscle and liver, are also influenced by increased cytokine production and macrophage recruitment, resulting in lower glucose uptake in skeletal muscle and higher glucose production in the liver, fueling the insulin resistance state further.

3. 4 Pancreas along with Macrophages

In case of normal physiological situations macrophages are fundamentally existent in pancreatic βcells islets which might possess a significant part in formation of pancreas along with its homeostasis. At the time of mouse embryonic generation macrophages are existent. In case of op/op mice with absenceof macrophages in the pancreas, the observation was that these mice possessed lesser βcells mass in contrast to normal mice along with subsequent to embryonic generation as well as following birth, pointing that macrophages in the pancreas are necessary for sustaining βcells mass.[108] No clarity is present regarding the mode of macrophages aiding in the generation, although it might be correlated with cytokines formation by the macrophages in view of lesser quantities of IL-1β possess the capacity of stimulating βcells proliferation.[109] Islet resident macrophages further possess protective actions along with sustenance of islet homeostasis. Expression of arginase, IL-10, along with CD206etc islet resident macrophages takes place akin to M2 macrophage. Different studies have illustrated that macrophage infiltration in case of islets is **e**nhanced in T2D, C57BL6 mice that received HFD along with db/db mice[109], as well as islet resident macrophages quantities are usually associated with the extent of βcells – impairment.[110] Escalated glucose quantities can result in chemokines liberation from the islets that facilitated monocytes along with neutrophils migration. It is feasible that the T2D microenvironmen**t** might stimulate chemokines generation along with facilitate macrophage infiltration into pancreatic islets. Islets possess 2 subpopulations of macrophages namely $CD11b^+$ $Ly6C^+$ monocytes/ macrophages as well as $CD11b^+$ $Ly6C^-$ macrophages.[111] Maximum islet resident macrophages were $CD11b^+$ $Ly6C^-$ cells that possessed M2 phenotype in case of baseline situations. in contrast to control db/db or KKTa mice proportion of these M2 kind of cells were not changed in db/db or KKTa mice. Nevertheless, the quantities of $CD11b^+$ $Ly6C^+$ macrophages were significantly escalated in case of T2D models. Inflammatory cytokines are expressed by these cells like IL-1β along with TNFα besides illustrated a M1 phenotype that might point that macrophage polarity apparently are switched towards M1 in T2D islets.

4. Modes of inflammation along with insulin resistance

Numerous inflammatory signaling pathways are responsible for hampering insulin function that can correlate inflammation with insulin resistance. c-Jun-N-terminal kinase (JNK), IKK/ nuclear factor κB(NFκB **)**, janus kinase / Signal Transducers and Activators of Transcription(JAK/STATs), along with other pathways possess main part regarding generation of chronic inflammation.[112] Several modes are implicated in the activation of inflammatory signaling like the liberation of endogenous factors like saturated fatty acid along with heat shock proteins(HSP) labelled as damage–associated molecular patternsreceptor (DAMP)that get recalled by pattern recognition receptors(PRR), along with activate inflammatory events as well as inflammatory factors without any exogenous factors like pathogens.[113] Usually DAMPs are generated by cellular stress, tissue injury as well as inflammation.[114] PRR's inclusive of toll like receptors (TLRs), RIG 1- likeRNA helicases(RLH), NOD –like receptor(NLRs) as well as AIM-2 like receptor(ALRs).[115] These PRR's further possess the capacity of recalling pathogen –associated molecular pattern receptor (PAMP) present on pathogens besides biological allergens inclusive of LPS**,** peptidoglycans along with bacterial DNA.[116]

4. 1JNK pathways

It was observed by Hotamisligil etal.[65], that mRNA along with protein quantities of TNF-α αare escalated in AT at the time of obesity as well as IR. with **e**nhancement of insulin sensitivity takes place subsequent to TNF-α neutralization.[65, 117] Subsequent studies observed that TNF-α represents an AT obtained proinflammatory cytokine, that is implicated in obesity stimulated IR. Aided by TNFR1, TNF-α possesses a significant part in activation along with enrolment of immune cells for inflammation progression. Then it was recalled that TNF-α gets obtained from adipocytes in the case of obesity. It was observed by Xu etal.[117], that TNF-α is further liberated by WAT stromal vascular fraction(SVF).[118] Furthermore, DeTayee etal.[119], documented that macrophages represent the main resources of TNF-α in obese WAT[119], transplanted mice with TNF-α deficieny with enough TNF-α or TNF-α deficient BM, observed that macrophages obtained TNF-α, aids in the generation of inflammation along with insulin resistance in case of DIO.[119] TNF-α knockout mice possess **e**nhanced insulin sensitivity in contrast to control group.[120] Furthermore, they observed that downstream signaling at the TNF-α stimulated kinase quantities. TNF-α stimulates a double kinase system inclusive of JNK kinases along with IKK complex.[120] Regarding IR, JNK1 along with IKK signals upregulation takes place at the time of IR in AT[118], skeletal muscles[122], along with liver.[123] JNK comprises of 2 subsets JNK1 along with JNK2. JNK1 possesses crucial part regarding generation of IR in AT as well as muscle.[124] TNF-α, IL-1β along with ultraviolet rays possess the capacity of activation of JNK.[125] JNK pathway is implicated in dysfunctional insulin signaling by resulting in serine phosphorylation of insulin receptor substrate-1(IRS-1), that causes reduction of tyrosine phosphorylation of IRS-1, hence decreases phosphatidyl inositol 3 - kinase(PI3K) as well as AKT signalling.[126]

Innovative research has observed that the proinflammatory molecule leukotriene B4(LTB4) further stimulates IR generation via JNK pathway.[127] LTB4 represents a neutrophils chemotactic substance that is generated by arachidonic acid metabolism.[128] It gets liberated by immune cells, like macrophages, eosinophils besides primary tissue cells like adipocyte, hepatocyte, myocytes as well as endothelial cells.[127] LTB4

possesses crucial part regarding IR generation via the G-protein coupled receptor BLT1, that has major distribution amongst immune cells along with primary metabolite cells.[127] On generation of LTB4 by primary tissue cells it results in macrophages chemotaxis along with migration into tissues, besides macrophages liberate escalated quantities of LTB4 that work on primary tissue cells in a positive feedback loop that further stimulates chronic tissue inflammation.[127] Treatment with LTB4 might stimulate JNK action along with escalate IRS-1 serine phosphorylation causing dysfunctional insulin sensitivity in case of target cells.[127] Adipocytes along with hepatocytes treatment with LTB4 in vitro stimulates IR along with knockout of BLT1 can result in **e**nhancement of AT inflammation as well as insulin sensitivity in case of obese mice.[127]

4. 2 IKK/NFκB pathways

Besides the JNK signaling pathway IR is intricately associated with NFκB activation, that gets stimulated by TNF-α.[101] NFκB represent a transcription factor belonging to the Rel family of proteins along with is implicated in the inflammation as well as immune reaction. IKBmaintains NFκB in the hampered cytoplasmic complex at a steady status along with IKK phosphorylation might phosphorylate IκBα in case of inflammation whose separation breaksdown IκBα from NFκB.[128], aiding free NFκB to translocate to the nucleus along with crosstalk with DNA response element binding that stimulates **t**ransactivation of inflammatory genes like TNF-α, IL-1β along with IL-6 further aid in IR generation.[129] IKK 2 represents a central coordinator of the inflammatory reaction for the activation **of** NFκB. Yuan etal.[130], initially illustrated the significance of NFκB signaling inmetabolic situations regarding IKK 2 homozygous elimination in mice possessed **e**nhanced glucose tolerance along with reduction in glucose along with insulin quantities in case ofHFD in contrast to controls.[130] Chuang etal.[131], observed that HFD feeding resulted in escalated NFκB activation in mice that resulted in escalated IKKε quantities in the hepatocyte as well as adipocyte along with IKKε knockout mice possess protection from theHFD induced obesity besides chronic inflammation.[131]

IL-1β takes part in IR via NFκB pathways. IL-1β is a part of IL-1 superfamily that gets generated by monocytes along with macrophages as well as is controlled by inflammasome action.[132] The quantities of IL-1β escalated at the time of hyperglycemia[133], as well as **e**nhancement of IL-1β is correlated with the generation of T2D.[134] IL-1β binding to interleukin-1-receptor type(IL-1R1) stimulates intracellular signaling cascades. IL-1R1 results in activation **o**f JAK protein kinases, followed by NFκB translocation to the nucleus from the IκB complex, hence facilitating inflammatory gene expression.[135] In case of peripheral tissue IL-1β results in dysfunctional insulin signaling as well as decreases insulin sensitivity, liberation in β cells.[136] Macrophages conditioned(MC) medium significantly resulted in reduction of protein enrichment of insulin signaling molecule was the observation of Gao etal.[132], in case of human adipocyte, besides blockade of IL-1β actions, that possesses the capacity of reverting the actions of MC) medium on insulin signalling.[132] Moreover, IL-1β elimination totally alters the hampering actions of MC medium on insulin signaling molecules like IRS-1 as well asPI3K, that pointed that IL-1β is a crucial factor in modulating macrophagen stimulated IRin adipocytes.[132]

Furthermore, monocytes besides tissue resident macrophages reveal escalated expression of PPAR-γ.[137] PPAR-γ represent a members of the nuclear factor superfamily that is implicated in the expression of cellular differentiation, lipid metabolism besides glucose metabolism genes.[138] Natural ligands of PPAR-γ are comprised of lipids as well as prostaglandins (PG), with PG possessing the capacity of repressing PPAR-γ functions.[139] in case of inflammation generationof PG's take place considerably that is positively correlated with IR.[140] Conversely Synthetic agonists of PPAR-γ decrease IR significantly along with are usually utilized in treatment of T2D.[141] PPAR-γ represses the NFκB transcription action besides hampers inflammation by crosstalk amongst p65 for induction of ubiquitination as well as breakdown. Moreover PPAR-γ causes upregulation of IRS-1 protein, that **e**nhances IR caused by obesity.[142] Macrophages having PPAR-γ knockout result in systemic glucose tolerance reduction, **e**nhanced IR, along with escalated quantities of inflammatory factors expression in liver along with skeletal muscle.[143]

4. 3 JAK/STATs pathways

IL-6 possesses a crucial part regarding control of metabolism along with immunity. Furthermore, it is escalated in case of obese patients in contrast to lean controls that is inimical for metabolic balance.[144] IL-6 functions by binding to IL-6 receptor chain GPR30 signaling chain complex in a canonical membrane bound pathway followed by initiation of the JAK2/STAT3 based transcriptional activation of target genes, inclusive of Suppressor of cytokines signaling 3(SOCS3).[145] SOCS3 represents a negative controller of IL-6 signaling as well as might result in dysfunctional insulin signal transduction at **I**RS protein level. IL-6 stimulated SOCS3 results in proteasome breakdown of IRS-1).[146] Contradictory outcomes have been illustratedin studies regarding IL-6 functions on insulin sensitivity. Significant reduction of IL-6 quantities in case of AT along with serum result subsequent to low calorie diet as well as with weight reduction besides **e**nhance**ment of** skeletal muscle insulin sensitivity in contrast to controls).[147] IR results in subsequent to acute IL-6 infusion).[148] Nevertheless, mice deficient in IL-6 generate IR along with maturity onset obesity).[149] A different study illustrated that mice deficient deficient in IL-6at 4mth age possessed glucose intolerance along with escalated fat pad weight.[150] Greater assessment is

needed regarding positing the actionof IL-6 on insulin sensitivity.

4. 4Other Signaling Pathways

Cytokines obtained from the macrophage inclusive of TNF-α, IL-6 along with IL-1β possess the capacity of impacting lipolysis. TNF-α influences lipid metabolism by induction of lipolysis, hampering FFA uptake along with lipoprotein lipase activity).[151] The observation of Starnes etal.[152], subsequent to TNF-α delivery to patients was an escalation of FFA metabolism by 60%)[152], besides obese mice deficient in insulin TNF-α possessed lesser quantities of FFA.[119] IL-6 escalated lipolysis as well as fatty acids oxidation in case of mice along with humans.[153] At the time of acute IL-6 infusion, Wolsk etal.[154], observed that the unidirectional liberation of muscle fatty acids resulted in escalated systemic fatty acids, pointing towards IL-6 might be a direct controller of fat metabolism in skeletal muscles.[154] Furthermore, IL-1β stimulated lipolysis indirectly by decreasing the generation along with activity of proteins which hamper lipolysis along with escalated the liberation of FFA as well as glycerine.[155] Escalated quantities of lipid metabolites inclusive of FFA, ceramides diacylglycerol(DAG) might result in impairment along with IR.[156] Escalated quantities of FFA are, believedto be markers regarding IR along with T2D.[157] Escalated FFA hamper pyruvate dehydrogenase**, e**nhance serine phosphorylationof IRS-1, result in dysfunctional insulin stimulated glucose uptake, in addition to reduction in glucose oxidation.[158] Numerous studies have observed an association amongst DAG accrual along with dysfunctional insulin function.[159] Protein kinase C(PKC) subsets like PKCϴ as well as PKCδ are activated by DAG.[160] PKC avoids insulin stimulated tyrosine phosphorylation of IRS-1 directly results in disturbance of the insulin signaling pathway.[159] Conferring of protection takes place in PKCϴ knockout mice agains**t** fat stimulated insulin signaling abberations along with systemic IR.[161] Ceramides work in the form of antagonist of insulin action besides ceramides are present in greater quantities in the plasma of obese or subjects with T2D.[162] Ceramide is basically implicated in the generation of IR by 2 ways:i) signal from the ceramide induces the binding of PKCς along with AKT, ensuring that AKT has incapacity of binding phosphatidylinositol 3, 4, 5-triphosphate, (PIP3), hence hampering insulin signalling.[163] Conversely activation of protein phosphatase 2 A(PP2A) takes place by ceramide along with causes its phosphorylation, hence hampering AKT.[164] Reduction of plasma quantities of ceramide take place at the time of pioglitazone treatment in addition to hampering ceramide formation or stimulating its breakdown **e**nhances insulin signaling, pointing towards a major distinctive role of ceramides in the generation of obesity along with IR.[161]

Moreover, galectin 3(gal3) represents amember of galectin family that is implicated in the generation of IR.[165] Gal3 binding takes place directly with the insulin receptor along withhampers downstream signalling.[192] The quantities of gal3 are greater in the blood in obese in contrast to lean status.[165] Adipocyte, hepatocyte as well as myocytes treatment with gal3 in vitro causes induction of IR.[165] In vivo delivery of gal3 furthercauses glucose intolerance along with IR in mice in addition to gal3 knockout mice possess greater insulin sensitivity along with glucose tolerance.[165] These outcomes pointed that gal3 might be a key molecule regarding IR.

Besides cytokines liberated from or associated with macrophages, macrophage autophagyis key regarding the controlling of systemic insulin sensitivity.[166] In case of macrophages, autophagy regulates inflammation by controlling mitochondrial turnover in addition to ROS formation.[194] Downregulation of autophagy at the time of obesity along with inflammation takes place in macrophages as well as macrophages particular autophagy knockout mice possess dysfunctional insulin sensitivity in case of liver along with ATon HFDfeeding, hampering ROS in macrophages with **a**ntioxidants can aid in insulin sensitivity reverting in adipocytes[167](see fig 2 &3).

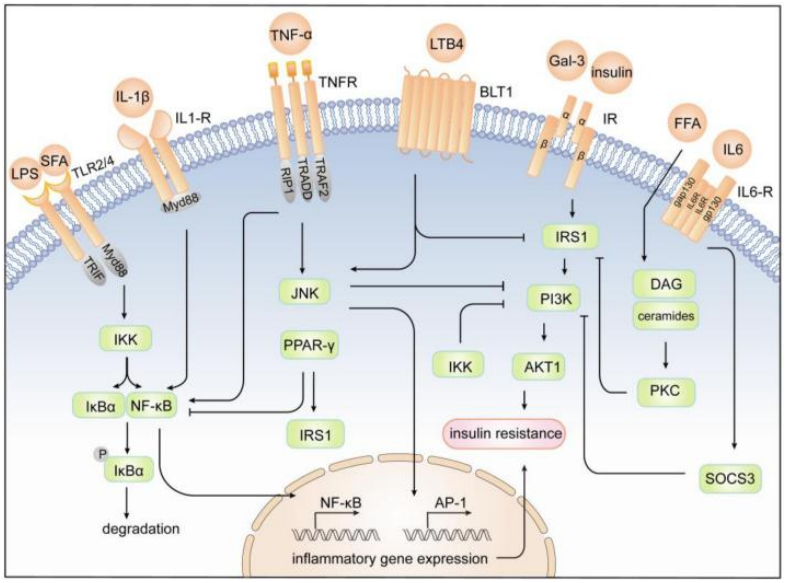

Figure 2: Courtesy ref no-107-Cytokines regulate insulin sensitivity in insulin target cells. Activation of the insulin receptor leads to tyrosine phosphorylation of IRS-1 and initiates insulin signal transduction. Activation of TLR2/4 and TNFR results in the promotion of NF-κB and JNK signaling pathways. The serine kinases IKK and JNK-1 could reduce the signaling of IRS-1 and impair downstream insulin signaling. Moreover, the activation of IKK causes phosphorylation and degradation of IκB; thus, NF-κB could translocate into the nucleus. JNK promotes the formation of the AP-1 transcription factor, which in turn transactivates inflammatory gene expression by NF-κB and AP-1, further contributing to insulin resistance. PPAR-γ suppresses the NF-κB transcription activity and upregulates IRS protein, which favors the improvement insulin sensitivity. LTB4 promotes JNK activation through BLT-1 and leads to subsequent IRS-1 serine phosphorylation, ultimately promoting cellular insulin resistance. Gal-3 directly inhibits the insulin receptor and impairs all the major steps in the insulin signaling pathway. Additionally, IL6 induces SOCS-3 and leads to proteasomal degradation of IRS-1 through binding to the IL-6 receptor. IL-1β stimulates the translocation of NF-κB to the nucleus through IL-1R1, promoting inflammatory gene expression. Also, lipid metabolites, including FFAs, ceramides, and DAG, activate the PKC to impair IRS-1, which directly interfere with insulin signaling.

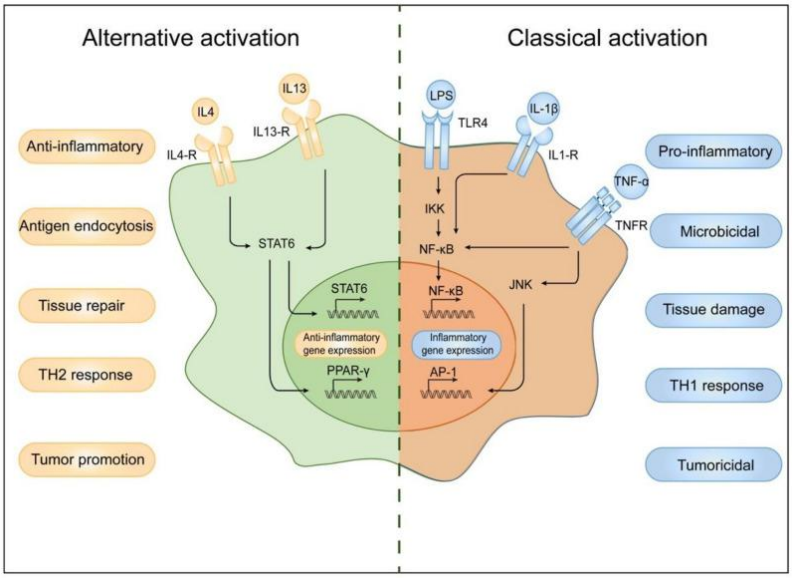

Figure 3: Courtesy ref no-107-Cytokine stimulation leads to classical activation and alternative activation of macrophages. IL4 and IL13 activate macrophages to M2 polarization state through STAT6 and stimulate anti-inflammatory gene expression. M2 macrophages participate in Th2 response, anti-inflammatory, antigen endocytosis, and tumor promotion. On the other hand, when stimulated by LPS, IL-1β, and TNF-α, macrophages activate the inflammatory signaling cascades mediated by JNK and NF-κB, which stimulate M1 polarization of macrophages and inflammatory gene expression. M1 macrophages are involved in Th1 response, proinflammatory process, tissue damage, and so on.

5. Other immune cells along with insulin

Other than macrophages, resident immune cells in adipocytes along with Intestines, inclusive of cells of innate along with adaptive immune system are further implicated in chronic inflammation secondary to obesity. In the event of obesity immune cells inclusive of i)innate lymphoid type1 cells(ILCs1), innate lymphoid type2 cells(ILCs2), ii)mast cells, iii) dendritic cells (DC's), iv)eosinophils, v)neutrophils, vi)T cells, vii)B cells, impact the polarization along with enrolment of macrophages, that possess significant part in chronic inflammation along with IR. ILCs2 possess significant part regarding sustenance of metabolic homeostasis status in part by sustenance of macrophage polarization status. ILCs2 represents a family of innate immune cells which simulate T cells.[168] They liberate Th2 correlated cytokines inclusive of IL-5 along with IL-13, that facilitate theM2 macrophages accrual as well as of eosinophils.[169] The elimination of ILCs2 result in a significant reduction in VAT M2 macrophages as well as of eosinophils along with escalate obesity, besides, IR subsequent to HFD feeding.[170] Furthermore, eosinophils have further been held responsible for regarding sustenance of metabolic homeostasis along with M2 macrophages.[171] In case of obesity due to HFD feeding there is reduction of eosinophils in AT that gets reverted back on reverting to low fat diet.[172] 3) Eosinophils might generate IL-4 along with IL-13 which facilitate differentiation of macrophages into M2 status.[198] Dysfunctional eosinophils accrual in AT causes escalated IR in obesity[170], with lack of eosinophils resulting in systemic insulin resistance.[172]

4)Mast cells reflect the first line of attack towards the pathogens entering by their fast degranulation capacity[173], of generating a broad variety of inflammatory modulators inclusive of histamines, PG's, along with proinflammatory cytokines(IFN-γ, TNF-α, IL-6, IL-1β) that stimulate T cell along with M1 macrophage activation.[174] In case of obese subjects, Liu etal.[175], observed that an escalation of mast cells takes place in case of obese AT, besides mast cells deficiency might escalate insulin sensitivity.[175] 5) In addition to that certain studies illustrated that DC's are implicated in tissue enrolment along with macrophage activation; mice possessing of deficiency of DC's had a reduction in quantities of ATM along with KC's besides enhancement of glucose intolerance.[176] 6)At the time of obesity, neutrophils possess greater quantities of elastase**,** neutrophil alkaline phosphatase, myeloperoxidaseII, IL-6, IL-1β, IL- 12, IL-8, TNF-α, along with lesser expression of IL- 10 that facilitates the activation of M1 macrophages as well as generationof chronic inflammation.[176] Neutrophils elastase results in dysfunctional insulin signaling by facilitating IRS-1 breakdown along with elastase knockout in case of HFD mice result in **e**nhancement of glucose tolerance along with insulin sensitivity.[177] 1. B) Furthermore, certain recent studies illustrated that ILC1 take part in the generation of inflammation along with IR. HFD stimulated obesity escalates the quantities of ILC1 in addition to stimulated them to liberate IFN-γ as well as TNF-α, in the visceral adipose tissue(VAT), followed by ILC1 obtained IFN-γ as well as TNF-α aggravated M1 macrophages accrual along with facilitate generation of IR.[177]

7)T cells, B cells along with macrophages are all present in the CLS's which are surrounding adipocytes undergoing demise.[178] Macrophages along with T cells accrual in the CLS's anticipates the robustness of obesity along with IR.[178] The classification of T cells is done $CD4^+$ T cells along with $CD8^+$ T cells dependent on phenotypic expression of their surface co receptors**.** Escalated enrolment along with differentiation of $CD8^+$ T cells has been observed in case of animal as well as human obese WAT.[179] T cells receptor-beta chain deficient mice illustrated **e**nhancement of obesity stimulated hyperglycemia along with IR, by repression of macrophage infiltration along with reduction of inflammatory cytokines expression.[180] In case of obesity there is escalated quantities of Th1 cells, generating greater IFN-γ quantities, facilitating M1 polarization in ATM.[181] Adoptive transferring of Th1 cells into HFD lymphocytes free mice causes escalated inflammation, dysfunctional glucose tolerance, along with macrophage infiltration.[180] Furthermore, specialized regulatory T cells (Treg) liberate, IL-10 at the time of lean status aiding in preservation of an antiinflammatory milieu along with M2 polarization.[182] Dramatic reduction of Tregs in VAT takes place at the time of obesity in case of HFD feeding mice.[218] Conversely to $CD4^+$ T cells, $CD8^+$ T cells are basically believed to be cytotoxic. $CD8^+$ T cells liberate perforins, granyzymes, along with cytokines which control the generation as well as macrophage activation.[148] Escalated infiltration of $CD8^+$ T cells in WATwas observed in obese mice that stimulates the generationof AT Inflammation as well as favours macrophage enrolment.[184] Elimination of $CD8^+$ T cells might decrease macrophage infiltration along with AT Inflammation as well as aid in improvement of IR.[184]

The dysfunctional adaptive reaction of B cells results in Inflammation in obese subjects.[185] B cells liberate greater quantities of IL-6 along with NF κB in addition to lesser IL-10 quantities in obese subjects in contrast to lean subjects that facilitates enrolment of M1 macrophages.[186] Winer etal.[187], illustrated that B cells accrual takes place in VAT early at the time of HFD feeding along with facilitate activation of T cells along with M1 macrophages via the generation of particular IgG **a**ntibodies, ultimately stimulating IR.[187] B cells knockout obese mice possess reduced systemic Inflammation along with **e**nhancement of insulin sensitivity as well as glucose tolerance in contrast to obese control mice[188](fig 4).

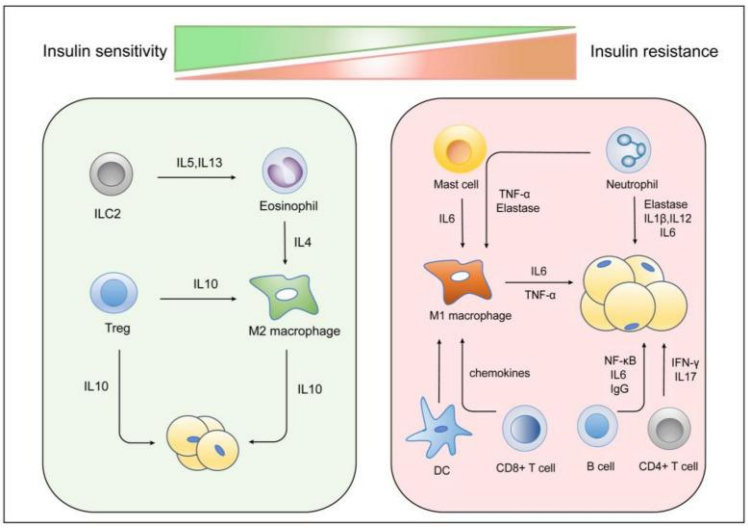

Figure 4: Courtesy ref no-107-Role of the immune system in regulating polarization of macrophage and insulin resistance. In an insulin-sensitive state, ILC2 cells produce IL-5 and IL-13 to assist in the maturation and recruitment of eosinophils. Eosinophils and Treg cells promote the activation of M2 macrophages in the adipose tissue via IL-4 and IL-13 secretion. M2 macrophages and Treg cells secrete anti-inflammatory factors such as IL-10 to maintain insulin sensitivity in lean adipose tissue. In the obese state, recruitment of monocytes and differentiation into M1 macrophages are induced significantly. Mast cells produce IL-6 to trigger T-cell and M1 macrophage activation. Neutrophils contribute to M1 polarization of macrophages and impaired insulin signaling via the production of elastase, IL-6, and IL-1β. CD4+ and CD8+ T cells stimulate M1 macrophage polarization by secreting IFN-γ, IL17, and chemokines. B cells release NF-κB, IL6, and IgG that further contribute to M1 macrophage polarization and insulin resistance.

6. Macrophage- AssociatedT2D therapeutic targets

Antidiabetic drugs i)work on adipose tissue along with skeletal muscles for escalating insulin sensitivity ii) targeting liver for hampering glucose biogenerationiii)or stimulating β cells for liberating insulin, hence reducing the rate of generation of insulin resistance. Nevertheless, they do not possessthe capacity of totally avoiding or reverting the generation of T2D, that warrants urgent formation of newer Antidiabetic drugs.[189] The studies which were conducted presently with utilization of macrophage- obtained factors or surface markers inclusive of TNF-α, IL-1β along with IL-6 mRNA as well as folate receptor(FR) in the form of therapeutic targets for T2D.[190]

TNF-α is believed to be a probable target regarding treatment of IR in case of obesity; it represents a proinflammatory cytokine that stimulates M1 macrophage polarization. Therapy utilizing shRNA for downregulation of TNF-α aid in the enhancement of IRS-1 phosphorylation as well as insulin reaction that escalates insulin sensitivity.[191] As per Burska etal.[192], illustrated that therapy with TNF-α hampering agent escalated insulin sensitivity in case of patients with rheumatoid arthritis(RA).[192] Additionally, it was illustrated that topical applicationof anti TNF-α neutralizing antibodies might switch macrophages towards M2 phenotype as well as augmentation of wound repair.[193] Wang etal.[194], documented a glucose sensitive TNF-α antibody administration system for regulating local longterm inflammation as well as improvement of osteogenesis in T2D.[194] No enhancement in glucose homeostasis was observed subsequent to Clinical trials with anti-TNF-α antibodies, Ro2081 as well as CDP571 along with insulin sensitivity.[192] Still studies are required to validate the efficacy of TNF-α in the form of a target. Additionally, on hampering IKK/NFκB pathway by Pharmacological hampering agents of IKK 2 salicylates as well as aspirin, animal models illustrated improvement of obesity stimulated IR along with decreased TNF-α generation.[148]

Escalation of IL-1β takes place at the time of obesity, that stimulated IR by hampering the insulin signaling pathway.[190, 196] IL-1β antibody treatment escalate IR, glycemic regulation in addition to β cell functions in mice with HFD stimulated obesity.[10] IL-R antagonists further enhance glycemia, β cell functions along with, decreases systemic inflammation in case of patients with T2D; hence it received approval for the treatment of RA(Clinical trial. govidentifier NCT00303394).[197] Human monoclonalantibody(mAb) canakinumab as well asXoma 052 are utilized for neutralization of IL-1β in particular as well as validate that by blockade of IL-1β**,** regeneration of β cells gets restored.[198] In case of high risk patients with T2D, canakinumab assessment was performed(Clinical trial. govidentifier NCT01327846), which illustrated that modest **e**nhancement of HbA1c, glycemia, in addition tohyperinsulinemia.[135] Greater outcomes of ongoing trial is required to get clarity of IL-1β in the form of a target.

Another proinflammatory cytokine that takes part in the generation of T2D is Interleukin-6(IL-6). Human

monoclonalantibody(mAb)Tocilizumab might hamper IL-6 signaling selectively along with treatment with Tocilizumab results in significant decreases in HOMA-IR along with IR in case of nondiabetic RA subjects.[199] Thus these studies pointed that IL-6 hampering might result in improvement of IR along with T2D. Furthermore, IL-10 represents an anti inflammatoryfactor that stimulates M2 activation of macrophages along with causes improvement of obesity stimulated insulin resistance.[119] For the treatment of autoimmune diseases, neurodegenerative diseases, etc recombinant IL-10 has been validated in Clinical trials.[200] Hence IL-10 might be an attractive target for treatment of T2D.

Macrophages might liberate miRNAs that are cargo of extra cellular vesicles (ECV) for impacting proinflammatory or anti-inflammatory actions miRNAs might aid in the generation of insulin resistance by controlling macrophages polarization. In view of miRNAs being endogenous controllers with decontrolled quantities in T2D. The therapeutic objective is to get miRNAs towards normal quantities.[226] Currently, 2 major therapeutic strategies are there:i) miRNA mimetics for normalization of the down regulated miRNA in Diabetes, miRNA mimetics depict double syntheticRNA, liposomes, adeno- associated virus productions fashion with the idea of packaging miRNA.[201] ii)secondly hampering miRNAs whose expression is significantly greater than normal, locked nucleic acids anti**i**miRNAs along with morpholinos which are efficacious hamperors of miRNA reduce plasma cholesterol with minimum toxicity in mice.[202] In view of the miRNA simulators being not stable besides hurdles in particular targeting, it is warranted that further development of miRNA therapy is done for treatment of T2D.

Furthermore, therapeutic substances possessing folate conjugates might result in selective dysfunctional FR active macrophages.[203] FR represents a marker **of** macrophage activation. Non activated resident macrophages do not express FR, other cells inclusive of granulocytes, lymphocytes or erythrocytes-rich populations illustrated bad folate conjugate binding characteristics**.** Moreover folate FITC binding toactive macrophages is FR particular, making the folate receptor an ideal target for activated macrophages implicated in IR.[204]

6. 2Role of Sodium –glucose specificcotransporter 2(SGLT2) Inhibitors

As already detailed obesity- correlated low-grade inflammationis implicated in insulin resistance besides correlated metaboliccomorbidities, like type 2 diabetes (T2D) along with nonalcoholic fatty liver disease(NAFLD). Escalated ectopicfat deposition in obesity result in situations of energy homeostasis along with low-grade chronicinflammation in metabolic tissues. Specifically obesity- stimulated enrolment along with activation ofadipose tissue macrophages possess a crucial part in the pathogenesis of insulin resistance as well as T2D. Hence treatment approaches regarding energy metabolism along with macrophage polarization in obesesubjects are required. Sodium-glucose cotransporter (SGLT) 2 inhibitors increase urinary glucose excretion by inhibiting renal glucose reabsorption, thus havingfollowing anti-hyperglycemic actions decreasing body weight. Recently Xu &Ott revealed that the SGLT2 hampering agent empagliflozin enhanced fat utilization along with browning in white adipose tissue and ameliorates obesity- inflammation and insulin resistance by activating M2 macrophages subsequent to their earlier work.[206] Hence they summarized how SGLT 2 hampering agent empagliflozin aids in enhancing energy homeostasis as well as obesitycorrelated inflammation and insulin resistance[205](see fig 5&6) for detailed mode in increasing M2 macrophage polarization.

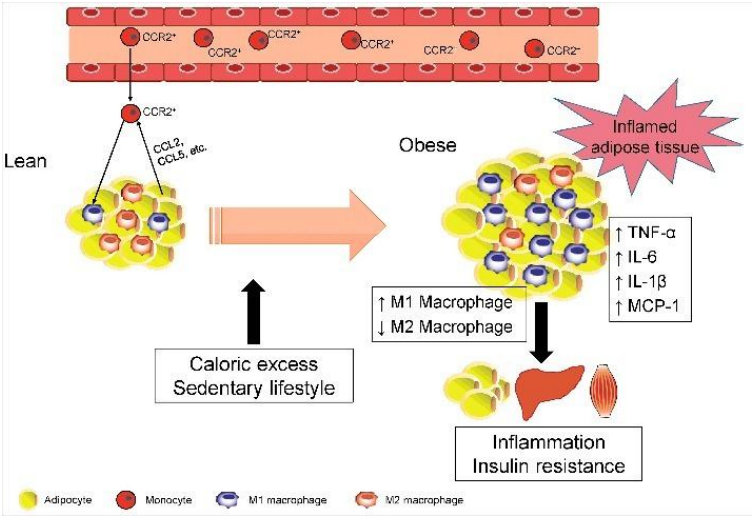

Figure 5: Courtesy ref no-205-Obesity-related macrophage polarization and insulin resistance. In a lean state, M2 macrophages are the primary resident macrophages and maintain insulin sensitivity. In contrast, excess calories or a sedentary lifestyle cause adipocyte hypertrophy, which initiates secretion of CCL2 and CCL5,

leading to the recruitment of circulating monocytes in adipose tissues. Subsequently, CCR2+ macrophages accumulate and presumably maintain inflammation as M1 macrophages in obese adipose tissue. Once these ATMs are present and active, they maintain a vicious cycle involving ATM recruitment and the production of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, in conjunction with adipocytes and other infiltrated immune cells. These secreted proinflammatory cytokines subsequently cause inflammation and insulin resistance in adipose tissue, liver, and skeletal muscle.

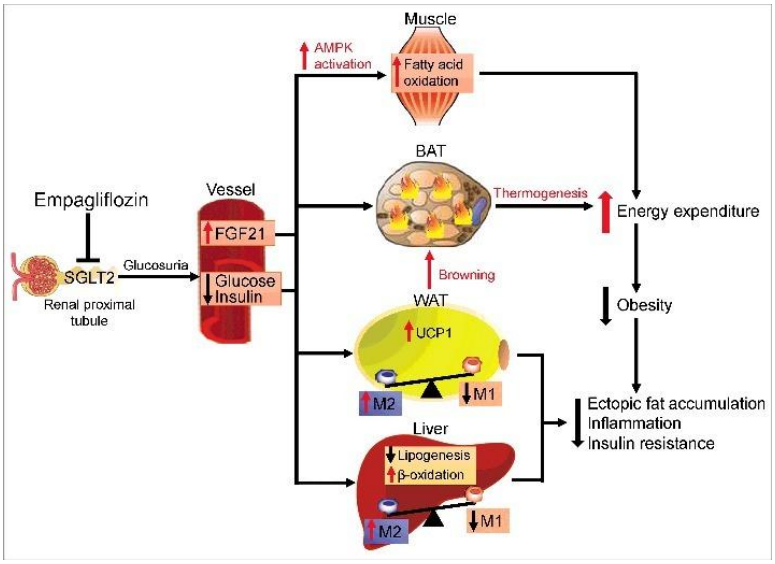

Figure 6: Courtesy ref no-205-Protective effects of empagliflozin in high-fat diet-induced obese mice. Inhibiting SGLT2 with empagliflozin directly decreases blood glucose levels, leading to the following: (1) Empagliflozin promotes fat utilization by enhancing AMPKα and ACC phosphorylation in skeletal muscle and increasing hepatic and plasma levels of FGF21. (2) Empagliflozin enhances browning and thermogenesis in WAT and BAT, which results in increased energy expenditure. (3) Empagliflozin improves insulin sensitivity by polarizing M2 macrophages in fat and liver.

6. 3Having described the kind of metabolic alterations in M1 along with M2 macrophages like M1using the tricarboxylic acid(TCA)/Krebs Cyclewhich represent a mitochondrial metabolic pathway that aids in ATP synthesis and thus provide substrates for the electron transport chain(ETC) which supports oxidative phosphorylation (OXPHOS)[rev in ref 37]. Regarding proinflammatory macrophages, this Krebs Cycle gets disrupted at 2 crucial steps i)the collection of citrate because of reduction in isocitrate lyase and ii) the collection of succinate. Citrate efflux from mitochondria gets escalated in M1 macrophages. The collection of citrate has functional importance for inflammatory polarization, being needed for the synthesis of ROS, NO, as well as prostaglandins. Citrate further acts as a substrate for conversion into acetyl CoA, thus, feeding FAS via ATP citrate lyase(ACLY)[Rev by us in ref no207. Inhibition of FAS via silencing of FAS in myeloid cells, has been demonstrated to have protection against diet induced IR that blocks recruitment of ATM as well as chronic inflammation in mice. Here lies the importance of lipid metabolism in the Polarization as well as function of macrophages, as well as manufacture along with composition of the plasma membrane [rev I 37]. Ultimately the collection of citrate results in reduction in the amounts of cisacotinate that is the precursor of itaconate, that has been a well detailed anti inflammatory intermediate. Itaconate's anti inflammatory actions get exerted via inhibition of succinate dehydrogenase(SDH), ROS synthesis, as well as liberation of proinflammatory cytokines. Whereas M2 macrophages basically utilize fatty acidsβoxidation along with Oxidative phosphorylation for generationof energy enrichment of molecules like ATP that are implicated in tissue healing in addition to downregulation of inflammation. In view of T2Ddiabetes as well as obesity possess properties of metabolic changes at the level of organism, these changes might further stimulate changes in macrophage metabolism leading to distinctive macrophage activation paradigms in diabetes and obesity. Russo etal[208], recently detailed crosstalk amongst metabolic reprogramming of macrophages and situations of metabolic impairment like diabetes along with obesity. They further concentrated on various probabilities of determination of a variety of metabolitesboth intra-and extracellularly in a concise and extensive fashion with the idea of greater advantageous isolation of the subsets of polarized macrophages that are distinctto diabetes along with obesity. Advantages and disadvantages of the currently commonest utilized metabolite assessment strategies were emphasized. Furthermore, they detailed how their use in combination might work for provision of a comprehensive overview of the metabolic alterations that take place intracellularly at the time of macrophage activation in situations like diabetes as well as obesity formation[208](see fig 7).

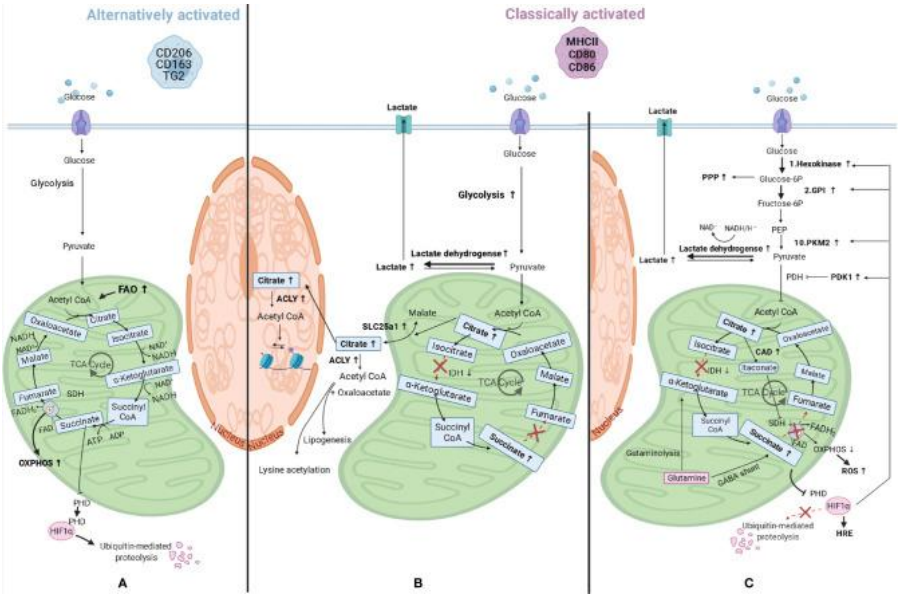

Figure 7: Courtesy ref no-207-Macrophage metabolic reprograming. (A) Alternatively activated macrophages have an induced fatty acid oxidation (FAO) and produce pyruvate from glycolysis and this is converted in acetyl-CoA, which is then used by the tricarboxylic acid (TCA) cycle to give electrons in the form of NADH and FADH2 to the mitochondrial oxidative phosphorylation (OXPHOS) complexes to produce ATP. (B) When macrophages polarize to classically activated macrophages, metabolic reprogramming takes place and lactate is produced instead of pyruvate, and the TCA cycle is broken at two points, after citrate, and after succinate, resulting in the accumulation of these three metabolites. Citrate accumulates due to lower expression of isocitrate dehydrogenase (IDH) and can either be transported to the cytosol through solute carrier family 25 member 1 (SLC25a1), where it can be converted in acetyl-CoA by ATP citrate lyase (ACLY), or to the nucleus where the same conversion can take place. Acetyl-CoA can then be used for lysine acetylation or for lipogenesis. (C) Other changes in classically activated macrophages include succinate dehydrogenase (SDH) inhibition by itaconate, which is produced by upregulated cis-aconitate decarboxylase (CAD), and this results in succinate accumulation. Succinate levels can also increase as a consequence of augmented levels of glutamine anaplerosis, either through an upregulated GABA (γ-aminobutyric acid) shunt or through glutaminolysis. SDH is also part of the mitochondrial respiratory chain and its inhibition will lead to decreased mitochondrial respiration and increased ROS (reactive oxygen species) production. Succinate inhibits prolyl hydroxylase domain (PHD) proteins, resulting in less hydroxylation of hypoxia-inducible factor 1-alpha (HIF-1α), which circumvents its degradation and allows its binding to hypoxia response elements (HRE) on target genes (48). HIF-1α also promotes the switch to glycolysis by inducing glycolytic enzymes like hexokinase 2 (1st reaction of glycolysis), pyruvate kinase M2 (PKM2, 10th reaction), and glucose-6-phosphate isomerase (GPI, 2nd reaction). The enzyme product of the latter is used in the oxidative phase of the pentose phosphate pathway (PPP), which is also upregulated in classically activated macrophages. HIF-1α also upregulates the enzymes lactate dehydrogenase and pyruvate dehydrogenase kinase 1 (PDK1) leading to higher lactate production and lower acetyl-CoA synthesis, respectively. PEP, Phosphoenolpyruvate; PDH, Pyruvate dehydrogenase.

6. 4Earlier we had reviewed the part of flavonoids along with other natural products.[36] Reduction in neuroinflammation can be attained by utiilzing natural compounds, inclusive of flavonoids, acknowledged to attenuate inflammatory reaction. Of the flavonoids, quercetin possesses numerous pharmacological applications along with multiple controlling biological activities. Tsai etal,[209], observed that quercetin effectively hampered the expression of lipocalin-2 in macrophages as well as microglial cells stimulated by lipopolysaccharides (LPS). The generation of nitric oxide (NO) along with expression quantities of the pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS) as well as cyclooxygenase (COX)-2, were further ameliorated by quercetin treatment. Their results further illustrated that quercetin significantly decreasedthe expression quantities of the M1 markers, like IL-6, TNF-α, as well as IL-1β, in the macrophages as well as microglia. The M1 polarization- correlated chemokines, C–C motif chemokine ligand (CCL)-2 and C-X-C motif chemokine ligand (CXCL)-10, were furtherdecreased with efficacy by the quercetin therapy. Additionally, quercetin considerably decreased the generation of several reactive oxygen species (ROS) in the microglia. The microglial phagocytic capacity stimulated by the LPS was further decreased with efficacy by the quercetin treatment. Significantly, the quercetin escalated the expression quantities of the M2 marker, IL-10, besides the endogenous antioxidants, heme oxygenase (HO)-1, glutamate-cysteine ligase catalytic subunit (GCLC),

glutamate-cysteine ligase modifier subunit (GCLM), as well as NAD(P)H quinone oxidoreductase-1 (NQO1). The escalation of the M2 markers and endogenous antioxidants by quercetin was activated by the AMP-activated protein kinase (AMPK) and Akt signaling pathways. Together, their study revealed that the quercetin hampered the actions of M1 polarization, inclusive of neuroinflammatory, ROS generation, and phagocytosis. Furthermore, the quercetin escalated the M2 macrophage polarization along with endogenous antioxidant expression in both macrophages as well as microglia. Their observations highlighted that quercetinmight work as a potential drug for the treatment of diseases correlated with inflammatory conditions in the central nervous system besides in T2D.[209]

6. CONCLUSIONS

There is escalating proof that macrophages possess a central part in chronic low grade inflammation along with insulin resistance(IR) in obesity. Macrophages take part in inflammatory pathways inclusive of JNK, IKK/ NFκB, JAK/STATs via liberation of proinflammatory cytokines like TNF-α, IL-1β IL-6 along with LTB4, thus stimulating chronic Inflammation of adipose tissue, skeletal muscles along with liver thus resulting in IR. Furthermore, other immune cells inclusive of ILCs2, mast cells, dendritic cells (DC's), eosinophils, neutrophils, T cells, B cellsimpact macrophages polarization status that in turn stimulate the formation of insulin resistance along with type2 Diabetes mellitus. In the last decade lot of innovative **research** has been conducted in immunometabolism with direct/indirect targeting of macrophage liberated **factor or** macrophage correlated markers might **e**nhance IR along with decrease the generation of T2D by modes inclusive of **e**nhancement of insulin sensitivity, reduction of Oxidative stress along with inflammation. The hotspots regarding present research are inclusive of targeting TNF-α, IL-1β IL-6 along with miRNAs. Moreover recent use of **SGLT2 Inhibitors** therapeutics have further illustrated that they possess beneficial actions on macrophage polarization as well as browning of adipocytes. Despite, numerous issues continue to be not resolved macrophages might be beleved to be attractive targets for T2D therapy.

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