OPEN ACCESS Freely available online

Journal of Diabetes & Metabolism

Review Article

Targeting Macrophage Polarization for Therapy of Diabesity–The Feasibility of Early Improvement of Insulin Sensitivity and Insulin Resistance: A Comprehensive Systematic Review

Kulvinder Kochar Kaur*, Gautam Allahbadia, Mandeep Singh

Kulvinder Kaur Centre for Human Reproduction, 721, GTB Nagar, Jalandhar, 144001 Punjab, India

ABSTRACT

The incidence of obesity is increasing in mammoth proportions so much so that associated comorbidity T2DM incidence is increasing markedly that we had to coin a term Diabesity to target both together. Earlier trying to review etiopathogenesis of both obesity and type 2 DM we found that whatever drugs that are formulated usually do not work with some complications and till now other than bariatric surgery we have no permanent cure for long term maintenance.Further T2DM might be a disease of 2 etiopathogenesis, namely inflammatory, as well as metabolic.Although metabolic inflammation has the properties of being systemic, their common initiating point is tissue resident macrophages, whose successful physiological or abnormal pathological adaptation to its microenvironment dictates disease course as well as severity. Earlierv we reviewed macrophage polarization in case of non alcoholic fatty liver disease (NAFLD) . Here we review it more comprehensively regarding crucial modes, of macrophage polarization, inflammatory, as well as non inflammatory which sees to the formation Of insulin resistance(IR) as well as Type 2 diabetes mellitus(T2DM) .Details of macrophage polarization, bioenergetics macrophage adaptations in different scenario is discussed in detail along with role of transcription factors like Interferon Regulatory Factor 5(IRF5), Nuclear Factor Kappa B(NFKB), Toll Like Receptor 4 (TLR4) Liver X Receptor (LXR), Activator Protein 1(AP1), Hypoxia Inducible Factor 1(HIF1), Signal Transducers and Activators of Transcription (STATS) in all these signaling besides per oxisome Proliferator Activated Receptor (PPAR) .

Keywords: Diabesity; Macrophage polarization; T2DM; IR; Transcription factors; IRF5; NFKB; STATS

INTRODUCTION

The incidence of obesity is increasing globally and with that the other comorbidities like Type2 Diabetes Mellitus (T2DM). T2DM is a disease having double etiologies namely inflammatory, as well as metabolic. In the last 2 decades, inflammation has been escalating recognized to have significant role in enhancing risk of Insulin Resistance (IR) as well as can be visualized as an etiological starting point for metabolic failure. Various studies have tried to describe the kinetics among inflammation as well as IR, where certain reports document local IR as preceding inflammation [1], while others documenting inflammation before IR [2]. But blunting of inflammatory response has constantly been documented as being protective metabolically, ameliorating the formation of IR as well as T2DM. Hence inflammation is observed to be the deciding factor in loss of tolerance to metabolic imbalance. IR in liver, Adipose Tissue (AT) as well as skeletal muscle is initially confronted with a burst of activity in pancreas which sustain normal level of glycemia the prediabetic stage [1]

Once this stage is prolonged as well as insulin synthesis can not meet insulin demands any longer frank T2D forms that predisposes subjects to a lot of sequelae as well as comorbidities. These sequelae as well as comorbidities are mainly hepatic as well as Cardiovascular System (CVS) in nature and have a direct relation to escalating inflammation, hyper glycemia as well as dyslipidaemia. Earlier we have reviewed the etiopathogenesis of both obesity as well as T2DM and grouped 2 as diabesity with the markedly escalating incidence and tries further to emphasize

***Correspondence to:** Kulvinder Kochar Kaur, Kulvinder Kaur Centre for Human Reproduction, 721, GTB Nagar, Jalandhar, 144001 Punjab, India, E-mail: kulvinder.dr@gmail.com

Received: January 25, 2021; **Accepted**: February 10, 2021; **Published**: February 17, 2021

Citation: Kaur KK, Allahbadia G, Singh M (2021) Targeting Macrophage Polarization for Therapy of Diabesity–The Feasibility of Early Improvement of Insulin Sensitivity and Insulin Resistance: A Comprehensive Systematic Review. J Diab Metab 11: 865.

on the role of macrophages and tries to find various ways of trying to treat both with different agents including natural agents like resveratrol, monoterpenes etc. Here we further deeply explore the role of macrophages in etioathophysiology of T2DM [2].

LITERATURE REVIEW

We conducted a systematic review utilizing the Pubmed search engine on macrophage polarization, along with transcription factors regulating it using the MeSH terms T2D; macrophage polarization; macrophage bioenergetics needs; metabolic adaptations; IRF5; STATS; PPAR's; AP1; LXR1'HIF1; Epigenetics from1970's till date.

RESULTS

We found a total of 1751 articles out of which we selected 190 articles for this review. No Meta analysis was done.

METABOLISM AND INFLAMMATION RELATIONSHIP

This was initiated by Hotasmiglil as well as Spiegelman discovering escalated expression of proinflammatory cytokine tumor necrosis factor alpha(TNF-α) in Adipose Tissue (AT) in case of obese rats models of obesity [3]. On neutralization of TNF-α in these obese rats resulted in marked enhancement of glucose uptake in insulin response. 10 yrs later macrophages were pointed to be the major source of TNF-α as well as other proinflammatory cytokine like IL-6 as well as nitric oxide synthase(iNOS) in obesity [2]. Further macrophages dramatically collect within AT at the time of obesity, resulting in insulin resistance(IR) .These early studies emphasized on the role of Inflammation along with metabolic failure related to IR as well as Type 2 diabetes T2D) .

Following that a lot of importance has been laid on immune system as the main controller of metabolic homeostasis. Innate immune cells i.e macrophages, reside in all metabolic tissues which coordinate glycemic homeostasis namely AT, liver as well as pancreas. Tissue –resident innate immune cells form a tissue particular immune niche, as well as every niche having its specificities to deal with microenvironmental signals. Of these innate immune cells, macrophages have been the ones that have been studied the maximum (25% of AT innate immune cells. 20-35% of non parenchymal hepatic cells in the liver [2], and almost 90% of immune cells in pancreatic islets.

POLARIZATION OF MACROPHAGES-CONTROL OF ACUTE AND CHRONIC INFLAMMATION

Initially macrophages got recognized by Metchinkoff as phagocytic cells. They constituted part of myeloid lineage with the capacity of rapid nonspecific responses for a wide variety of pathogens. Phagocytosis is a cellular method related to innate immune responses to pathogens, is key for the clearing of cellular debris, tissue repair, as well as maintenance of tissue homeostasis throughout the organism. These tissue –resident macrophages, form *via* progenitors within yolk sac, fetal liver as well as circulating monocytes which get origin *via* bone marrow [3]. During physiological circumstances, tissue-resident macrophages exert critical part in the integrity sustenance as well as homeostasis of the particular tissues.

In response to environmental cues, macrophages, rapidly respond as well as thus adapt their function, they detect alterations in their microenvironment *via* cell surface receptor getting engaged. Basic receptors that convey environmental signals are Toll Like Receptors (TLR's), that form part of the larger family of PRR. Ligating TLR's/ PRR by damage or pathogen-associated molecular patterns (DAMP/PAMP) existing in the microenvironment stimulated transcriptional programs within macrophages to bring about an adapted functional phenotype. These transcriptional modes have been well known, macrophages further adapt their cellular metabolism for meeting the bioenergic needs and get out maximum effector function [4]. This has got a lot of limelight in current research.

Currently the dichotomy utilized for telling the Polarization states of macrophages is i) like M1 is a proinflammatory or classically activated vis a vis M2 the antiinflammatory or alternatively activated.

This knowledge comes *via* type1 as well as type 2 immune responses that are canonically related to signaling molecules that get liberated on polarization. Macrophage signaling further polarizes the adaptive immune compartment for maintainance of chronic T helper (Th1/17 orTh2 response. M1 State correlates with type1 responses as well as synthesis of proinflammatory mediators correlated with bacterial or viral responses. M1 Macrophages possess robust microbicidal as well as Antigen Processing capabilities. They synthesize proinflammatory cytokines that are very powerful like Tumor Necrosis Factor Alpha (TNF-α), Interleukin (IL-6), IL-1β, as well as reactive oxygen species (ROS). M2 macrophages produce type 2 signaling, specifically in response to extracellular pathogens (helminths, parasites), synthesizing anti-inflammatory cytokines like IL-10 as well as transforming growth factor beta(TGF-β). M2 Polarization is also thought of as a pro-resolution response, that correlates with the latter parts of inflammation that is resolving. This adaptive immune system properly goes through Th2 Polarization that manufacture regulatory as well as remodeling cytokines like IL-4, IL-5 as well as IL-13. Hence the immunoregulatory response is secondary to specialized regulatory T cells (Treg) subpopulation. The pro-resolution effect can come out as scarring or tissue remodeling, which if abnormal =>tissue fibrosis, type2 effector molecules further also escalate allergic responses [5]. Despite this classification, a continuing diverse response as well as Macrophage phenotypes. Innovative functional classifications show Polarized Macrophages along a sliding scale between M1 as well as M2 based on their chemokine/cytokines liberation, transcriptional factor engagement as well as recently on the cellular metabolic phenotype

METABOLIC PHYSIOLOGY AS WELL AS PATHOLOGY: ROLE OF TISSUE MACROPHAGES

Good interaction among insulin signaling as well as insulin target tissues like pancreas, AT, liver as well as skeletal muscles are the ones responsible for sustainance of metabolic homeostasis following physiological challenges which cause

transient difference in glycaemia, lipaemia like in fasting or feeding [5]. IR suggest transient or partial loss of interaction among tissues, when insulin target tissues get resistant to insulin signaling, even following early compensation *via* pancreas. T2D represents a stage when total loss or near loss of communication occurs when insulin synthesis does not meet body's needs of controlling glycaemia. All of these tissues have its own specific niche of macrophages having essential physiologic function that sustain integrity of tissues, adapting at every stage of T2D formation [6].

MACROPHAGES FROM PANCREATIC ISLETS

Pancreatic Islets are the ones distributed through out the exocrine pancreas, represent micro-organs necessary for systemic glucose homeostasis. Maximum of these Islets are composed of β cells, that respond to glucose within seconds by liberating proper levels of insulin needed for appropriate energy supply to insulin sensitive tissues. Innate immune cells form part of pancreatic Islets also.In case of steady state, Macrophages represent the instant immune cells in both mice as well as humans. Following >20yrs of their finding, Islets Macrophages phenotype is still not known. Converse to ATM as well as liver macrophages Islets Macrophages don't stick to M1 as well as M2 polarization paradigm related to metabolic protection as well as dysfunction, respectively.Actually M1 indicators(like CD11c, MHC II) get constitutively expressed by macrophages on healthy pancreatic Islets, as well as high expression of IL-1β, TNF-α as well as other proinflammatory transcription factor interferon regulatory factor(IRF)-5 [4-7]. Further no expression of M2 pointers (CD206), as compared to stromal Macrophages of the exocrine pancreasis seen.

Role of Islets Macrophages with regard to Islets homeostasis has only started to gain significance. Imaging done in situ showed that Macrophages are very near to both β cells as well as vasculature, in mice [7]. Islets Macrophages are the ones that keep checking the β cells insulin secretion relating to glucose by finding endogenous ATP which gets released along with insulin [8]. Macrophages, in turn might directly stimulate or escalate insulin secretion *via* production of factors like retinoic acid. In contrast to any other tissues β cells express the maximum IL-1 receptor 1(IL-1R1) that markedly points to a physiological part of IL-1β in β cells function. Now it is well known that that acute but not chronic exposure to IL-1β stimulates insulin secretion in mice as well as humans [8]. Basic mechanism is not known, although might have a > insulin granule docking at the plasma membrane following escalated exocytosis. For corroborating this posit using transgenic murine models β cells targeted removal of IL-1R1 interferes with peripheral glucose tolerance through decreased glucose stimulated insulin secretion *via* 2 studies. Others show that feeding stimulates a physiological enhancement of circulating IL-1β, that further escalates insulin secretion. It was said that peritoneal Macrophages are the ones responsible for IL-1β secretion, that responded in response to glucose metabolism as well as bacterial products, liberated IL-1β, which then in turn stimulated the β cells. It is not yet been sure that probably Islets resident Macrophages might also synthesize IL-1β Post prandially, actually these Macrophages might turn out to be the major IL-1β source in Islets microenvironment. In toto these findings prove that physiological IL-1β amounts have a key role in exaggerating insulin secretion.

Greater insulin synthesis is needed in case of obesity for maintainance of amounts of glucose. Due to this both the β cells numbers as well as Islets size escalate, by local proliferation of earlier existent β cells mainly. Herein slow collection of macrophages might participate significantly in β cells adapting to early rise of weight as well as insulin resistance (IR) formation. This way β cells might allow β cells mass expansion as well as needed angiogenesis in the 1st wk of High Fat Diet (HFD) as well as initial adapting of young db/db mice. Actually in case of macrophages removed mice displayed <β cells proliferation rate, reduced insulin secretion as well as altered glucose tolerance as compared to controls. This enhancing of β cells proliferation by Islets macrophages is brought about by Platelet Derived Growth Factor Receptor (PDGFR) signaling path [8].

On obesity becoming chronic, ultimately insulin secretion does not compensate regarding enhanced insulin needs, ending in hyperglycaemia as well as T2D.The β cells failing correlates with local inflammation of the Islets as well as synthesis of inflammation effectors (IL-1β, TNF-α, CCL2). 2 Separate subsets of macrophages have been isolated within the islets; i) resident macrophages as well as proinflammatory macrophages. Islet resident macrophages (CD11b+Ly6C-or F4/80highCD11clow) are high at steady state while as well as proinflammatory macrophages (CD11b+Ly6C+ or F4 /80lowCD11chigh) collect in the course of obesity formation [9]. Whereas CD11b+Ly6C+ macrophages get recruited *via* monocytes, the F4/80 low CD11 chighmacrophage replicate in situ. Regarding this chlodronate liposome macrophage removal rescues glucose stimulated insulin secretion in models of genetic as well as palmitate stimulated obesity in mice .Intriguingly even following escalation of islets macrophages amounts diet induced obesity(DIO) does not influence macrophages phenotype [9]. Other source of inflammation factors which might take part in islets inflammation are endocrine cells themselves that has β cells as well. Actually RNA seq of Islet cells from T2D patients showed an inflammation signature correlated with β cells dysfunction relative to Islet cells from healthy controls, which was thought to be secondary to not only immune cells but to endocrine cells as well, fuelling this local inflammation [8]. These outcomes a little contradicting, point that islets macrophages are not the only ones causing inflammation of islets in obesity. Thus >studies are needed for full definition of their phenotypes and to evaluate role of immune cells might have like innate lymphoid cells(ILC) as well as their probable part in control of insulin secretion as well as β cells mass expansion [9].

DEVELOPMENT AS WELL AS MAINTAINANCE OF MACROPHAGES POLARIZATION IN T2D

Currently trying to define extracellular metabolic as well as molecular signals related to Macrophages Polarization in metabolic inflammation as well as IR, is being actively worked. The Candidate metabolic immunogens that might be candidates are lipids, hypoxia, cell death as well as stress [9].

In genetically obese mice 90% of adipose tissue macrophages(ATM's) surround dead adipocytes in fat depots, that points that dead adipocytes are the ones that contribute to Damage Associated Molecular Patterns (DAMP's) which results in crown like structures(CLS) development and/or collection of ATM's. Further hypoxic areas exist in obese AT along with expression of hypoxia related genes, that include hypoxia inducible factor 1 alpha (HIF 1- α). This transcription factor further facilitates the proinflammatory abilities of ATM's in relation to obesity. Moreover, lipolytic products as well generally lipids whose levels are escalated in obesity are very good candidates for stimulation of inflammatory response in ATM's. Nutritional Fatty acid's activate TLR-4 in Macrophages which states signaling pathways [10]. Triglyceride –rich lipids like palmitate or Very Low Density Lipoprotein (VLDL) activate Macrophages, that upregulate intracellular amounts of ceramides and further accelerate proinflammatory responses [9]. These modes activate NLRP3ASC inflassome that states caspase 1 modulated cleavage of pro IL-1β as well as pro IL-18 into their active states. Intriguingly saturated Fatty acid's like palmitate have been demonstrated to activate the NLRP3 inflassome *via* an AMPK-autophagy–mitochondrial-ROS signalling axis, resulting in liberation of IL-1β as well as IL-18 [10]. Notably this IL-1β liberation by itself correlates with insulin resistance. Actually IL-1β avoids signalling *via* Tumor necrosis factor alpha dependent as well as in dependent modes. On getting established these proinflammatory environmental factor, the formation of proinflammatory cytokines which recruit monocytes as well as other immune cells which maintain low grade chronic inflammation.

Proinflammatory cytokines represent crucial factors in disrupting insulin signalling resulting in IR [10]. They work *via* paracrine modes on insulin sensitive cells like adipocytes. Physiologically, On insulin binding to its receptor the phosphorylation of tyrosine residues of insulin receptor substrate 1(IRS1) activates intercellular signaling pathways bringing about insulin action [11]. With regards to metabolic inflammation, JNK1 as well as IKK have the ability of influencing insulin signalling by phosphorylation of inhibitory serine/threonine residues of IRS1, thus disrupting insulin signaling. On the same hand, pathways involving JNK1 as well as IKK might be activated *via* binding of fatty acids (FA's) to TLR's. Further IL-1β that also signals *via* IKK β as well as NFκB, stimulates IR by repressing IRS1 expression at both transcriptional as well as post transcriptional levels. IL-6 signalling inhibits insulin sensitivity *via* separate modes that involve JAK-STAT pathway which regulates the transcription of its own suppressor, called suppressors of cytokine signaling (SOCS3) .High amounts IL-6 stimulate>expression of SOCS3 that physically cross acts with tyrosine phosphorylated residues and this inhibits IRS1 binding to the insulin receptor.

Certain glycolytic enzymes possess noncanonical parts in macrophages. Importantly pyruvate kinase isoenzyme 2 (PKM2), that gets induced *via* LPS is present in the form of a dimer. This dimer might translocate towards nuclei and work as a cofactor for HIF1. Thus PKM2 takes part in a positive feedback loop with upregulation of proinflammatory as well as glycolytic genes secondary to HIF1 M1 activation. Further HK1 can get inhibited *via* bacterial products as well as subsequently dissociate from mitochondria, that activates the NLRP3 inflassome as well as a downstream formation of Proinflammatory cytokines. Although mode of resolving of glycolytic programming have not been worked out, a recent work by Ip etal., showed that IL-10 signaling causes antiinflammatory actions via inhibition of translocation of GLUT 1 towards the membrane. Besides being a substrate for glycolysis, glucose also fuels the pentose phosphate pathway (PPP), needed for manufacture of nucleotides as well as NADPH meant for ROS synthesis *via* NADPH oxidase. On LPS stimulation as well as M1 polarization also induction of PPP occurs.

The Tricarboxylic Acid (TCA)/Krebs Cycle 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) . 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 [11]. Citrate further acts as a substrate for conversion into acetyl CoA, thus, feeding FAS *via* ATP Citrate Lyase (ACLY). 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. 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.

An itaconate negative feedback loop has been detailed regarding LPS as well as IFNγ stimulation where itaconate shut down the inflammatory response. Conversely succinate accumulation, facilitates SDH action as well as synthesis of mitochondrial ROS. Succinate might trigger the expression of IL-1β *via* stabilization of HIF1α. Hence proinflammatory macrophages have the properties of rise in glycolytic activity as well as reduction in OXPHOS. Acute LPS treatment causes a burst of oxidative metabolism in Macrophages that enhances the pool of acetyl Co A that becomes available. This corroborates histone acetylation as well as downstream transcription of proinflammatory genes. Shutting down of oxidative metabolism, that is a hallmark of M1 macrophages, takes place after prolonged LPS treatments [12].

Lastly, amino acids, the immunometabolism of which is relatively little known can also get mobilized and effect macrophages polarization. Like glutamine catabolism feeds the TCA Cycle by producing Alpha-ketoglutarate, that acts as a cofactor for histone modifying enzymes that are involved in macrophage differentiatio. Arginine is also metabolized to L-

citrulline as well as a NO by iNOS, that facilitates killing of bacteria.

The basic findings regarding macrophage bioenergetics were mostly determined with use of ex vivo modeling systems (like murine bone marrow or human monocyte derived Macrophages) as well as in response to known polarizing agents. Although they are applicable to most of macrophages, typically infiltrating macrophages responses towards complicated metabolic stimuli as well as heterogeneity of tissues resident macrophages needs to be worked out. Tissues resident macrophages face a competition regarding nutrients, normoxic as well as hypoxic areas as well as crosstalk with other cells. They produce a response to complicated stimuli instead of unique stimuli. Bioenergetics adaptations of Tissues resident macrophages in obesity as well as IR have to be still worked out.

Significantly, ATM's of obesity possess a unique hypermetabolic profile with both escalated glycolysis as well as OXPHOS as compared to lean ATM's, while sustaining a proinflammatory phenotype. More specifically, the proinflammatory ability of the obese ATM's is modulated via glycolysis independent of HIF1α. This bioenergetic profile is also separate from peritoneal macrophages, inspite of sharing of systemic glucolipotoxicity that is brought in by obesity. These findings underlie the specificity of metabolically activated macrophages as well as ATM's [13].

Hypoxic areas form within AT on inappropriate expansion in obesity as well as IR. Hypoxia as well as imperfect angiogenesis are luring modes causing Macrophage metabolic activation as well as their inflammatory Polarization. On other hand the excess of free fatty acids (FFA) or lipolytic products in AT makes for a nutrient/substrates-rich micro environment. The action of this lipid loading on Macrophage metabolism as well as polarization needs to be evaluated under iso or hypercaloric situations. Like the action of obesity on Macrophage Glutamine metabolism needs to be examined. Glutaminolysis is reduced in the AT of obese subjects as compared to lean ones as well as Glutamine amounts in serum are reduced in patients having obesity or diabetes, pointing that there is an influencing part of Glutamine Metabolism in ATM's Polarization [14]

MACROPHAGE POLARIZATION -TRANSCRIPTIONAL REGULATION

Transcriptional Regulation regarding Macrophage Polarization has been well examined downstream of TLR ligation. Excellent studies found major TLR ligands along with critical transcription factors which modulate inflammatory responses. A lot of these pathways have been evaluated in Metabolic diseases and represent crucial mediators of macrophage activation in obesity, IR as well as T2D.

INFLAMMATION IN T2D-TLR-DEPENDENT

Highly conserved transmembrane receptors namely TLR's are expressed both in as well as on macrophages. This is secondary to the evolutionary need for recognition of structurally conserved molecules as well as pathogens. Every TLR from TLR 1 to TLR3 can recall specific ligands varying from LPS, to nucleic acids, viral particles as well as chitin. Besides their canonical part in host-defense, Various TLR's are involved in metabolic inflammation as well as IR. That way TLR's can recognize besides infectious pathogens *via* PAMP's, metabolic stressors or DAMPs correlated with sterile inflammation as well as glucolipotoxicity.

The basic TLR's involved with diabetogenesis are TLR 2 as well as TLR4.When these 2 TLR's get engaged chronic inflammation as well as IR results *via* direct interference with insulin signaling. TLR 2 as well as TLR4 share common adaptor proteins in macrophages, the myeloid differentiation primary response (MyD 88) protein as well as Mal/TIRAP which recruit IRAK kinases on TLR binding as well as dimerization. IRAK 1, 2 as well as 4 downstream signaling activates NFκB as well as activator protein 1 (AP1). Further TLR4 activates other downstream signaling as well. It represents the only TLR which forms complexes with all adaptor proteins, Mal/TIRAP as well as MyD 88 for initiation of early phase NFκB responses, the complex then gets endocytosed along with endosomal TLR's correlate with TRAM as well as TRIF adaptors. Canonically TRAM as well as TRIF mobilize the type 1 interferon response, that gets transcriptionally modulated *via* Interferon Regulatory Factors (IRF's). AP1 as well as late phase NFκB activation. Both early as well as late phase action is needed for maintainance of synthesis of inflammatory cytokines. Coordination of actions of TLR's, adaptor proteins as well as kinases causes sustained activation of 3 main transcriptional programmmes, lead by IRF's, AP1, NFκB as well as JAK-STAT [15].

CONCLUSION

Lot of advances have been made in last decades that implicated tissue macrophages in IR formation. Actually macrophages have been found to be the central players in sustaining tissue as well as organism homeostasis in response to every day challenges of temporary over as well as under nutrition-from inflammatory signaling essential for insulin liberation, to the house keeping part they have in buffering AT lipolysis as well as non inflammatory signaling in NAFLD.

Till date concentration of studies had been on getting to know the molecular modes which regulate macrophage responses to dysmetabolism, basically restricting classification into M1 like vs M2 like macrophages. With the recent technological improvement of single cell sequencing have given us to give a much >in depth classifying macrophage subsets, i.e. immune cell ontogeny, hence single cell sequencing has resulted in a functional reclassification of innate immune subtypes. Significance of these studies lies in giving the properties of macrophages in tissue niches which had been overlooked till now, like pancreatic islet macrophages or SNS related macrophages.

This switch in paradigm in macrophage functional reclassification can further be extended to their metabolic properties, their bioenergetic needs as well as adaptations to the particular challenges of IR. Various studies of infection as well as immunity have mostly used typical immune cell activation. Tissue macrophage bioenergetics need to be found at the formation stage, at steady state as well as at onset of IR. Macrophage metabolism is a luring therapeutic target which will

manipulate inflammation without markedly influencing effector functions by turning the immune response '' on'' or ''off''.

After recent findings of non immune as well as non inflammatory signaling *via* macrophages, we have gained insight into noncanonical part of the innate immune cells, like dendritic cells, NK cells, as well as ILC's. Since innate immunity, with all its diverseness, we know maintains homeostasis, without definitely engaging inflammation, steady state characteristics as well as responses to physiological variation need to be mapped to get more understanding of deregulation of innate immune effector function that causes metabolic pathology.

Inspite of consistent strong correlations as well as modes relation between inflammation as well as IR there have been relatively little successful translation innovations. Antidiabetic therapy at present aims to normalize glycaemia *via* a variety of modes and have been demonstrated to also buffer systemic inflammation (like TZD s, DPP4 inhibitors, GLP-1 RAs). These positive effects implicate improvement in the inflammatory profile for improvement of Metabolic responses. Knowing that lot of proof is there that macrophage polarization is central to T2D pathology very few clinical trials target inflammation in T2D.

Till date anti- inflammatory strategies in clinical trials have targeted cytokines with neutralizing antibodies (like ant-TNF. Anti IL1) or have applied agents that have uncharacterized modes (like chloroquine, diacrein). Studies on these drugs have been promising, enhance insulin sensitivity secretion or fasting blood glucose secretion. The biggest problems in their routine use are absence of longterm studies. Other problems in translation of anti- inflammatory methods is the fact that inflammation in T2D has multiple causes, with the disease itself predisposing patients to a group of complicated sequelae as well as comorbidities (in a case where the increase of precision medicine tries to find modes of response or those at risk). Technical barriers further effect translational potential like clinical trials investigating inflammation on the basis of relatively non-specific circulating markers like CRP, that at best reflects systemic inflammation. While in preclinical studies scientists aim to examine tissue specific inflammation, extrapolating these to human studies is a big hurdle. Specifically delivering drugs to macrophages also is a big challenge clinically as well as leaves the door open for unanticipated side effects. With the above work promising methods are slowly enhancing the translation potential of targeting infllammation in Metabolic diseases, like repurposing of well tolerated agents from other pathologies or fields, as was the case with anti malarial chloroquine as well as hydroxyl chloroquine as well as diacrein used for treatment of arthritis. In basic research, >attention is being given in earlier disease course, where mechanisms which might delay or negate the natural course of T2DM are getting described and will give the basis for innovative therapeutic targets. Developing small molecule inhibitors or antisense oligonucleotides are luring on targeting epigenetic or transcriptional pathways and are proving to be of >value in clinical research community. In same line search for metabolic immunogens or characterization of circulating immune cell populations will aid in forming predictive biomarkers of susceptibility to diseases or at risk proneness of disease propagation once IR has got established.

References

1. American diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009.
2. American association of diabetes eductors. Educator insight in using chronicle diabetes: A Data management system diabetes education. 2013.
3. Fourlanos S, Honeyman M, Varney M, Colman P, Trait B, Hairrison L, et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diab care. 2008;8:1546-1549.
4. Bowes S, Lowes L, Warner J, Gregory J. Chronic sorrow in parents of children with type 1 diabetes. J Advanced Nurs. 2009;5(65): 992-1000.
5. Sullivan-Bolyai S, Bova C, Leung K, Trudeau A, Lee M, Gruppuso P. Social Support To Empower Parents (STEP): An intervention for parents of youetesng children newly diagnosed with type 1 diab. J diab. 2010;36:88-97.
6. Boulton AJM. Management of Diabetic Peripheral Neuropathy. Clin Diabetes. 2005;23:9–15.
7. Arnold N. FDA requires new respiratory depression risk gabapentinoids warnings [Internet]. U.S. Food and Drug Administration. FDA; 2019.
8. Marcum ZA, Hanlon JT. Recognizing the risks of chronic nonsteroidal anti-inflammatory drug use in older adults. Ann Longterm Care. 2010;18:24-27.
9. Mcpartland JM, Guy GW, Marzo VD. Care and feeding of the endocannabinoid system: A systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS ONE. 2014;9.
10. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors. J Exp Med. 2012;209:1121-1134.
11. Ward SJ, Mcallister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. Br J Pharmacol. 2014;171:636–645.
12. Dansinger M. CBD and Diabetes. WebMD. WebMD, LLC; 2019.
13. Ferini-Strambi L. Neuropathic pain and sleep: A review. Eur J Pain. 2017;6:19–23.
14. Stehouwer CDA. Microvascular Dysfunction and Hyperglycemia: A Vicious Cycle With Widespread Consequences. Diabetes. 2018;67:1729–1741.
15. Meza R, Barrientos-Gutierrez T, Rojas-Martinez R, Reynoso-Noverón N, Palacio-Mejia LS, Lazcano-Ponce H-ÁM. Burden of Type 2 Diabetes in Mexico: Past, Current and Future Prevalence and Incidence Rates. Prev Med. 2015;81:445–550.