Utilizing Knowledge on Advances in Macrophage Polarization for Prevention and Treatment of Diabesity-A Short Communication

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Abstract:

Both obesity as well as type 2 diabetes mellitus (T2D) and other metabolic disorders are causing a huge impact on global health but is in epidemic proportions right through the world. Thus, the term diabesity had to be coined. Earlier we have reviewed various therapies that can be used to treat both obesity and T2D medically including various combination therapies like topiramate with phentermine, bupropion and naltrexone, GLP1 agonists like luraglutide ,thylakoids and different plant products like monoterpenes, PTP Inhibitors etc although permanent efficacy not maintained other than by bariatric surgery .Further we discussed the use of weight neutral antidiabetic drugs once DM develops like liraglutide ,role of empagliflozin in CVOT trials .Here we discuss more of prevention along with treatment of both obesity and diabetes and once DM has developed how to treat by targeting macrophages with a lot of insight in the bioenergetics ,detailed classification of macrophages beyond M1 ,M2 dichotomy and detailed transcriptional and epigenetic regulation of macrophages. A crucial player in dysmetabolism is chronic low grade inflammation in ,that by definition is the inability to maintain homeostasis leading to loss of lipid regulation ,oxidative stress and insulin resistance .We have further reviewed role of macrophages in non-alcoholic fatty liver disease(NAFLD) and in obesity and DM .Here we further emphasize on how we can target macrophages by the newer insight on macrophage metabolism, transcriptional factors that regulate macrophages like IGF 1,HIF 1,AP,NF‐B along with trying to understand the microglial control .Further emphasis on metabolism of proinflammatory macrophages utilizing glycolytic cycles whereas anti-inflammatory macrophages utilizing Oxidative phosphorylation that we have earlier reviewed in nutrients role in immuno metabolism and how deficiencies get created within the body with the vicious cycle of these metabolic features and how we need to target inflammation right at the initiation of obesity and T2DM to prevent it further worsening without affecting the immune role of these macrophages in infections.

Results and conclusions:

Thus, obesity exposes tissue macrophages to a microenvironment which consists of excessive nutrients along with stress signals via damaged as well as apoptotic parenchymal cells. These environmental cues might activate macrophages as well as rewire their cellular metabolism in a manner that facilitates maladaptive inflammation as well as macrophage dysfunction. Initially macrophage activation might be of benefit to promote the removal of apoptotic cells, clear excess lipids as well as restore tissue homeostasis. But abnormal reprogramming of macrophages in the setting of the sustained lipid provokes tissue injury which probably stimulates pathologic macrophage phenotypes .Once this takes place ,the macrophage secretome might act locally or systemically to drive metabolic disease formation .This proposal is especially true in tissues which are faced with a great metabolic load in obesity like AT and liver .For harnessing the treatment potential of reprogramming macrophages metabolism for human diseases ,it will be necessary to find the mode through which macrophages enhance or worsen the obesity associated complications .

Though it has been proven that interfering with macrophages cellular metabolism can improve metabolic disease phenotypes ,the exact cellular and molecular details are not well understood .Partially this is because most of the data in this field arrives via knockout or overexpression of crucial metabolic genes in relation to in vitro models or non selective myeloid knockout systems .Finally determining the heterogeneity of macrophages in a variety of organs and their association to metabolic disease will aid in more specific therapeutic targeting .Still insight regarding this has been limited in view of absence of tissue specific macrophage markers for finding and manipulating resident macrophages in various tissues. Basically, maximum studies have utilized generic myeloid knockout models, like Lys M-Cre or BM Transplantation. The finding of unique markers of tissue macrophages via the utilization of sophisticated unbiased approaches like scRNA seq, has the potential of opening newer methods for evaluating the role of separate macrophage subsets in tissues and whole-body metabolism. Like recently it was demonstrated that liver resident KC's uniquely express surface receptors Tim4 and Clec 4f. This discovery promoted the formation of Clec 4f-Cre transgenic mice, that will aid in the study of KC's particular function in liver pathology and metabolic disease.

The pathogenesis of obese associated metabolic disorders ,like IR is very complicated and involves metabolic perturbations in lot of organs .Tissue Macrophages liberate a plethora of factors which might influence Macrophages polarization and finally tissue function in distant organs .Already proof is there for corroborating the evidence that adipose tissue macrophages(ATM) can direct relevant pathological events in the liver in the setting of obesity .On the other hand it is luring to posit that signaling from liver macrophages to AT might be occurring too. It will be significant to find the crucial molecules involved in inter organ interaction and to assess their influence on tissue macrophages biology.

Despite significant process in this area, future evaluation and integrating in these fields will be essential to utilize the therapeutic potential of reprogramming of macrophage metabolism in case of obesity and DM. Additionally, defining the molecular basis of crosstalk among macrophages as well as parenchymal cells in AT, liver and brain will also need more examination. Another significant issue that needs resolution is if targeting macrophage metabolism can ameliorate pathologic inflammation during obesity without disabling the basic roles of these immune cells in tissue repair and maintenance of homeostasis. Ultimately, the utilization of targeted small molecules or nanoparticles are attractive possibilities to manipulate macrophage function. Although still lot needs to be understood targeting the macrophage biology is promising as a therapeutic method for manipulating metabolic diseases.

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