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Alteration in Natural Killer (NK) cell Function in Obesity-correlating with comorbidities development like cancer and type 2 diabetes-A Minireview

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Mini Review

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Abstract

Recently obesity has become a worldwide epidemic, with over 600 million adults worldwide being obese of which 10.8% are males and 14.9% females. Now obesity has overtaken undernourishment for the first time and is increasing by leaps and bounds. Hence marked efforts are being done to understand the aetiopathogenesis. In our earlier reviews we have tried to understand the aetiopathogenesis involving different aspects like inflammation in general in obesity, hypothalamic inflammation, GIT inflammation, and others which have influenced development of medical treatments having edge over bariatric surgery but have not been successful in getting any stable medical therapy that can be used for long. Natural Killer (NK) cells represent one of the populations of the lymphocytes belonging to the innate immune system. By definition they are the cells that have the capacity to kill infected or transformed cells without needing any previous activation. Besides their cytotoxic capacity, they can also produce inflammatory cytokines like interferon gamma (IFNγ) and thus are a key part of early immune responses. In view of these abilities which make them stand out, these NKcells are very important parts for host protection, mainly antitumor and antiviral immunity. In the last 10years, a lot of work has been done to study the effect of obesity on NKcell biology, giving a full briefing of systemic dysregulstion of NKcell functions. Recently various publications have examined the role of NKcells in the homeostasis of adipose tissue (AT) and the aetiopathogenesis of obesity. Here we review studies pertaining to the role of how NKcells are involved in obesity.

Keywords: Natural Killer Cells, Obesity; Cancer; Adipose Tissue

Abbreviations: WHO: world health organization, BMI: body mass index, T2DM: type 2 diabetes mellitus, CDC: Centre Of Diseases Control, CVD: Cardiovascular Disease, IL1: Like Interleukin 1, HLA: Human Leukocyte Antigen, KIRs: Killer Cell Immunoglobulin Like Receptors, CSC: Cancer Stem Cells, 2DG: 2-Deoxy Glucose; mTOR: Mammalian Target Of Rapamycin, TRAIL: TNF Related Apoptosis Inducing Ligand, DIO: Diet Induced Obesity, AML: Acute Myeloid Leukaemia, TGFβ: Transforming Growth Factor Beta, HIIT: High Intensity Interval Training; FFA: free fatty acids, CSFR1: colony stimulating factor 1 receptor, ILC: innate lymphoid cells, SI: Small Intestine, NKT: Natural Killer T.

Introduction

In the last century obesity has surfaced as the biggest global health problem in view of both ,the changes in environment along with changes in society where positive energy balance and thus weight gain has resulted, main changes being consumption of high calorie foods /high fat foods, associated with inadequate physical activity, moving towards sedentary lifestyle [1]. As a result obesity prevalence practically doubled since 1980 all over the world, with world health organization (WHO) showing that greater than 39%of adults greater than /equal to 18year were overweight of which 13% were obese [2]. Additionally minimum of 41million children below 5yrs were overweight or obese. Importantly severe obesity, a body mass index (BMI) greater than 35kg/m^2 is becoming a part of this global epidemic, and that has severe bad effects on health, with increase in BMI implying increased mortality risk just like low BMI does [3-5]. However now overweight or obese have become bigger killers in contrast to malnourished or underweight. As per WHO overweight and obesity are the causative factors for 44% of type 2 diabetes mellitus (T2DM), result in 23% of ischemic heart disease patients and roughly 7-41% of some cancers. Of these greatest association is of T2DM with obesity, with obesity related T2DM expected to double to 300 million by the year 2025 [6]. We reviewed the importance of treating both obesity and diabetes together in view of that [7]. To further understand the aetipathogenesis we decided to review a role of Natural Killer cells in obesity in this review.

Methods

Thus we used the PubMed search engine to find articles using MeSH terms like ''NK cells'' ''obesity'', ''cancer'', ''inflammation'' and obesity''.

Results

We found a total of 356 articles out of which we selected 73articles for this review. No meta-analysis was done.

Cancer and Obesity

Worldwide, cancer has become a leading cause of mortality, with 7.6 million deaths occurring yearly [8]. A report from centre of diseases control (CDC) in United States have pointed to obesity being responsible for 40% of cases of cancer, that accounts for 630,000 diagnosis in 2014 alone [9]. This study is similar to what has been found all over the world [10]. Multifactorial changes like hormones, cytokines and immunity observed in cancers related to obesity. Obesity is related to increased insulin levels that further promotes the development of some obesity related cancers like colorectal, pancreatic, liver and endometrial [11-13]. Various studies have also picked up links with leptin, an adipokine levels that are raised in obese children and adults and cancer. Most researchers trying to study leptin in relation to obesity have mainly concentrated on breast cancer, in which case leptin has the ability to directly stimulate breast cancer cells proliferation [14]. Also the other part common to obesity related cancer occurring is the chronic inflammation present in obesity [15]. Various studies have emphasized on the interaction between inflammation and cancer developing as exemplified by colonic carcinogenesis in pts suffering from inflammatory bowel disease [16].

Obesity and Immune Regulation Disorder

Systemic inflammation development is driven by obesity that besides being behind the formation of malignancies, leads to other morbidities like development of T2DM and cardiovascular disease (CVD). Various cytokines that are increased in obese subjects have been demonstrated to interfere with normal homeostasis processes, like interleukin 1 (IL1) and insulin signaling or IL-17 and adipogenesis [17,18]. Inflammation that has been stimulated with Obesity has been demonstrated to stimulate the liver carcinoma development [19]. This chronic inflammation originates initially through a dysregulated immune system. Changes in a subset of immune system, associated with a loss of control and rise in inflammatory profile has been found by many researchers [20-23]. This altered immune system besides occurring in adults having established comorbidities, is also seen in obese children even as old as 6 years of age, much before the overt disease come in the scene [24].

This supports this hypothesis that obesity is the one that stimulates chronic inflammation that comes before comorbid diseases that includes cancer origin. In addition to the raised inflammatory burden, there is a negative effect of obesity on the bodies tumor effector populations, like natural killer cells (NK) cells.

Natural killer cells (NK) cells

NK cells constitute a subset of innate lymphocytes, that have a very important role in early host protection [25]. Difference from classical T and B lymphocyte is that NK cells can respond to infected or transformed cells at a fast pace, not needing any activation, through their manufacture of lytic molecules like perforins or granzymes [26]. NK cells might also modulate the consequent immune responses via their production of cytokines immediately like IFNγ, TNFα, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). NK cells activation is controlled tightly via the germline coded receptors expression, that in response to environmental cues can change the interrelation of activating and inhibitory signals remaining in balance, that =>activation of the cells. If self-identifying molecules like human leukocyte antigen (HLA) are lost that normally give an inhibitory signal, through killer cell immunoglobulin like receptors (KIRs) will=>activation of NK cells, and the lysis of the target cells. Further NK cells also get activated by binding of activation molecules like NKG2D that get up regulated by stressed and transformed cells [27]. Cancer stem cells (CSC) can be targeted by NK cells too, that can seed metastasis and promote tumor bulk [28]. Besides being activated in response to malignant cells or CSC, NK cells might also get activated through soluble cytokines that includeIL-2, IL-12, IL-15, and IL-18. A critical component of NK cells activation that has been emphasized is immunometabolism, at rest NK cells metabolize glucose through glycolysis coupled to oxidative phosphorylation with great levels of energy getting released. On activation, NK cells immediately increase their rates of aerobic glycolytic metabolism that fuels biosynthetic precursors for cytokine and lytic granule synthesis for NK cells effector function has been shown by inhibition of glycolysis with the use of 2-deoxy glucose (2DG), that inhibition of NK cells cytokine production along with lytic molecule synthesis [29-31]. Mammalian target of rapamycin (mTOR) is a master regulator of NK cells metabolism. The requirements have been shown to be indispensable for NK cells effector function. Initially it was considered that NK cells don't have any memory, but various researchers have demonstrated that murine NK cells can form memory [32]. Similarly workers showed that human NK cells have been demonstrated to learn during training, where an early cytokine stimulation => a boosted response various days or weeks later [33,34]. A new therapeutic avenue has been released with usage of trained NK cells as a potent immunotherapy.

NK Cells in Cancer

NK Cells are extremely important part of antitumor immunity, since they are rich in potent antitumor machinery that includes cytotoxic granules, proinflammatory cytokines and death –inducing ligands like FAS ligand and TNF related apoptosis inducing ligand (TRAIL). For protection from cancer gets supported by the increased prevalence of cancer in humans with defective NK cells like in Chediak-Higashi disease, and validated by the exacerbation of cancer in NK cell deficient mouse models [35]. Association between low NK cell activity and cancer risks have also been emphasized by some studies. In a study that extended for 11years, a longitudinal study showed that subjects with low NK Cells activity levels were at a >risk of developing cancer that emphasizes on how essential NK Cells are in the prevention of overt malignancy and immunosurvellace [36]. Further in 872 patients cohort, cases with low NK Cells activated (IFNγ production) had a 10 fold >risk of colorectal cancer as compared to those with high NK Cells activity [37]. On the other hand, in a colorectar cancer cohort patients and matched controls, expression of high NK cell activity haplotype of NKG2D, HNK1, was correlated with decrease in risk of colorectal cancer. Besides the cancer risk NK Cells have an important role in predicting the prognosis of patients developing cancer [38]. 50 patients with primary squamous cell lung carcinoma, high NK cell infiltration into the tumor was associated with a good outcome. Besides cancer can also induce defects in NK cell, using a KRAS mutation model of pancreatic cancer, Kaur, et al. demonstrated the defect in NK cell frequencies and functions during the preneoplastic stages of pancreatic cancer, suggesting that cancer induces early defects in NK cell that allow the progression and expansion of the disease. In that v study diet induced obesity (DIO), compounded the change of NK cell in the tumor microenvironment that helped in the expansion of pancreatic tumors [39]. Those who studied the NK cell functions in cases of acute myeloid leukaemia (AML) also demonstrated that NK cells were dysfunctional with decreased cytokine production and degranulation. Incubation of NK cells that were obtained from healthy donors with AML blasts induced similar defects suggesting that the defects that were

communicated were indiced by cancer [40]. Mamassier, et al. gave an exhaustive explanation on this concept by demonstrating that human breast cancer cells could promote tolerance in NK cells by decreasing the expression of activating receptors like NKG2D, and those tumor derived factors like transforming growth factor beta (TGFβ), directly decreased NK cell activity [41]. In view of their high effector functions, NK cell become an attractive target for cancer immunotherapy. Various methods have been demonstrated, which vary from adoptive transfer of NK cells into patients, cytokine therapy or targeting /modifying NK cells receptors to enhance their cancer killing function [42]. Adoptive transfer of NK cells means isolation of either autologous or allogenic cells that was followed by their expansion and activation before transfusing them to the patients [43-46]. Clinically important responses have not been shown from studies that were investigating autologous transfer. More positive effects were documented with allogenic approach, mainly with KIR mismatch in those subjects presenting with haemoatological cancers like AML Use of Adoptive transfer of allogenic, NK cells in 2010, Rubnitz et al. presented astounding data in childhood AML, demonstrating 100%remission rates [47]. Transferring cytokine trained NK cells is other method that holds promise, involves harnessing the training of memory potential of NK cells. NK cells separated whether autologous or allogenic get activated in vitro with the use of a mixture of cytokines (IL-2,IL-15,and IL-18)and following restimulation, demonstrated enhanced effector responses. Cytokine trained NK cells showed increased effector functions in a phase-I clinical trial and a clinical response in 5/9 patients with 4 total remissions [48]. Together these studies project a key role for NK cells in tumor immunity and their potential therapeutic responses.

Obesity and NK cells

Lynch et al reported in 2009 that NK cells were changed in a cohort of morbidly obese patients [49]. A reduction in NK cells frequencies were reported in obese as compared to lean ones along changes in the surface repertoire of NK cells activating and inhibitory molecules. NK cell cytotoxic abilities were decreased in the same group of patients with NK cells that were isolated from obese patients killing much less of the K562 myeloid leukaemia cells compared to healthy controls. Variety of other publications also emphasized on the negative effect of obesity on NK cells [22,50-52]. Viet, et al. in 2017 demonstrated raised expression of activation markers like CD69 on NK cells from obese patients in parallel with a loss of function as measured by degranulation and the synthesis of macrophage inflammatory protein (MIP)-1β or IFNγ. The resident NK cells in tissues also get influenced by obesity, as shown by Shoae-Hasseini et al. in 2017, that NK cells resident in AT of obese subjects had low expression of NKp30 and NK p44 as compared to lean controls. Thus for finding when these defects get established, NK cell frequencies and functions of a cohort of obese children between 6-16yrs of age, free of overt metabolic diseases, did show greater evidence of IR. Tobin et al. suggested that defective tumor lysis by NK cells isolated from obese children, was possibly due to disturbed synthesis of granzymes B and perforins. This pointed that NK cells defects get seeded very early in obesity much prior to the development of overt metabolic diseases .A good thing was that the impact of weight loss after bariatric surgery was shown to cause normalization of these NK cell cytotoxicity six mths after surgery as shown by Moulin, et al. [53]. Thus pointing that once weight loss achieved, defects in NK cells induced by obesity could be reversed. Further this was proved by 2 researchers, 1st being by Jahn et al. who demonstrated that weight loss in obese subjects with the use of diet along with exercise =>increased IFNγ synthesis by NK cells [54]. Barra, et al. in the 2nd one demonstrated that high intensity interval training (HIIT) raised NK cells frequencies and function in obese women along with mice, besides obesity, breast cancer cells were injected intravenously into the mice and it was shown that HIIT decreased tumor burden, with a hypothesis by the authors that this got mediated through increase in NK cells activity (Figure 1) [55]. Right now how HIIT restores NK cells functions is not clear.

How obesity causes defects in NK cells have gradually started to be understood, with various studies demonstrating that leptin and adipokine levels are increased proportional to the AT mass, hence are increased in obese adults as well as children, might influence NK cell functions. Leptin is a peptide hormone that is synthesized by adipose tissue mass, hence are mainly acting as a safety signal [56,57] normally physiologically, is increased in obese adults and children [24,58]. Besides regulating energy expenditure leptin has been found to be an essential controller of Immune system [59,60]. NK cell frequencies were decreased in the periphery, liver and spleen in leptin receptor deficient (db/db) mice, that points to the importance of leptin in regulating NK cells development [61]. Additionally activation of NK cells was also impaired in leptin receptor deficient mice. Nave, et al. confirmed the importance of leptin in regulating NK cells and gave a mechanism via

which resistance of leptin signaling in NK cells was the important factor in their dysfunction in murine models of obesity [62]. Leptin resistance has been known to be an important part of obesity that has more roles than simply regulating NK cells and with the classical actions of leptin in energy homeostasis [63]. Laue, et al. found that the leptin receptor expression was higher on NK cells from obese subjects as compared to healthy controls; but authors found decreased downstream signaling in obese donors. Leptin stimulation caused a rise in cytokine production (IFNγ) IN NK cells from healthy donors but not obese donors, in same study, though proliferation levels were not the same [64].

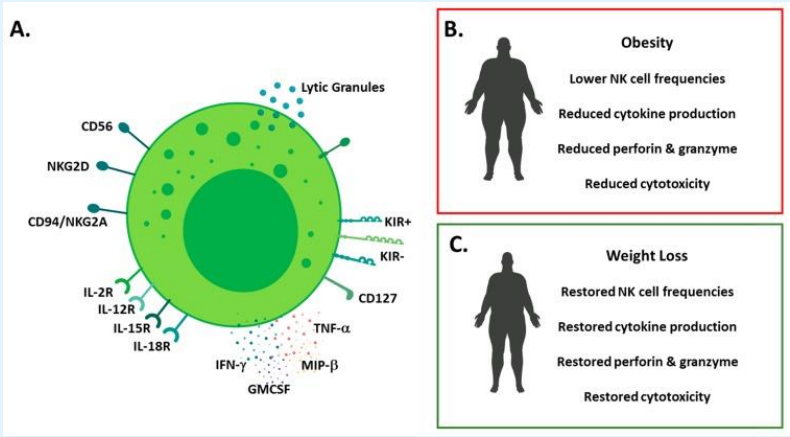

Figure 1: NK Cells in Obesity [74].

Besides leptin resistance, Michelet, et al. found a separate mechanism driving defective NK cells in human obesity. Now it is well known that for normal function NK cells are intrinsically dependent on cellular metabolism, with various publications showing the absolute need of NK cells to engage in glycolysis and oxidative phosphorylation [30,31,65,66]. NK cells isolated from obese patients dysregulated metabolism, with inability to engage in glycolytic metabolism. Using RNA sequencing in same study authors highlighted that NK cells isolated from obese patients showed increased expression of genes that were involved in lipid handling and metabolism. On further exploration they found that culture of NK cells with free fatty acids (FFA) oleate and palmitate, recapitulated obesity like defects in NK cells, with loss of tumor lysis, blunted cytokine production and a failure of metabolic programming. With the use of murine models of malignancy, they demonstrated decreased antitumor immunity with FFA treated NK cells, emphasizing a direct link between obesity induced NK cell defects and cancer (Figure 2).

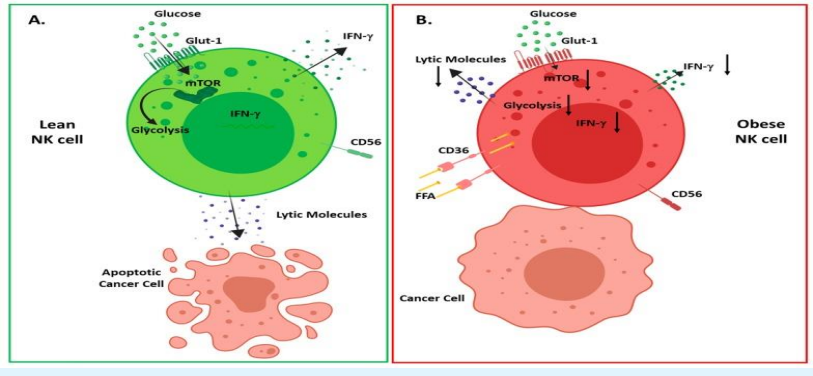

Figure 2: NK Cells [74].

Adipose Tissue and NK cells

Besides their role in host protection, NK cells influence tissue homeostasis, at sites that include uterus and adipose depots. As seen by Perdu, et al. showing that maternal obesity defective NK cells in the uterus, with decreased numbers along with hyper responsiveness resulting in increased expression of décor in that can limit trophoblast survival altered placental development. How essential NK cells are for adipose tissue homeostasis and initiating IR has been demonstrated in various studies [24,67-69].

O'Rourke et al working on NK cells in human AT, showed an increased activation profile in AT as compared to NK cell from the blood, and in a future study, they gave proof for the 1st time that NK cells could regulate AT macrophages, pointing to a positive role in the development of IR. Systemic NK cell ablation reduced accumulation of macrophages in the AT and modest improvement in insulin sensitivity [70,71]. Wensveen, et al. showed how NK cells were important in monitoring AT stress through the expression of natural cytotoxicity receptors (NCRs). On recognition of NCR's, while expression was up regulated on stressed adipocytes in HFD fed animals, NK cells were demonstrated to produce IFNγ, that promoted recruitment of macrophages into AT. These macrophages infiltrating initially had the task of phagocytosing apoptotic adipocytes, also synthesized high levels of inflammatory cytokineIL-1β. In IR role of IL-1 has been implicated, besides in the pathogenesis of T2DM. This role of NK cells in pathogenesis of IR was substantiated by further studies from Lees's laboratory, who demonstrated that HFD increased NK cells numbers along with synthesis of pro-inflammatory cytokine TNFα, in epididymal, not subcutaneous, AT. On depletion of NK cells, an improvement was seen in obesity induced IR in parallel with reduction in both AT macrophages and inflammation. On the other hand expansion of NK cells after IL-15 administration or reconstitution of NK cells into NK cell deficient mice increased both AT macrophage infiltration and inflammation exacerbated IR. Theirich, et al. elaborated on specific subsets of NK cells that expressed IL-6Ra and colony stimulating factor 1 receptor (CSFR1) that were expanded in obese mice and humans and described their contribution to IR. Ablating CSFER1 expressing NK cells abrogated the development of obesity and IR, giving more proof for a homeostatic role for NK cells in metabolism.

O'Sullivan, et al. further elaborated on a role of AT resident innate lymphoid cells (ILC), specifically ILC1, in the development of IR. Although NK cells belong to ILC 1 Lineage, these authors demonstrated that ILC1 in the AT were phenotypically different from classical NK cells. Agreeing with this Boulenoaur, et al. demonstrated that under steady state conditions, IL1C's are enriched in AT from both mice and humans, and these cells show an AT specific phenotype. Further they demonstrated that these ILC's can regulate AT macrophage through their capability to kill inflammatory macrophages. AT macrophages express the NKG2D ligand, Rac1 that makes them a target for NK cell lysis. On initiation of HFD feeding NK cells lost their capacity to kill macrophages and increased synthesis of IFNγ that promoted the recruitment of inflammatory macrophages promoting obesity associated metabolic defects. Further Sasaki, et al. showed mice lacking ILC2 or ILC3 cells but not NK cells are resistant to obesity. Adoptive transfer of naïve ILC2's isolated from small intestine (SI) but not from white AT restores the induction of DIO in Il2rg-/- Rag 2-/- mice. Analysis of transcriptional differences showed that SI-ILC's express higher levels of IL-2 than do WAT-ILC2s and that blockade of IL-2 signaling impairs weight gain and reduces the populations of ILC2 and ILC3 in the SI, Suggesting a role of the IL-2/ILC3/3axis in the induction of obesity [72]. Further Rakshandehroo, et al. tried to explain how over production and /or accumulation of ceramide and ceramide metabolites, including glucosylceramides, can lesd to IR. The physiological functions of glucosylceramides being, they are presented by APC as endogenous lipid antigens via CD1 to activate a unique lymphocyte species, the CS-1d restricted invariant (i) Natural killer T (NKT). Recently adipocytes have emerged as lipid APC, which can activate AT-resident iNKT cells and thus contribute to whole body energy homeostasis. Thus they investigated a role of glucosylceramides biosynthesis pathways, in the activation of iNKT cells by adipocytes. UDP-glucose ceramide glucosyltransferase (Ugcg), the 1st rate limiting step in glucosylceramide biosynthesis pathway, was inhibited through chemical compounds and shRNA knockdown. Subsequently, (pre)adipocyte cell lines were tested in co-culture experiments with iNKT cells (IFNγ and IL4 secretion). Inhibition of Ugcg activity shows that it regulates presentation of a considerable fraction of lipid self-antigens in adipocytes. Furthermore decreased expression level of either B4Galt5or 6 indicate that B4Galt5 is dominant in the production of cellular lactosylceramides, but that inhibition of either enzyme resulted in increases iNKT cell activation. In addition, in vivo inhibition of Ugcg by the aminosugar AMP-DNM results in decreased iNKT cell effector function in AT; Inhibition of endogenous glucosylceramide production

results in reduced iNKT cells activity and cytokine production, underscoring the role of this biosynthetic pathway in lipid self-antigen presentation by adipocytes (Figure 3) [73]. In total these researches give enough proof that NK cells are involved in the initiation of the macrophage-driven inflammatory phenotype reported in obese AT.

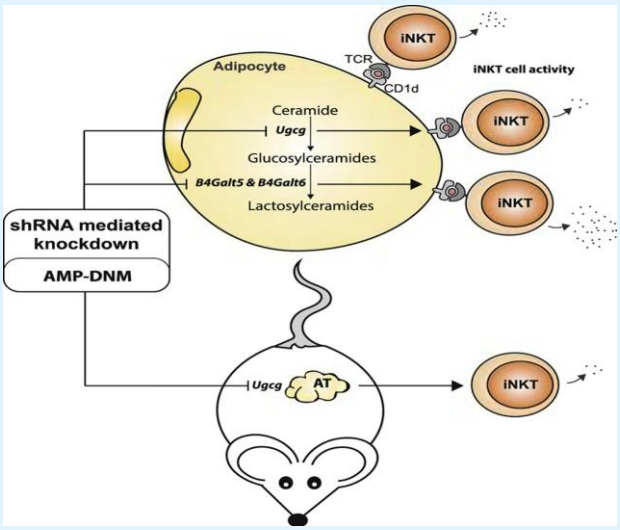

Figure 3: Adipocytes in NK cells [73].

Conclusion and Future Directions

With obesity becoming a worldwide epidemic and its associated comorbidities like T2DM, CVD and many cancers need is there to find a solution, NK cells are essential frontline effectors cells in protecting the host that includes surveillance of tumor surveillance and clearance. NK cell immunotherapy looks to be a good strategy for the therapy of cancer, especially blood based cancers. A negative effect of obesity right from childhood into adulthood occurs on NK cell function has been presented in this review. It seems that the obese microenvironment drives defects in NK cell metabolism that causes functional failures. Hence doubt might be there regarding NK cell therapies will be able to be of help in obese mainly acting as a safety signal [56] patients. More work in murine models of obesity and obese patients will be required to get a certain answer. Besides their role in protecting host, NK cells have important role in maintenance of tissues like AT. NK cells and ILC1 also directly control macrophages, but on HFD feeding NK cells lose their capacity along with changing their control of AT. This activation along with accumulation of inflammatory macrophages which drive IR-a crucial player in driving DM and cancer. If targeting this NK-Macrophage interaction will become a possible way to treat IR and tumorigenesis still remains a query.

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