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Suppressive effects of obesity on NK cells: is it time to incorporate obesity as a clinical variable for NK cell-based cancer immunotherapy regimens?

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ABSTRACT

NK cells mediate numerous antitumor effects and are under increased scrutiny as potential targets for cancer immunotherapeutic regimens, either as direct effectors or in contributing to overall antitumor efficacy. Obesity, a condition of excess adiposity and altered metabolomics, has reached pandemic levels and continues to rise. Obesity and the meta-inflammatory state associated with it have been correlated with increased incidence, progression, and poorer clinical outcomes for many cancers. Obesity has also been demonstrated to be suppressive for most immune cell types, including natural killer (NK) cells, which may affect tumor outcomes. However, there is also the "Obesity Paradox" in which some immunotherapeutic regimens, such as immune checkpoint blockade, result in greater T-cell responses in obesity. Recent evidence also suggests that the inhibitory effects of obesity on NK cells can be both direct and indirect. Many questions still exist concerning the different pathways and stages of NK cells affected by obesity and functional consequences, as well as the models to assess them. These data indicating the inhibitory properties of obesity on NK cells suggest it should now be considered as a key parameter potentially affecting NK cell-based cancer immunotherapy regimens efficacy.

MAIN TEXT

The breakthrough success and approval of T-cell-centered cancer immunotherapies, such as immune checkpoint inhibition (ICI), bispecific antibodies, and genetically engineered chimeric antigen receptor (CAR) T cells, has resulted in an ever-increasing attempt to extend their application and improve efficacy. It has also stimulated renewed interest in unlocking the potential of additional immune effector cells, such as natural killer (NK) cells. NK cells, defined by their ability to spontaneously mediate cytotoxicity towards virally infected and transformed cells in a major histocompatibility complex-unrestricted manner have been long sought as potential antitumor effectors. NK cells are generally viewed as mediating antitumor effects on hematopoietically-derived cancers or tumor cell metastases,[1] but their presence has also been associated with improved clinical outcomes in certain solid tumors.[2] In addition, while they may not function as the primary effector population against some tumors, evidence suggests that they may contribute to the overall antitumor effects of many regimens involving biological response modifiers as well as augment the T-cell arm in tumor control.[3 4] While NK and T cells share many characteristics and often respond to similar cytokines and stimuli, there are critical differences that need to be considered regarding variables that affect their function.[4] Long-lived memory T cells reside and traffic in tissues, and when under continuous stimulation or in immunosuppressive environments, demonstrate "exhaustion" with impaired functionality, which can be ameliorated by ICI.[5] In contrast, NK cells do not clonally expand, have a relatively short lifespan, reside in hematopoietic and lymphoid tissues, and are continuously replenished throughout life.[1] In addition, while evidence for NK cell anergy or exhaustion with repeated stimulation does exist,[6] it is far less clear what the impact of this is on overall antitumor effects given that few preclinical tumor models have assessed anergy or exhaustion in the context of cell-mediated antitumor efficacy. Due to recent advances in genetic engineering and the development of more specific targeting agents, there has been renewed interest in applying NK cell-based therapies in cancer.[2 4] The attractiveness of NK cells resides in these differences from T cells with respect to lack of alloreactivity (opening the potential use of third-party sources), shorter lifespan (allowing for potential control), their inherent ability to detect transformed cell-types via natural-killer group 2, member D

(NKG2D) and other receptors they constitutively express, as well as potentially being able to target potential immunologically resistant cancer stem cell tumor subpopulations.[7] Difficulties in applying NK cells as a broad cancer therapeutic are underscored by their complex biology and receptor systems, heterogeneity of subsets, relatively short lifespan, and lack of robust solid tissue homing ability needed for solid cancers.[1 8] There is also the issue that many approaches to augment their function may also affect T cells, making definitive data delineating their exact role or effect difficult.[1] Nonetheless, NK cell-based therapies such as CAR NK cells as well as NK cell-specific targeting agents such as tri-specific killer cell engagers are under clinical evaluation,[9] making the need to understand variables affecting NK cell function more pressing.

Obesity, defined as an excess of adipose tissue, has been classified by the WHO as a body mass index (BMI, kg/m^2) of 30 or higher. It has reached pandemic levels globally and is rising continually, such that in the USA, approximately 39% of the population is classified as obese, with even more being overweight (BMI of >25).[10] Obesity has been consistently implicated as a negative prognostic indicator regarding cancer incidence, progression, and clinical outcomes.[11] While BMI is often used as the primary tool for assessing obesity, it has been increasingly recognized that other parameters such as: hip to waist ratio, determination of lean muscle mass via imaging, and assessment of key metabolic parameters are more accurate parameters for prognostic purposes.[11] Obesity exerts marked immunological effects and is classically associated with a "meta-inflammatory" state due to increased pro-inflammatory cytokine responses affecting all tissues.[11 12] Obesity is also associated with an overall immunosuppressive phenotype resulting in: increased T-cell memory conversion and exhaustion, skewing to Th17 responses, increased regulatory T cells (Tregs), increased myeloid-derived suppressor cells, M1/M2 macrophage polarization, impaired primary antigen-specific responses, increased pro-inflammatory cytokine production, altered dendritic cell function, as well as impaired NK cell maturation and function.[11] The causes of these immune effects in obesity are multifactorial and complex, with increased adiposity, alterations in hormones such as adipokines, leptin and insulin, increased fatty acids, and even alterations in the microbiome all likely playing roles depending on the immune cell type and location.[11 13] Many of these same pro-inflammatory immunosuppressive conditions likely directly fuel cancer growth and progression, and underpin the association between obesity and worse outcomes in many cancers.[11 12] Obesity has also been associated with increased off-target toxicities such as cytokine release syndrome following acute infections or after some immunotherapies.[14] Yet despite these multiple negative associations, obesity is only now being considered as a key stratification variable for data interpretation in clinical trials, but not as an exclusionary criterion.

Obesity may not be considered as totally negative however, as recent clinical and preclinical reports suggest that an "obesity paradox" may also exist, which is associated with increased efficacy and T-cell responses following ICI compared with normal BMI cohorts.[15 16] The mechanisms underlying this increased efficacy are still not clear, but may in part, be due to the nutrient-rich environment of sugars and fatty acids in obesity needed to fuel T-cell function once removal of the inhibitory signals by ICI are provided. It has not been determined whether this same type of obesity paradox also applies to NK cells if an ICI approach is applied since most studies have only reported on the net inhibitory effect obesity has on both NK cell numbers and function.[12] Part of the complicating issue revolves around the study of NK cells in general, as interpretation of clinical data has been hampered by the divergent markers used to delineate NK cells and subsets, as well as the reliance on circulating NK cells for assessment (vs assessment of intratumoral NK cells or resident NK cells in solid tissues such as the liver and lung).[4] Preclinical studies involving obesity, while more controlled, have been limited by the significant species differences between mouse and human NK cells (species differences regarding NK cells which, surprisingly, are much greater than with T cells),[1] as well as issues with xenogeneic studies as human NK cells engraft very poorly in mice unless provided with exogenous human cytokines.

Thus, critical questions remain regarding the inhibitory impact of obesity on NK cells. How exactly is obesity impairing NK cell function? Is it solely a functional deficit or are differentiation and/or survival pathways also affected? Are the effects direct, indirect, or both, given the increased immunosuppressive cell types in obesity (figure 1)? Do the inhibitory effects occur over certain periods of time? What NK functions (proliferation, activation, survival, cytokine production or skewing, cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), subset differences) are affected? To what extent are any direct effects reversible? How would this affect adoptive NK cell transfer in obese patients? Are increased off-target effects or toxicities possible given what has been observed with other immune-stimulatory therapies? Finally, what preclinical models and readouts would best address these questions? Recent studies indicate that certain fatty acids and lipids that dominate in obesity may directly impair NK cell function and these suppressive effects may be reversible.[13 17] This is also supported by studies demonstrating that bariatric surgery[18] and more recently, glucagon-like peptide-1 (GLP-1) agonists, also appear to mitigate NK dysfunction.[19] Delineating the effects of excess adiposity versus dietary or metabolic effects is also important to consider. While the effects of obesity on endogenous NK cells have been studied, the effects on adoptive cell therapies (ie, CAR-NK, cytokine-induced memory NK cells) have not, and preclinical studies would be revealing given the potential for off-target toxicities, which may also be augmented due to the meta-inflammatory state in obesity. The question then arises as to whether the inhibitory effects of obesity should be viewed as an exclusionary clinical criterion when designing NK cell

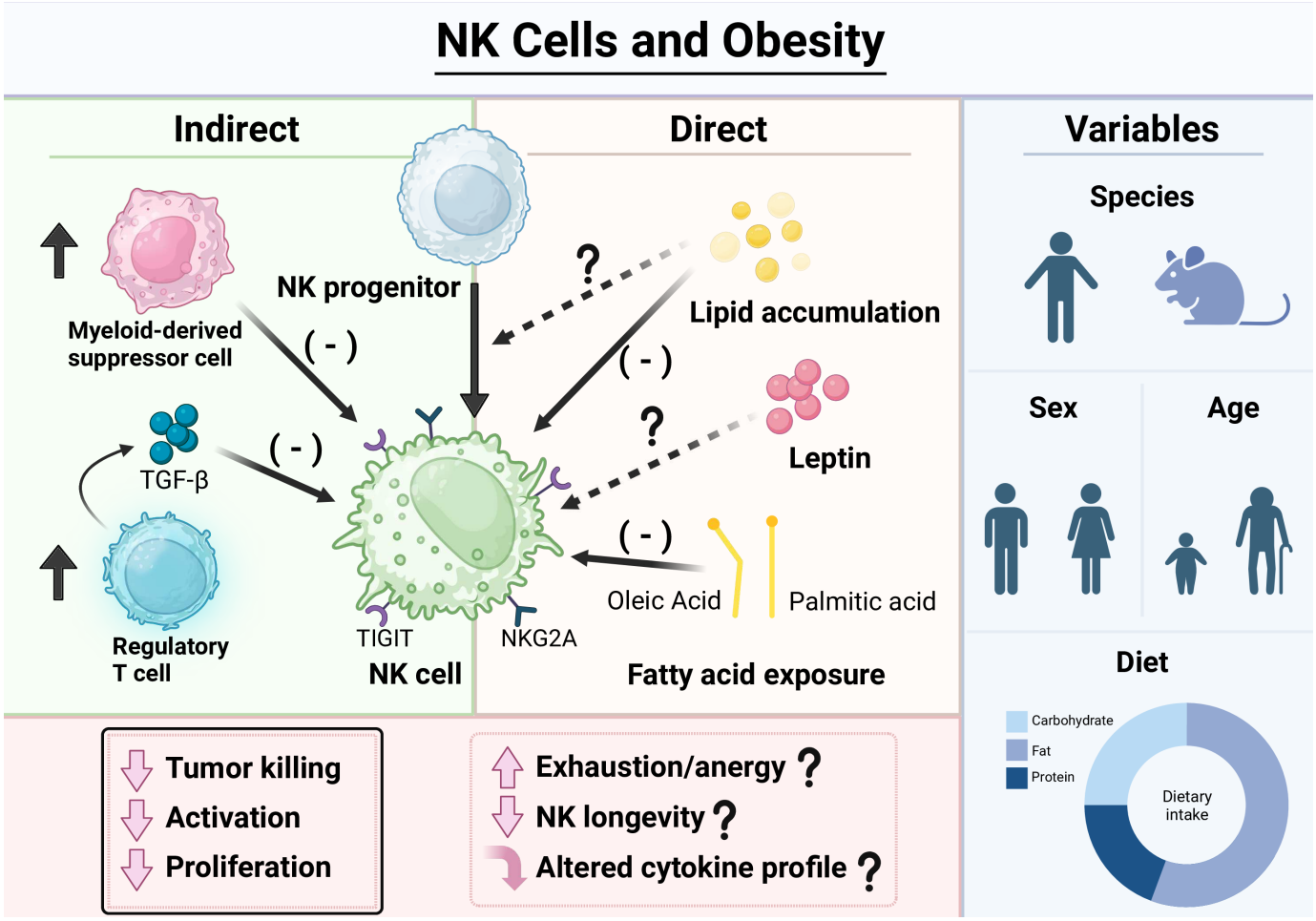

Figure 1 Framework for obesity-driven suppression of NK cells. Obesity increases regulatory T-cell and myeloid-derived suppressor cell numbers. These immune mediators can indirectly suppress NK cells either through inhibitory receptor-ligand interactions or cytokines such as transforming growth factor-β (TGF-β). The high free fatty acid content in obesity can directly suppress NK cells and intracellular accumulation of lipids also can impair NK cells by affecting histone deacetylation. Increased adipokines (such as leptin) may also directly affect NK cell biology. Impaired NK cells in obesity are characterized phenotypically by high expression of inhibitory receptors such as TIGIT and NK group 2 member A (NKG2A) and functionally associated with poor tumor killing, activation, and proliferative capacities. It is unclear if NK cell differentiation is adversely impacted. Obesity may also drive NK cell exhaustion/anergy but also reduce NK cell longevity and alter their cytokine profile and due to normal NK cell turnover rates, it is unclear if these effects are reversible on the mature NK cell. Assessment of obesity-driven suppression of NK cells is confounded by significant species differences in NK cell biology and can be affected by additional variables such as sex, diet, and age. NK, natural killer; NKG2A, NK group 2 member A; TIGIT, T cell immunoglobulin and ITIM domain.

therapies or simply considered as a confounding factor since it may significantly impact efficacy determination. Fortunately, these critical questions can be addressed by using more comprehensive preclinical modeling incorporating obesity into both syngeneic and xenograft studies. This would allow better determination of whether NK cell exhaustion or anergy is increased in obesity as well as how NK differentiation and/or survival pathways are impacted. If NK exhaustion or anergy is increased in obesity, then an interesting question arises if a similar paradigm of the T-cell obesity paradox exists where even greater increased function occurs if a checkpoint target such as targeting T cell immunoreceptor with Ig and ITIM domains (TIGIT) or lymphocyte activation gene 3 (LAG3) is applied compared with lean subject responses. Thus, despite the suppressive effects obesity has on NK cells, the question remains as to when to include obesity as a limiting factor regarding NK cell therapies and what effect it should have on patient selection. This will also likely be highly contingent on the therapy and NK cell function needed for efficacy. Given the current trajectory of obesity within the patient population, these issues and questions will only grow in importance.

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