frontiers | Frontiers in Immunology

REVIEW
published: 04 July 2022
doi: 10.3389/fimmu.2022.943333

Translating MSC Therapy in the Age of Obesity

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Mesenchymal stromal cell (MSC) therapy has seen increased attention as a possible option to treat a number of inflammatory conditions including COVID-19 acute respiratory distress syndrome (ARDS). As rates of obesity and metabolic disease continue to rise worldwide, increasing proportions of patients treated with MSC therapy will be living with obesity. The obese environment poses critical challenges for immunomodulatory therapies that should be accounted for during development and testing of MSCs. In this review, we look to cancer immunotherapy as a model for the challenges MSCs may face in obese environments. We then outline current evidence that obesity alters MSC immunomodulatory function, drastically modifies the host immune system, and therefore reshapes interactions between MSCs and immune cells. Finally, we argue that obese environments may alter essential features of allogeneic MSCs and offer potential strategies for licensing of MSCs to enhance their efficacy in the obese microenvironment. Our aim is to combine insights from basic research in MSC biology and clinical trials to inform new strategies to ensure MSC therapy is effective for a broad range of patients.

Keywords: mesenchymal stromal cells (MSCs), disease microenvironment, obesity, immunomodulation, metabolic disease

OPEN ACCESS

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Specialty section:
This article was submitted to Alloimmunity and Transplantation, a section of the journal Frontiers in Immunology

Received: *13 May 2022*
Accepted: *10 June 2022*
Published: *04 July 2022*

Citation:
Boland L, Bitterlich LM, Hogan AE, Ankrum JA and English K (2022) Translating MSC Therapy in the Age of Obesity. Front. Immunol. 13:943333. doi: 10.3389/fimmu.2022.943333

INTRODUCTION

The recent SARS-CoV-2 pandemic has prompted an increased interest in mesenchymal stromal cells (MSCs) as a therapeutic to treat acute respiratory distress syndrome (ARDS) (1–6). In contrast to unregulated and often predatory "stem cell clinics" that have cast MSC therapy in a bad light, academic labs, regulatory bodies, professional societies and industry continue to advocate for and adopt rigorous standards, thoughtfully designed clinical trials, and diligent scientific studies to develop high-quality cellular products for patients with life-threatening disease (7). Ten MSC cell therapy products have been approved for use in major indications including graft versus host disease (GvHD), Crohn's disease, and myocardial infarction (8). As more MSC based therapies gain approval, it is prudent to look to the challenges that exist on the horizon as these therapies are applied to a broad, complex, and heterogeneous patient population. An increasingly common challenge to the translation of other immunotherapies has been the influence of metabolic disease on a patient's clinical response (9, 10). Obesity and other metabolic syndromes alter the immune system and have proven consequential to

patient responses to immunotherapies, begging the question: how will MSC therapy perform as an immunomodulatory therapy when placed within metabolically diseased environments?

With the rising incidence of obesity throughout the world, the average patient being treated with cellular therapies, including MSC therapy, will increasingly have comorbid obesity (11–13). As of 2018, over 40% of Americans are living with obesity and about 1 in 10 American women are classified in the severe obesity category (BMI≥40 kg/m^2) (14). In Europe, 36% of the population are considered pre-obese and 17% obese, based on a study in 2019 (15). Obesity is associated with a substantially increased risk for a number of comorbid diseases, including type 2 diabetes mellitus (T2DM), hypertension, and coronary artery disease (16–18). In the clinic, these epidemiological shifts translate to a rise in complex patients presenting with metabolic comorbidities in addition to their primary diagnosis, as well as to 42% higher total healthcare expenditures in patients living with obesity (19). Unfortunately, the ubiquity and chronicity of obesity often lulls us into a belief that it is innocuous; however, the pathological effects of obesity cannot be understated. Patients living with class 2 or 3 obesity have a ~30% higher risk for all-cause mortality than their non-obese age- and sex-matched counterparts (13, 20). Additionally, an umbrella review from 2017 concluded that 11 out of 36 cancer types are positively associated with obesity (21). As we aim to translate MSC therapies in the era of obesity, we must take the time to understand the consequences metabolic disease has on specific applications of MSC therapy.

Obesity is clinically defined as a body mass index (BMI) greater than 30 kg/m^2 (11). However, underlying cellular and molecular changes reveal a much more complex story of obesity than BMI can capture (22–26). Key pathologic features of overt obesity include ectopic lipid deposition, broad hormonal disturbances, and a substantially elevated risk of developing metabolic syndrome (27–29). While a significant focus of obesity research has been on the function of the liver and adipose tissue in obesity, systemic ramifications should not be overlooked (30, 31). Early observations in the 1990s of obesity-induced increases in systemic pro-inflammatory cytokines were integral in recontextualizing obesity not solely as a disturbance of metabolism, but of the immune system, as well (32–34). Since that time, insight into the degree and specificity of obesity's effects on particular immune populations has grown rapidly. Obesity-induced alterations in the composition, activity, metabolism, and effector response of the immune system have lent much needed insight into the potential mechanisms by which obesity alters disease severity, progression, and response to therapies for immune-mediated pathologies (35–40). Because MSC therapy relies on paracrine activity and cell-to-cell interactions (41, 42), significant questions remain regarding whether MSCs can appropriately function within this environment. It remains unknown if patient BMI may affect responsiveness to MSC therapy. Since the immune system is grossly altered in patients with comorbid obesity it remains to be seen whether the recipient immune populations are present, functional, and responsive to MSC mechanisms of action. Additionally, critical features that make allogeneic MSC therapy possible (43, 44), notably the high hemocompatibility and low immunogenicity profile of MSCs, may be modified by exposure to obese environments, thus potentiating the risk for adverse events (45–49).

There are still notable outstanding questions that remain to be answered to determine how and if MSC therapy can optimally function within an obese environment. Questions that remain unanswered include: do biomarkers within patients with obesity help predict responsiveness to MSC therapy? and does treating obesity or T2DM improve MSC immunosuppression? In this review, we examine emerging data from cancer immunotherapy as a model for the challenges MSC immunotherapies may face in obese environments. We then summarize the current evidence that obesity alters critical features intrinsic to the health and function of autologous MSCs, drastically modifies the host immune system, and reshapes crosstalk between MSCs and immune cells. We challenge the assumption that essential features of allogeneic MSC therapy (high hemocompatibility and low immunogenicity) will inherently be maintained in obese environments. Finally, we suggest ways to re-train MSCs from individuals living with obesity, to restore their therapeutic efficacy. Our goal is to draw critically needed attention to the influence of metabolic environments on MSC therapies in order to guide new clinical and basic research questions that will ensure that emerging therapeutics are available to all patients regardless of metabolic health.

LESSONS FROM CANCER IMMUNOTHERAPY

Cancer immunotherapy has served as a forewarning for the potent modifying effect of obesity on immunotherapies and provides insight as to the potential effects that obesity may have on MSC therapeutic functions that are necessary for other indications. For some varieties of cancer, immunotherapies have replaced classic cytoreductive therapies as primary treatment modalities due in part to lower rates of adverse events and decreases in systemic off-target effects (50). Cancer immunotherapies harness the immune system to precipitate an anti-tumour response (51, 52). However, obesity has been shown to alter the efficacy, tolerance, and toxicity profiles for multiple cancer immunotherapies (10, 53–56). As a therapeutic regimen that relies on modulation of the patient's immune response, cancer immunotherapy can be used as a proof-of-concept model for MSC therapy, which relies on interactions with many of the same players in the adaptive and innate immune system (57–59).

Obesity has emerged as a potent modifier of the efficacy and toxicity of a variety of cancer immunotherapies. In three distinct preclinical murine models of obesity (high-fat diet, aged-related *ad libitum* fed, and leptin-receptor deficient *db/db* mice), immunostimulatory therapy with anti-CD40 antibodies and IL-2 resulted in complete lethality in obese mice, while non-obese mice and calorie-restricted aged mice survived and showed a positive anti-tumour response (55, 60). Lethality in obese

animals was driven by elevated levels of serum inflammatory cytokines, which is a common driver of immune-related adverse events in patients treated with immunotherapy. Blocking macrophage responses with TNFα neutralizing antibodies or depletion by clodronate liposomes abrogated the toxic effects of immunostimulatory therapy in obese animals. Therefore, obesity-induced alterations to specific immune cell populations can alter the risk of adverse events during treatment with immunomodulatory therapies.

Intriguingly, immune checkpoint blockade with an anti-CTLA-4 antibody shows a differential response between obese mice cohorts (61, 62). In an orthotopic model of renal cell carcinoma, diet-induced obese (DIO) mice showed no therapeutic anti-tumour response to anti-CTLA-4 therapy. However, obese *ob/ob* mice, which have a genetic deletion of the satiety hormone leptin, showed effective anti-tumour responses. DIO mice had serum leptin levels 40-times higher than *ob/ob* animals, more closely reflecting obesity in humans. To determine if leptin contributed to the differential response to immunotherapy, the researchers neutralized leptin prior to anti-CTLA-4 therapy, which restored anti-tumour effects in DIO mice. This work specifically implicated elevated leptin levels as a modifier of immunotherapy response. Therefore, in addition to changes in host immune populations, obesity-induced hormonal changes can modify responsiveness to immunomodulatory therapies. With a hormone-centric focus, actual fat mass itself may be a poor predictor of therapeutic responsiveness, while serum hormone levels may serve as better response predictors (63–65). Similarly, immunotherapies targeting programmed cell death protein 1 (PD-1) show decreased success in obese mice (66), which a different study links to a leptin-dependant increase in PD-1 expression on $CD8^+$ T cells in humans (10). In the case of cancer immunotherapy, obesity can alter efficacy and toxicity, highlighting the need to understand both parameters when applying these lessons to MSC therapy.

Although obese murine models predicted that obesity in human patients would result in poorer overall response rates, emerging clinical data has demonstrated the opposite. In one retrospective study in patients with metastatic melanoma treated with anti-PD-L1, men living with obesity were found to have a significant survival advantage compared to normal-overweight men (67). An analysis of patients treated with anti-PD-L1 therapies showed a notable beneficial effect of elevated BMI regardless of sex, with patients living with obesity showing greater overall survival (10). In this study, obese, otherwise healthy, patients had increased circulating $PD1^+$ T cells with low proliferative capacity, suggestive of T cell exhaustion. Interestingly, obesity was associated with T cell exhaustion across several species and models and drove faster tumour growth in murine models; however, immunotherapy in obese human patients provided a significant survival benefit. A potential explanation for this surprising finding provided by the authors was that immune checkpoint blockade may revive an immune system otherwise exhausted by the chronic inflammation of obesity, thus potentiating a stronger immunologic anti-tumour response in patients living with obesity. In opposition to these findings, a more recent study reported obesity-induced lower PD1 levels in T cells, which correlated with lower PD-L1 levels in tumour cells of both mice and humans. However, immunotherapy was still effective in a mouse model, and human patients who underwent weight loss experienced tumour regression, suggesting that obesity-induced defects of T cells are reversible (68). It is important to note that immune checkpoint blockade, including anti-PD-L1 therapy, is an immunostimulatory therapy, in which a critical brake on the immune system is released to precipitate an anti-tumour response (69). In contrast, the main therapeutic aim of MSC therapy in diseases like GvHD is to dampen hyperactive immune responses (70). Therefore, it is unclear if MSC therapy in a similar patient base would show an equivalent benefit or be at a significant disadvantage in a more inflammatory and exhausted environment.

IMPACT OF DISEASE MICROENVIRONMENT ON MSC EFFICACY

The patient's microenvironment is a major factor in the efficacy of MSC therapy in GvHD. If MSCs are administered too early in pre-clinical models of acute GvHD, they fail to dampen the GvHD response as levels of the pro-inflammatory cytokine IFN-γ, which is known to activate MSC immunomodulatory function, are too low (71, 72). Furthermore, interactions between MSCs and immune cells are of utmost importance in dictating response to MSC therapy. A small study investigating differences between responders and non-responders to MSC therapy for GvHD found that patients with high peripheral blood lymphocyte counts ($CD3^+$ T cells and $CD56^+$ NK cells) before MSC therapy responded better (73). In addition strong cytotoxicity towards MSCs by peripheral blood mononuclear cells (PBMCs) from GvHD patients (74) was associated with a better response to MSC therapy. The gut is a key organ in the pathophysiology of aGvHD and retrospective assessment of gut mucosa biopsies from a small number of patients (n=16) pre and post MSC therapy for GvHD has shown that the tissue immune profile of the gut is distinct in non-responders to MSC therapy (75). Importantly, obesity can promote (76) and even worsen aGvHD, leading to decreased survival in both mice and humans (77). These effects have been partially ascribed to diet-induced changes in the host gut microbiota (77, 78). Surprisingly, no study has investigated the impact of the obese microenvironment on MSCs in GvHD and equally little is understood about how the host gut microbiota might influence MSC therapeutic efficacy.

Conversely, obesity seems to reduce mortality in ARDS. While obesity generally increases the risk for the development of ARDS (79–81) and can even lead to additional acute kidney injury (82), patients with moderate obesity experience a lower mortality from ARDS than lean patients (79–81, 83). This

"obesity paradox" makes it difficult to predict the efficacy of MSC therapy in ARDS patients living with obesity, as the inflammatory response is already impaired due to exhaustion from the chronic low-grade inflammation of the obese microenvironment (80), potentially making the patient unresponsive to further immunosuppression by MSCs.

Determining the effect of comorbid obesity on MSC efficacy and toxicity is currently difficult to do for two essential reasons. First, much of the clinical trial data testing MSC therapies remains unpublished (7, 84) and, second, metabolic parameters are either not captured or not reported in published MSC clinical trial data. A search on March 9, 2022 of ClinicalTrials.gov for "mesenchymal stem cells", "mesenchymal stromal cells" OR "mesenchymal precursor cells" returned 1487 clinical trials. However, pairing "BMI", "body mass index", "obesity" OR "obese" with this search returned only 14 trials. In the primary literature, however, some insight into the interactions of metabolic disease and MSCs is beginning to unfold. In two Mesoblast trials for the treatment of diabetic nephropathy and T2DM, the average patient's BMI was obese (85, 86). In another trial using autologous MSCs to treat diabetes-associated critical limb ischemia, severe obesity was part of the exclusion criteria (87). Thus, not only are patients living with comorbid obesity actively being treated with MSC therapy, but BMI is currently being used to decide patient "fitness" for treatment. The ultimate lesson to be learned from the results of cancer immunotherapy is that the metabolic status of patients can influence therapeutic efficacy and toxicity and, as such, should not be overlooked in the design of MSC products and trials.

THE EFFECT OF OBESITY ON MESENCHYMAL STROMAL CELLS

Efficacy of Therapy With Lean MSC in Obese Subjects

Nearly all studies investigating the therapeutic efficacy of healthy MSCs in subjects with obesity are pre-clinical models using high-fat diet (HFD). Application methods, treatment regimens, and tissue sources vary, but lead to similar outcomes (**Table 1**). Mice with diet-induced obesity that were given human adipose tissue MSCs (atMSCs) *via* intraperitoneal (i.p.) injections twice two weeks apart showed a decrease in fat mass and, more interestingly, a decrease of atherogenic index of plasma (AIP) levels (88). The AIP is a logarithmically transformed ratio of molar concentrations of triglycerides to HDL-cholesterol and serves as a marker of cardiovascular disease (96).

This suggests that therapy with lean MSCs has a positive effect on heart health, which is corroborated by a study in which HFD-fed mice with cardiac arrhythmias were given murine bmMSC, murine bmMSC conditioned medium (CM), or unconditioned cell culture medium intravenously multiple times over the course of a month. At the end of the treatment, the cardiac arrhythmias were reversed, adiponectin levels were restored to those observed in lean mice, and TGF-β1 levels were decreased. HFD-fed mice treated with cell culture medium as a control showed high levels of heart fibrosis which were much lower in their murine bmMSC or bmMSC-CM treated counterparts (95). As the AIP is associated with the concentration of triglycerides which are in turn correlated with the severity of non-alcoholic fatty liver disease (97) it would stand to reason that MSC should also be able to alleviate the symptoms of HFD-induced liver damage. Indeed, this seems to be the case (98–102). Intraperitoneal injection of human atMSC every 2 weeks for 10 weeks decreased both lipotoxicity and fat accumulation in the liver of HFD mice (89). A single dose of human atMSC that had been genetically modified with adenovirus constructs to overexpress one of two antioxidants, either superoxide dismutase 2 (Sod2) or catalase (Cat), improved hepatic steatosis and systemic inflammation significantly after just 4 weeks. Fewer fat cells were found in the liver of both treatment groups compared to the control, and plasma TNF-α levels were lower (91).

Additional positive effects on the systemic manifestations of metabolic syndrome have been described. Intramuscular injection of human atMSCs (90), injection of murine atMSCs into visceral epididymal adipose tissue (94), and intraperitoneal

TABLE 1 | Therapeutic effect of lean MSCs in obesity.

MSC type	Model	Therapeutic effect	Reference
human atMSCs	mice with diet-induced obesity	decreased fat mass, decreased AIP levels	88
human atMSCs	HFD-fed mice with liver damage	decreased lipotoxicity and fat accumulation in liver	89
human atMSCs	mice with metabolic syndrome	decreased blood glucose, improved insulin sensitivity, decreased triglyceride levels	90
human atMSCs (overexpressing Sod2 or Cat)	HFD-fed mice with hepatic steatosis	improved hepatic steatosis and systemic inflammation	91
human amniotic MSC CM	mice with metabolic syndrome	decreased blood glucose, improved insulin sensitivity, decreased weight gain	92
human umbilical cord MSCs	humans with osteoarthritis	improvement of osteoarthritis in both lean patients and patients with obesity	93
murine atMSCs	mice with metabolic syndrome	decreased blood glucose, improved insulin sensitivity, decreased triglyceride levels	94
murine bmMSCs	HFD-fed mice with cardiac arrhythmias	reversal of cardiac arrhythmias, restoration of adiponectin levels	95

HFD, high fat diet; AIP, atherogenic index of plasma; Sod2, superoxide dismutase 2 (Sod2); Cat, catalase.

injection of human amniotic MSC CM (92) all significantly decreased blood glucose levels and improved insulin sensitivity. The human and murine atMSCs further caused a significant drop in serum triglyceride levels (90, 94) which has the potential of being cardioprotective (96). Human amniotic atMSC CM led to increased energy expenditure, elevated thermogenesis, and inhibited adipogenesis by suppressing the expression of genes required for the differentiation of pre-adipocytes. As a result, these mice experienced lower weight gain than the control group (92).

A small human study showed that the administration of human umbilical cord blood-derived MSCs improves osteoarthritis of the knee in both lean patients and patients living with obesity, with patient age being a much more relevant factor in treatment outcome than body weight (93). In summary, lean MSCs administered into an obese microenvironment maintain their therapeutic value and can reduce the negative effects associated with metabolic syndrome, however, the therapeutic efficacy of MSCs in pro-inflammatory conditions such as GvHD and ARDS in the setting of an obese microenvironment remain to be investigated.

Therapeutic Efficacy of Obese MSCs

Although MSCs isolated from patients with sickle cell disease (103), GvHD (104), and Crohn's disease (105) show functional equivalence to MSCs from healthy donors, a growing body of evidence demonstrates that MSCs isolated from patients with metabolic disease are fundamentally altered (106–110) (**Tables 2**, **3**). Under the influence of the obese microenvironment, immune cells become dysregulated in their function and undergo phenotypic changes (116). Similar effects seem to apply to obese human atMSCs, as early studies from Kizilay-Mancini and colleagues demonstrated that atMSCs isolated from patients with obesity-related comorbidities had a significantly lower suppressive effect on activated T cells (108), and bmMSCs isolated from patients with >10 years history of T2D exhibit a compromised metabolism (117). Notably, while the study by Kizilay-Mancini et al. showed a drop in immunosuppressive ability, other studies have actually shown an increase in T-cell stimulation when using atMSCs from patients with obesity. Serena et al. found that conditioned media from obese-T2D atMSCs led to more T cell proliferation in mixed lymphocyte reactions secondary to NLRP3 inflammasome activation (109). Additionally, in a study by Ritter et al., obese atMSCs actively secreted higher levels of IL-6 and TNFα and lower levels of adiponectin compared to lean controls (113). Moreover, obese atMSCs can secrete harmful proteins like osteoclast stimulation factor 1 (Ostf1), which can promote osteoporosis (118), polarise murine macrophages towards a pro-inflammatory M1 instead of an anti-inflammatory M2 phenotype (111), and suffer from increased early senescence (112). This shift between pro- and anti-inflammatory cytokines could potentially explain the pro-inflammatory effect of obese atMSCs. It is critical to note that these findings suggest that obese atMSCs may not simply fail to appropriately suppress inflammation but may amplify existing inflammatory processes.

While the previous studies were conducted using *in vitro* potency assays, only a few studies have validated the effect of

TABLE 2 | Differences in therapeutic action of lean and obese MSCs *in vitro*.

MSC Source	Modulated cells	Lean MSCs	Obese MSCs	Cause of difference in therapeutic action	Reference
Human atMSC CM	Human PBMCs	suppression of proliferation	weak suppression of proliferation	inflammasome activation (T2DM > Obese)	109
Human atMSC CM	Mouse T cells (MOG)	suppression of proliferation	increased proliferation	not clear	110
Human atMSC CM	Human THP1 Macrophages	polarisation towards M2 phenotype	weak polarisation towards M2 phenotype	inflammasome activation	109
Human atMSC	Macrophages (RAW264.7 and SIM-A9 (microglia)	no effect on phenotype	strong polarisation towards M1 phenotype	not clear	111
Transwell		increased migration	no effect on migration	not clear	111
		no effect on phagocytosis	decreased phagocytosis	not clear	111
Human atMSC	HUVEC	promotion of angiogenesis: tube formation and enhanced production of VEGF in injured HUVEC cells	no promotion of angiogenesis: tube formation, no production of VEGF in injured HUVEC cells	not clear, but may be associated with senescence phenotype in obese human atMSC	112
Human atMSC	None tested	normal cilia and cilia associated functions in lean atMSC. Normal differentiation, motility and secretion.	shortened and deficient cilia. increased production of IL-6 and TNF-α and decreased adiponectin. Impaired differentiation, motility and secretion.	Obesity (hypoxia, TNF-α, IL6) induced expression of Aurora A and its downstream target HDAC6. Inhibition of Aurora A or HDAC6 rescues cilium length and function of obese atMSC	113
Human atMSC	Human CD4+ T cells	suppression of proliferation	weak suppression of proliferation	oxidative stress due to mitochondrial dysfunction	106, 108

T2DM, type II diabetes mellitus; MOG, myelin oligodendrocyte glycoprotein; HUVEC, human umbilical vein endothelial cells; VEGF, vascular endothelial growth factor; IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha; HDAC6, histone deacetylase 6.

obese atMSCs in *in vivo* model systems. In one study of experimental autoimmune encephalitis, only lean atMSCs could effectively lower clinical score (110). When obese MSCs were administered at the onset of disease there was a higher total lesion area in the spinal cord compared to vehicle treated controls. In addition, lean MSCs but not obese MSCs protected against ischemic injury, reducing renal atrophy and alleviating renovascular hypertension in mouse models of renal artery stenosis (94, 114, 115). Therefore, both *in vitro* and *in vivo* analyses of immunomodulatory behaviour in MSCs isolated from patients with metabolic disease support a compromised immunomodulatory phenotype (**Tables 2**, **3**). However, it remains to be determined which factors present in obesity alter MSC immunomodulation.

One possible reason for this dysfunction of obese MSCs is metabolic reprogramming, which leads to changes in the cellular metabolism resulting in altered functions. Obesity can lead to metabolic reprogramming in immune cells including natural killer (NK) cells, which become blunted in their ability to reduce tumour growth (37) and experience exhaustion when challenged with the pro-inflammatory cytokines IL-15 and IL-2 (119). A switch to glycolysis is required for NK cells to produce cytokines and exhibit cytotoxic effects on tumour cells, but is impaired in obese NK cells (37).

In MSCs, glycolysis is of similar importance for immunomodulation. When glycolysis of MSCs is impaired through silencing of hypoxia-inducible factor 1-alpha (HIF-1α), expression of ICAM, IL-6, and NO_2 is reduced, resulting in a decreased ability to suppress T cell proliferation (120). Correspondingly, boosted glycolysis promotes stronger T cell suppression (121, 122) and an overexpression of HIF-1α is associated with the recruitment of anti-inflammatory monocytes and a higher resistance of MSCs against lysis by NK cells (123).

Current gaps in knowledge regarding how components of the obese environment individually and collectively affect MSC phenotype will need to be addressed if we are to understand how best to use MSCs to treat patients with comorbid metabolic disease.

CONSEQUENCES OF OBESITY-INDUCED ALTERATIONS TO THE IMMUNE SYSTEM FOR MSC THERAPY

The breadth of alterations to immune cell populations in obesity is staggering (31, 39, 40). In the treatment of immune-mediated pathologies, MSCs directly or indirectly interact with immune cells to promote an immunosuppressive state (41, 42). Therefore, alterations in the basal immune system in the setting of obesity, may have critical consequences for MSC therapeutic efficacy. In this review, we focus on how obesity affects three immune cell populations; T cells, monocytes/macrophages, and NK cells, because of the extensive interactions of MSCs with these cells (**Figure 1**).

T Lymphocytes

T lymphocytes are essential players in the adaptive immune system that can initiate, maintain, suppress, and/or amplify inflammation and tissue damage in autoimmunity and hyperactive immune responses (124). As such, the ability of MSCs to modify T cell response has been a major focus in understanding MSC immunomodulation within diseases like GvHD and multiple sclerosis, wherein T cells drive pathology (72, 125, 126). Early work identifying the immunosuppressive mechanism of MSCs showed that MSC infusion correlated with increased numbers of T regulatory cells (T_{REG}), a potent regulatory population that aids in the maintenance of peripheral tolerance (125). This finding has subsequently been corroborated by several groups in both *in vitro* and *in vivo* analyses (127–129). The production of indoleamine-2,3-dioxygenase (IDO) appears to be critical for MSC induction of T_{REG} (130–133). In patients with multiple sclerosis, the total number of circulating T_{REG} is decreased, which has been suggested to play a role in the breakdown of self-tolerance (134). Additionally, during allogeneic hematopoietic stem cell transplant, increasing T_{REG} has been shown to decrease GvHD severity (135). Therefore, the MSC-T_{REG} axis is of crucial importance in the treatment of autoimmune disease and post-transplant tolerance (136–139).

TABLE 3 | Studies comparing lean versus obese MSC therapeutic efficacy in disease models.

MSC Source	Disease Model	Lean MSC	Obese MSC	Cause of difference in therapeutic action	Reference
Human atMSC (1x10^6 i.p.)	Mouse Experimental autoimmune encephalitis	improved clinical score (inflammation, lesion size, preserved myelin) in mice with experimental autoimmune encephalitis	no improvement in mice with experimental autoimmune encephalitis	increased expression of pro-inflammatory cytokines	110
Human atMSC (5x10^5 intra-aorta)	Mouse Renal stenosis	normalisation of ischemic kidney cortical perfusion in stenotic mouse kidneys	no effect on ischemic kidney cortical perfusion in stenotic mouse kidneys	increased cellular senescence	114
Human atMSC (5x10^5 intra-aorta)	Mouse model of renal artery stenosis	normalisation of renovascular hypertension	partial alleviation of renovascular hypertension	not clear	115
Human atMSC (5x10^5 intra-aorta)	Mouse model of renal artery stenosis (RAS)	small improvement in renal atrophy. decreased M1 macrophages, M1/M2 ratio and inflammation in RAS kidneys	no improvement in renal atrophy. M1 macrophages remained high	obese MSC had a pro-inflammatory phenotype releasing more TNF-α	94

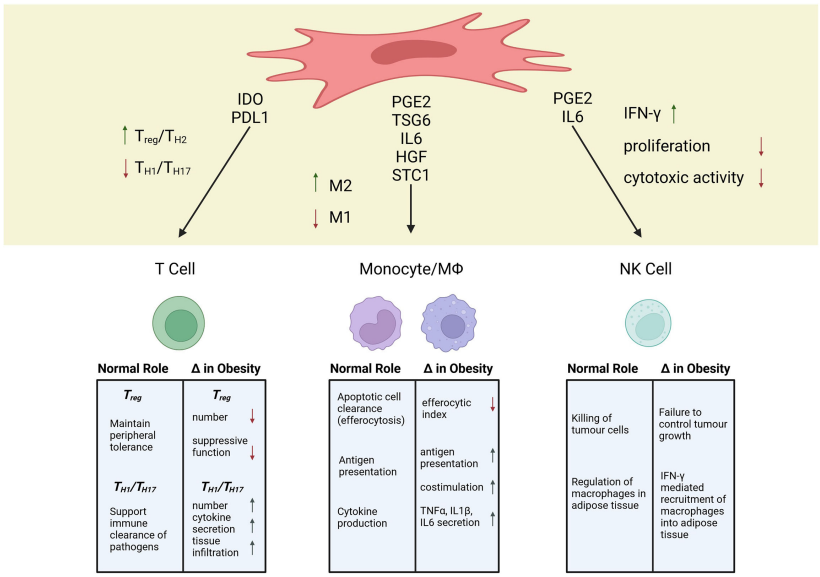

FIGURE 1 | Mechanisms of MSC Immunosuppression and Alterations to Immune Populations in Obesity. Created with BioRender.com.

In the setting of metabolic disease, T_{REG} show a number of alterations that could impact interactions with MSCs. In human visceral adipose tissue, there is a negative correlation between *FOXP3* transcripts (a marker of T_{REG}) and BMI, indicating a lower regulatory profile in patients living with obesity (140). In addition, human studies have found a negative correlation between circulating T_{REG} numbers and BMI, as well as, markers of systemic inflammation (141, 142). Although correlations have been identified, the mechanistic underpinning as to why T_{REG} are altered in metabolic disease is still an evolving research area (124). To date, specific components elevated in the obese serum environment have been shown to modify T_{REG} behaviour. Leptin, which tends to be elevated in the serum of patients with obesity (143), has been shown to suppress T_{REG} proliferation, while leptin deficiency is associated with a higher frequency of T_{REG} (144, 145). When exposed to high insulin levels, IL10 secretion by murine T_{REG} is attenuated, thereby reducing their ability to block TNFα production from LPS-stimulated macrophages (146). Hyperinsulinemia appears, therefore, to compromise the immunosuppressive potential of T_{REG}. If MSCs rely on T_{REG} to facilitate long-term immunosuppression, this finding could indicate that hyperinsulinemic environments may compromise MSC mediated immunosuppression. Notably, in patients with multiple sclerosis and metabolic syndrome, treatment with metformin, a commonly prescribed first-line treatment for T2DM, significantly enhanced the number and potency of circulating T_{REG} (147). Therefore, treating underlying metabolic disease can positively affect comorbid immune-mediated pathologies through modulation of T_{REG} function.

While the MSC-T_{REG} axis is clearly a major player in the setting of autoimmune disease, the ability of MSCs to dampen pro-inflammatory Th1/Th17 populations is also essential (70). *In vitro* studies of MSC immunomodulatory potency have routinely demonstrated that MSCs suppress the proliferation and activity of allogeneic Th1 cells (41). In a humanized mouse model of GvHD, the ability of MSCs to decrease mortality was independent of T_{REG} induction, but was, rather, due to suppression of $CD4^+$ T effector cell expansion and TNFα production (72, 148). An essential pathway by which MSCs control Th1 responses is through expression and secretion of PD-L1, a ligand for PD1 (57, 58). A less comprehensive picture exists for MSCs ability to modulate Th17 responses. Several early studies showed that MSCs could inhibit Th17 differentiation and cytokine production. However, nearly all of these studies were conducted with murine MSCs, which have distinct immunomodulatory programs compared to human (149, 150). Conversely, in a study of human bone marrow MSCs, *in vitro* incubation with MSCs resulted in higher Th17 cytokine secretion from activated PBMCs, due to MSC production of PGE2 (151). However, patients treated with MSC infusion for acute GvHD show either a modest suppression of or no difference in Th17 numbers (125, 152). Th17 and T_{REG} both differentiate from naïve T cells *via* TGFβ signalling (153). Therefore, one mechanism by which MSCs modulate Th17 cells may be through preferential induction of T_{REG}. However, further analysis of human MSCs and Th17 cells is critically needed to better understand their potential interaction *in vivo*.

Patients with metabolic disease have significant changes in Th1/Th17 immune cell populations. Within the visceral adipose of patients with metabolic disease, Th1 numbers and function are increased, which is integral to initiation and maintenance of meta-inflammation (31, 154). Additionally, both adults and children with obesity have elevations in Th17 cytokines, which is associated with T2DM and an IL-17 mediated disturbance of insulin signalling (35, 38, 155, 156). This increased Th17 cytokine production appears to be linked to obesity-associated

mitochondrial dysfunction in T cells (157). Given the poorly understood interaction between MSCs and Th17 cells, the dominance of this Th17 profile within patients living with obesity and T2DM is concerning. Interestingly, in a study of patients living with obesity but no metabolic disease, higher numbers of circulating T lymphocytes, but fewer naïve T cells were reported (158). Additionally, the percentage of $CD4^+$ effector memory T cells was higher in patients living with obesity. A murine model of high fat diet recapitulated this elevation in $CD4^+$ effector memory cells and showed that these cells infiltrated non-lymphoid tissues at higher rates compared to animals fed standard diet. Interestingly, this finding indicates that high-fat conditioning alone can influence the migration and activation state of $CD4^+$ T cells. Furthermore, Wang et al. showed higher rates of circulating T cells with an exhausted profile ($PD1^+$ with low proliferative rate) in obese, otherwise healthy patients (10). While intratumoural $CD8^+$ T cells from patients living with obesity have impaired function, expression of PD1 remains unchanged. This functional impairment is associated with alterations in $CD8^+$ T cell metabolism with decreased glutamine production which is required for normal cell function (68). Additionally, increased consumption of free fatty acids by tumour cells deprives $CD8^+$ T cells of this metabolite further impairing their activity (159).

While immunostimulatory therapies are effective at bolstering anti-tumour effects in the setting of obesity (10, 67), it is unclear how an immunosuppressive mechanism, like PD-L1 expression by MSCs, might behave in the same environment. It remains to be determined if MSCs are able to suppress activation of obese or T2DM T cells. What is clear is that particular T effector cell populations are sensitive to obese environments, supporting the idea that the obese "basal" immune system is unique and should be considered as such when designing and evaluating MSC therapies.

Monocytes/Macrophages

Given their broad and encompassing participation in many autoimmune and inflammatory disorders, monocytes and macrophages have been of keen interest in defining MSC immunomodulation (160–162). Monocytes and macrophages exist on a phenotypic spectrum that can broadly be defined as inflammatory (M1) or anti-inflammatory (M2) (163). However, the phenotype of monocytes and macrophages is highly plastic and, as such, can display a spectrum of intermediate and complex phenotypes (164). With that caveat in mind, incubation with MSCs or MSC conditioned media tends to cause a decreased inflammatory and increased anti-inflammatory profile in monocytes/macrophages (59, 165–168).

The ability of MSCs to modulate the balance between inflammatory and anti-inflammatory phenotypes in monocytes and macrophages has been linked to their production of PGE2 (169, 170, p. 14), TSG6 (171), IL6 (172), and HGF (173). PGE2 from MSCs modifies monocyte costimulatory ability and inhibits the maturation of monocyte subtypes (170, 174, 175). For bmMSCs, secretion of PGE2 is necessary to reprogram host macrophages toward an anti-inflammatory IL10-secreting profile (176). Additionally, Rozenberg et al. found that when $CD14^+$ cells were depleted from mixed PBMC cultures, MSC conditioned media could no longer dampen IFNγ production, indicating that MSCs effects on monocytes can influence subsequent T cell cytokine production (151). *In vivo*, a number of independent research groups have confirmed that secretome-based crosstalk between macrophages and MSC is essential in models of inflammatory and autoimmune diseases, including sepsis (176–178), allergic asthma (179, 180), peritonitis (181), colitis (182, 183), GvHD (184), and rheumatoid arthritis (185, 186). Although a unidirectional focus of MSC secreted factors to monocytes has been documented, a bidirectional crosstalk whereby secreted factors from either cell population can influence the other is likely more accurate. To this point, studies have shown that secretion of IL1β from $CD14^+$ cells was integral to initiating MSCs and MSC like cells -multipotent adult progenitor cells (MAPCs) immunosuppressive potency toward T cells (187, 188). Therefore, a bidirectional crosstalk of secreted factors both from and between monocytes and MSCs influences downstream immunosuppressive effects.

Interestingly, several secretome independent modes of MSC-myeloid cell interactions have recently been described. These emerging mechanisms include direct cytoplasmic communication through processing bodies (189), tunnelling nanotubules (190–192), transfer of extracellular vesicles and miRNAs (193, 194), and the uptake of apoptotic MSCs by host phagocytes (i.e. efferocytosis) (74, 195, 196). In a model of acute respiratory distress, Jackson et al. demonstrated that MSCs pass healthy mitochondria to stressed alveolar macrophages *via* tunnelling nanotubules (191). In addition, MSCs can release extracellular vesicles ranging in size and cargo. After uptake of MSC vesicles, macrophages show decreased sensitivity to mitochondrial damage by silica particles and attenuated inflammatory cytokine production (197). Finally, efferocytosis has emerged as an intriguing pathway by which MSCs leave a lasting impression on the host immune system. De Witte et al. found that by 24-72 hours after infusion the vast majority of MSCs were within circulating blood monocytes or resident macrophage populations (59). Additionally, Galleu et al. demonstrated that killing of MSCs by host cytotoxic T cells was predictive of the therapeutic response of patients treated with MSCs for acute GvHD (74). In a follow-up study, this group demonstrated that incubation with apoptotic MSCs increased immunosuppressive gene expression in macrophages, as well as secretion of IL10 and PGE2 (195). Overall, the unique feature of macrophages as professional phagocytes enables a broad range of MSC mechanisms of action that are still actively being uncovered. To date, no study has investigated if MSC efferocytosis is a functioning mechanism of obese monocytes/macrophages.

In obesity and metabolic disease, monocytes and macrophages are integral players in the initiation and sustained inflammation that drives systemic and adipose-specific physiological alterations (32, 33, 38–40, 198). A number of intrinsic features of monocytes and macrophages are compromised in patients living with obesity. Crown-like structures of macrophages within the adipose tissue are thought

to form to clear apoptotic adipocytes that die due to hypoxic, hypertrophic growth (28, 199). In murine models of diet induced obesity, clearance of apoptotic adipocytes was decreased in the absence of mannose-binding lectin, a protein that facilitates macrophage phagocytosis (200). As antigen-presenting cells within adipose, macrophages show higher levels of MHC class I and II expression and increased antigen-presentation to T cells in obesity (201). Adipose-tissue macrophages in HFD-fed animals also show increased costimulatory profiles, leading to higher overall T cell activation (202). In addition, in patients with asthma and comorbid obesity, airway macrophages and peripheral blood monocytes show a significant reduction in efferocytic index (40% and 36% decrease compared to non-obese asthmatic patients, respectively), suggesting that obesity dampens the efferocytic response of critical macrophage populations (203). If efferocytosis is a major mechanism by which MSCs exert long-term immunosuppressive effects (84), alterations in the basal efferocytic capacity of host phagocytes could lead to lower MSC therapeutic efficacy.

NK Cells

The primary role of NK cells is the killing of tumour cells or cells infected by a virus (204). A blunted NK cell function is associated with a worsened outcome of Covid19 (205), and a higher percentage of NK cells is associated with a longer survival of sepsis patients (206). However, the role of NK cells in autoimmune diseases like multiple sclerosis, lupus erythematosus, and arthritis is debated. There are indications for NK cells being both protective from and promoting the effects of autoimmune diseases (207–209).

Interactions between MSCs and NK cells happen in both directions. Activated NK cells lyse allogeneic MSCs, reducing the time during which they can exhibit their therapeutic efficacy (210, 211). At the same time, IFN-γ produced by NK cells promotes the production of monocyte chemoattractant protein 1 (MCP-1) in MSCs (212), which is associated with an anti-inflammatory polarisation of macrophages (213). Interestingly, IFN-γ- stimulated MSCs have been reported to reduce IFN-γ production by NK cells (214) and NK cell proliferation, at least partially through the production of PGE2 (215). Conversely, MSCs have also been shown to promote NK cell expansion (216) and increasing their IFN-γ production through both soluble factors and cell-cell interaction, at least partially by triggering the IL-12/STAT4 pathway of the NK cells (212, 217). These conflicting results likely arise due to several factors. Ratios of MSCs to NK cells range from 1:1 (216) to 1:8 (211), experiments were carried out *in vivo* (215) and *in vitro* (217), and MSCs were either pre-stimulated (214) or naïve MSCs (212). Additionally, while MSCs are able to successfully suppress IL-2 induced proliferation of resting NK cells, already proliferating NK cells are not as effectively suppressed (211). Some of the effects of MSCs on NK cells seem to also be time-dependant, as poly(I:C) activated MSCs initially promote NK cell function, followed by TGF-β and IL-6 induced cell death (218). Considering this delicate balance of interaction, a disturbance of NK cell function due to obesity could lead to impaired MSC therapeutic efficacy.

In the setting of metabolic disease numerous studies have detailed defective NK cells, with reduced peripheral frequencies and a loss of effector functions (119, 219–224) such as cytokine production and tumour cytotoxicity. Using murine models of cancer, Michelet and colleagues demonstrated that NK cells with an obese phenotype fail to control tumour growth highlighting the potential consequences of defective NK cell responses in people with obesity (37). The same study identified increased expression of PPAR controlled lipid uptake as the underlying mechanism of defect. Increased lipid uptake limited NK cell metabolic activity, which is critical for their effector functions (225). Leptin has also been identified as an important NK cell regulator, with reduced NK cell frequencies (peripheral, liver and spleen) and activity in leptin receptor deficient mice (db/db) (226, 227). Collectively these studies suggest the obese microenvironment underpins the dysregulation of NK cells in obesity. Further evidence for this comes from the reversibility of NK cell defects with weight loss, either *via* exercise or metabolic surgery (228–230). The unanswered question is whether or not obese NK cells are equally affected by MSC co-cultures as non-obese NK cells.

Another facet of NK cell biology impacted by obesity is their regulation of macrophages in adipose tissue. In 2014, O'Rourke and colleagues demonstrated that NK cells could regulate adipose tissue macrophage infiltration, with systemic ablation of NK cells reducing macrophage numbers in obese adipose tissue (231). In a subsequent study, Wensveen and colleagues provided detailed evidence for NK cell regulation of macrophages. The authors demonstrated that NK cells are activated by obesity induced adipose tissue stress, which leads to the rapid production of IFN-γ, which promoted the recruitment of macrophages into adipose tissue (232). In 2016, Boulenouar and colleagues showed that NK cells could regulate adipose tissue macrophages *via* their ability to kill inflammatory macrophages, but with the onset of obesity, NK cells lost their ability to kill macrophages and increased their production of IFN-γ which promoted the recruitment of inflammatory macrophages, promoting obesity related metabolic defects (233). Based on these findings, the ratio of MSCs to NK cells, or insufficient priming of MSCs, may exacerbate IFN-γ production by obese NK cells, and result in a pro-inflammatory effect.

IMMUNOGENICITY AND HEMOCOMPATIBILITY OF MSC IN OBESE ENVIRONMENTS

While alterations in the immune system critically shape the *in vivo* environment of patients with obesity, changes within the composition of the serum environment are also evident (27, 234). Obesity presents a unique challenge to MSC therapy due to increased immunogenic and prothrombotic risks. Increased immunogenicity within obesity has been well-documented within the organ transplant field. Molinero et al. demonstrated that in murine cardiac allograft, allo-sensitization and subsequent rejection were higher in HFD-fed animals due to increased frequency and co-stimulatory profile in host antigen-presenting cells (235).

Additionally, Okamoto et al. found that adiponectin ablation led to higher rates of cardiac allograft rejection (236). Adiponectin, therefore, appears to be protective against allo-sensitization and is, notably, decreased in patients with obesity (237). Leptin, on the other hand, tends to positively correlate with BMI (143) and is associated with a higher risk of allograft rejection (238, 239). In murine skin allograft, an increased rate of rejection in HFD-fed mice was due to the direct effect of $CD4^+$ T cell exposure to elevated palmitate (158). Obesity also appears to be associated with increased graft failure in solid organ transplants in humans. In a study of patients receiving kidney allograft, all obesity classes were associated with an elevated risk of graft failure (240). In an additional study, patients with obesity and comorbid diabetes had a significantly higher number of donor-reactive T cells, poorer graft function, and the highest rates of graft-failure (241). Therefore, the absence and excess of specific molecules within the obese environment can have crucial consequences for immunogenicity within allogeneic transplant scenarios. This highlights the need to investigate the impact of the obese environment on relative immunogenicity of MSC products.

In addition to increased risk of immunogenicity, obesity is a pro-thrombotic state (45). Due to elevated coagulability, patients with obesity are at increased risk of life-threatening thrombotic events including myocardial infarction, stroke, and pulmonary embolism (46). This raises the question: is hemocompatibility of MSCs affected by exposure to obese environments? Intravascular delivery of MSCs into a hypercoagulable obese environment could have severe consequences for adverse thrombotic and/or ischemic events (46, 47). In addition, both infection and inflammation can increase coagulability through direct effects on coagulation factors, platelet activation state, and vascular endothelium (48, 49); therefore, many patients treated with MSC therapy for immune-based pathologies may be pro-coagulant at time of infusion. The additive nature of these pro-coagulant risks, obesity and disease-specific inflammation, could have a detrimental impact not solely on MSC therapeutic efficacy, but safety, as well. As a more diverse and increasingly obese patient base is treated with MSC therapy, the need to understand how to maintain efficacy and decrease adverse thrombotic events within this environment will be critical to the broad scalability and generalizability of MSC therapy (242).

As the breadth of MSC products has expanded, transitive application of properties between tissue sources cannot be assumed to hold true (44). While bmMSCs show low levels of pro-coagulant tissue factor, both adipose and perinatal sources have relatively high levels of tissue factor expression (44, 243). In a clinical trial for critical limb ischemia using autologous atMSCs, adverse thrombi occurred only in diabetic patients, suggesting an intrinsic decline in the hemocompatibility of diabetic atMSCs (87). Diabetic atMSCs had decreased secretion of antithrombotic tPA and increased secretion of the pro-coagulant factor, PAI1, leading to less overall fibrinolytic activity. Interestingly, in the same study, healthy atMSCs appeared to have a differential response to being grown in either healthy or diabetic serum; however, this comparison was not the major focus of the study and therefore explicit quantification and statistical comparisons were not expressly reported. Follow-up studies showed that the atMSCs from diabetic patients who developed distal microthrombi exhibited high levels of tissue factor, linking changes in tissue factor expression with increased incidence of adverse thrombotic events (244). A better understanding of how the balance between pro- and anti-thrombotic factors is altered by intrinsic donor characteristics like comorbid metabolic disease will be critical to ensuring safety and efficacy for patients treated with MSC therapy.

RETRAINING OBESE MSCS TO RESTORE THERAPEUTIC EFFICACY

Due to the strong correlation of metabolic phenotype and immunomodulatory capacity in MSC (120), targeting the metabolism of obese MSC could lead to a restoration of their therapeutic efficacy. It is already known that culture conditions during *in vitro* expansion of MSC can considerably affect their therapeutic potential (245, 246). The metabolism of healthy MSC in early passages after isolation is typically highly glycolytic, but switches to OXPHOS over time due to a greater availability of oxygen compared to their niche in the body (247, 248). Expanding MSC in a hypoxic environment could counteract this switch. Similar to NK cells, which experience an impairment of their glycolytic function under obese conditions (37, 119), obese MSCs may suffer metabolic impairments. Human umbilical cord MSCs (ucMSCs) from mothers with obesity exhibit significant lower glycolytic capacity than ucMSCs from lean mothers (249). Pre-licensing obese MSCs to rescue or even amplify a glycolytic phenotype might rescue their immunosuppressive potential, however, this remains to be determined.

Pre-licensing human bmMSC with interferon γ (IFN-γ) has been shown to activate the protein kinase B (Akt)/mTor pathway, leading to increased glycolysis and increased expression of hexokinase isoform 2 (HK2), a key gene for glycolysis (250). Given that mTOR activation induces expression of HIF-1α (251), the involvement for the IFN-γ/Akt/mTOR/HIF-1α pathway can be theorised in this case. IFN-γ licensing also increases indolamine-2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2) production which are both important for MSC immunomodulation (250, 252).

TNF-α has also been shown to activate HIF-1α. Human fibroblasts, which share similarities with MSCs (253), experience an upregulation of reactive oxygen species (ROS) upon exposure to TNF-α, resulting in a hypoxia-independent expression of HIF-1α (254, 255). Similarly, exposing human fibroblasts to lactate also results in a HIF-1α mediated switch to glycolysis and an increase of c-Myc (256), a multifunctional transcription factor that regulates, among other things, cell proliferation and glycolysis (257, 258).

Confirming the beneficial effects of inflammatory pre-licensing on MSC metabolism, Mendt et al, showed that human ucMSC pre-licensed with a mix of IL-17, IL-1β, TNF-α, and IFN- γ resulted in an increase in glycolysis which promoted the production of

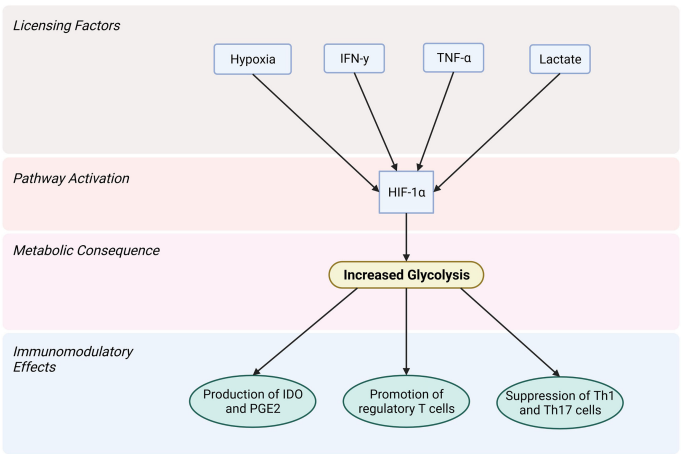

FIGURE 2 | Licensing factors that activate the HIF-1α pathway in MSCs lead to increased glycolysis and allow for the immunomodulatory actions carried out by MSCs. Created with BioRender.com.

immunomodulatory factors. *In vitro*, these pre-licensed human ucMSC were able to disrupt the glycolytic upregulation in T cells, causing those T cells to differentiate into a regulatory instead of an inflammatory phenotype improving the outcome of a murine graft versus host disease model (259).

Pre-licensing MSCs with both IFN- γ and TNF-α has been shown to prevent MSCs exposed to palmitate from taking on a pro-inflammatory phenotype, instead remaining strongly immunosuppressive toward activated PBMCs (260). Aside from shifting the MSC metabolism to a more hypoxic phenotype (**Figure 2**), simply culturing them in medium free from FFAs may also help to restore their immunosuppressive function. Following chronic exposure of human MSCs to palmitate, and subsequent loss of immunosuppressive potency, it is possible for the MSCs to recover upon removal of palmitate (260).

More research is needed to fully understand the role of altered metabolism in MSCs, the ways in which this might be best achieved and the functionality of licensed MSCs in inflammatory disease with an underlying obese environment.

FUTURE DIRECTIONS/CONCLUSION

For the use of immunomodulatory therapies, like MSCs, a careful and comprehensive understanding of how patient comorbidities affect the underlying immune system is pivotal to optimizing therapeutic performance. A one size fits all approach to MSC therapy is not scientifically justified and may compromise both patient safety and therapeutic efficacy (7, 84, 242). The expansion of patients treated with MSCs and the breadth of emerging MSC products warrants a more complete understanding of the interaction between characteristics of different *in vivo* transplant environments and intrinsic properties of the cell product. In patients living with obesity, the immune system and serum environment are fundamentally altered compared to metabolically healthy individuals (9, 10, 12). By not recognizing and identifying obesity as a unique transplant environment, we fail to tailor MSC therapies for the context in which they will perform. Moving forward, improved reporting of metabolic health in clinical trial data to the research community would allow for the evaluation of the function and health of MSCs within obese environments. Obesity and metabolic disease need not be exclusion criteria for the use of MSC therapy, as long as we understand how MSCs behave within these environments and the mechanisms of potential adverse events. In the future, both the patient and/or the cell therapy could be conditioned to reduce risk of adverse events, while maintaining therapeutic efficacy within obese environments. For example, given the pro-thrombotic nature of obesity, intravascular delivery of MSCs within patients with obesity could be paired with anti-thrombotic prophylaxis, thereby mitigating potential thromboembolic complications without excluding patients with obesity from vital therapeutic options. In addition, MSCs from donors with obesity could be licensed to regain their immunomodulatory potential. New immunomodulatory therapies should be available to all patients regardless of metabolic health, but for this to be true, critical gaps in our current knowledge regarding the interaction between MSC therapy and metabolic disease need to be filled.

AUTHOR CONTRIBUTIONS

LB performed a literature search, wrote the manuscript and approved the final manuscript. LMB performed a literature search, created the figures, wrote the manuscript and approved the final manuscript. AH, JA, and KE performed a literature search, wrote the manuscript and approved the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

LB is supported in part by the University of Iowa MSTP Grant, NIH T32 GM139776. LMB is supported through the John & Pat Hume Doctoral Awards of Maynooth University. KE is supported by an Irish Research Council Laureate Award (IRCLA/2017/288) and by a Science Foundation Ireland Frontiers for the Future Award (20/FFP-A/8948). JA is supported by the Straub Foundation, Diabetes Action Research and Education Foundation, and NIH P42 ES013661.

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