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Hypothesis and Evidence: Immune Cell Therapy Might Yield Poor Outcomes in Patients with Diabetes

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Abstract:

Immune cell therapy has rapidly emerged as a novel strategy for cancer treatment, particularly with the development of chimeric antigen receptor (CAR) immunotherapy. However, the clinical efficacy of CAR-T, CAR-NK, and CAR-M therapies remains controversial in patients with metabolic diseases. Diabetes mellitus (DM) is one of the most prevalent metabolic diseases, with studies suggesting that patients with diabetes often develop chronic inflammation and a deteriorated tumor microenvironment (TME), leading to an increased prevalence of tumors. This review summarizes the pathways and molecular mechanisms underlying the deterioration of the tumor immune microenvironment in DM. It highlights the upregulation of reactive oxygen species, fatty acids, HIF-1 & VEGF, O-GlcNAc, TGF-β1, EGF, PGE2, and IGF-1 levels; downregulation of HIPK2 levels; and promotion of a pro-inflammatory bias in microRNA and exosome expression profiles. These changes downregulate immune cell activity through various mechanisms, including signal crosstalk, metabolism, and cellular interactions, thereby influencing the clinical efficacy of CAR-T, CAR-NK, and CAR-M therapies. Additionally, potential drugs targeting these pathways are proposed, offering new insights for improving the TME in patients with diabetes patients and enhancing the efficacy of immune cell therapy.

Keywords: Diabetes Mellitus (DM), Immune therapy, CAR-T therapy, CAR-NK therapy, CAR-M therapy, Tumor microenvironment (TME).

1. Background:

1.1 Immune Cell Therapy as a Novel Strategy in Cancer Treatment

In recent years, immune cell therapy has emerged as a novel strategy in treating cancer and autoimmune diseases, particularly with developing chimeric antigen receptor (CAR) immunotherapy. Anti-tumor immune cell therapies primarily include CAR-T, CAR-NK, CAR-M, NKT, and γδT cell therapies. CAR-T cell therapy involves modifying patients' T cells to target and kill tumor cells by adding receptors that enable T cells to recognize specific tumor antigens. Five CAR-T therapies targeting B-cell markers, such as CD-19 and BCMA, have been approved by the FDA for treating refractory hematologic malignancies [1]. Clinical trials targeting various solid tumor-expressed antigens (e.g., HER2, interleukin-13Rα2 [IL-13Rα2], and GD2) have shown positive outcomes. For example, a clinical study targeting HER2-positive sarcomas included 17 evaluable patients. Four patients experienced stable disease for several months following CAR-T cell therapy, three undergoing tumor removal, and over 90% tumor necrosis observed in one case [2]. However, CAR-T therapy demonstrated less favorable outcomes in the remaining 10 patients.

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Despite significant advancements in CAR-T cell therapy, its efficacy may not always meet "reliable" standards for some patients with metabolic diseases.

CAR-NK cell therapy, which uses the cytotoxicity of natural killer (NK) cells, has shown a lower risk of cytokine release syndrome and neurotoxicity, with broader sourcing and faster preparation than CAR-T cells. Nevertheless, clinical trials have revealed that only 60% of evaluated patients with refractory acute myeloid leukemia achieved complete remission when treated with CAR-NK cells targeting CD33 derived from umbilical cord blood [3]. CAR-M therapy has also garnered attention. Macrophages, as key cells in the immune system, can recognize tumor cells through CAR and modulate the tumor microenvironment (TME) to activate additional immune cells in the anti-tumor response. Although CAR-M therapy shows promising prospects for solid tumor treatment, it is still in its early stages, with only one clinical trial initiated [1]. In summary, immune cell therapy does not guarantee favorable outcomes for all patients, and its lower efficacy remains a subject of scrutiny. The reasons for such variability are not yet fully understood. Observations suggest that some metabolic diseases may downregulate immune cell activity and diminish the effectiveness of cell therapy, particularly in conditions such as obesity and diabetes mellitus (DM) [4, 5]. Therefore, this review discusses the effects of immune cell therapy in patients with diabetes by analyzing the impact of diabetes-induced TME on immune cells.

1.2 Impact of Hyperglycemia on Immune Cell Function

DM is one of the most prevalent metabolic diseases globally, affecting approximately 150 million individuals, with developing countries exhibiting an 11.2% prevalence rate [6]. Recent research suggests that DM is associated with immune dysregulation. Elevated glucose metabolism in immune cells activates Toll-like receptor signaling pathways, leading to increased expression of IL-1β via the NF-κB pathway [7]. Additionally, NOD2 activation releases IL-1β and IL-18, initiating inflammatory responses in patients with diabetes [8]. Evidence indicates hyperglycemic conditions can increase reactive oxygen species (ROS) production, pro-inflammatory mediators, cell apoptosis, and fibrosis [9-11]. Moreover, bone marrow-derived cells (BMDCs) in patients with diabetes tend to express higher levels of tumor necrosis factor-α (TNF-α), contributing to inflammation [12, 13]. These pro-inflammatory signaling pathways support the concept of meta-inflammation, characterized by low-grade chronic inflammation, which is linked to the pathogenesis of diabetic complications [14, 15]. Chronic inflammation is recognized as a major factor in cancer development [16-18]development, establishing a connection between DM and tumor occurrence. Research indicates that cancer cases associated with high body mass index and diabetes are twice as common, with six cancers closely linked to diabetes [19, 20]. Despite the significant impact of diabetes on the immune system, research on the efficacy of cell therapy in patients with diabetes remains limited.

2. DM is Associated with a Deteriorated TME

The TME comprises cellular and non-cellular components embedded in the extracellular matrix (ECM), including cytokines, growth factors, enzymes, proteoglycans, and glycoproteins. These components facilitate proper communication and development of tumor tissue. Deterioration of tumor conditions in patients with diabetes is frequently observed. Hyperglycemia and advanced glycation end-products (AGEs) activate mast cells and increase the expression of pro-inflammatory cytokines, such as TNF-α, which promotes mast cell degranulation and forms an inflammatory microenvironment conducive to tumor development [21]. DM is associated with elevated TNF-α expression in BMDCs in gastric and renal cancers, contributing to inflammation rather than repairing damaged gastric mucosa [13, 22]. These infiltrating immune cells are crucial in reshaping the TME [23, 24]. A key feature of the TME is hypoxia, which induces functional changes in the cells within this environment [25, 26]. Patients with diabetes often experience more severe tumor hypoxia than non-diabetic patients due to their unique metabolic conditions. Low oxygen levels stimulate the proliferation of regulatory T cells via the HIF-1α pathway, inhibiting the differentiation of effector T cells [27-29] and leading to T cell exhaustion and the formation of terminally exhausted T cells [30]. Hypoxia also promotes the recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor transformation site, ultimately promoting tumor growth and suppressing anti-tumor immunity [26].

Evidence supports that remodeling and stiffening of the tumor-associated ECM are key factors behind the highly invasive phenotype of the TME [31-33]. This remodeling supports cancer cell survival, progression, and metastatic invasion [34, 35]. Fibronectin and type I collagen are the most common and abundant fibrous components in cancer-related ECM [36-38]. Their increase, resulting from excessive fibrosis primarily mediated by α-smooth muscle actin-expressing myofibroblasts, contributes to ECM stiffening [39, 40]. Most ECM fibrous proteins exhibit higher levels of AGEs, which are long-lived targets in DM and chronic hyperglycemia [41]. The cross-linking of AGEs with load-bearing proteins leads to ECM stiffening, favoring cancer cell survival and proliferation and promoting interactions between metastatic cancer cells and endothelial cells [42]. Chronic hyperglycemia generates a reservoir of AGEs, which may trigger various receptors for advanced glycation end products (RAGE)-dependent mechanisms, further deteriorating the TME [41]. Recent studies have shown that epithelial-mesenchymal transition is significantly enhanced in a high-glucose environment. In summary, DM can deteriorate the TME and accelerate tumor progression by suppressing anti-tumor immune activity.

3.Influence of DM on immune cell Anti-Tumor Resposes

Following observations that DM exacerbates the TME, we focused on understanding how these microenvironments affect the anti-tumor activity of immune cells.

We aimed to identify the pathways responsible for the diminished efficacy of cellular therapies in diabetes-aggravated tumors. We discovered that DM is associated with the upregulation of ROS, fatty acids, HIF-1α & VEGF, O-linked protein β-N-acetylglucosamine (O-GlcNAc), TGF-β1, EGF, PGE2, and IGF-1 levels in the TME, whereas homeodomain-interacting protein kinase 2 (HIPK2) levels were downregulated. These changes have been shown to inhibit various immune cells. Additionally, microRNA (miRNA) and exosome expression profiles in patients with DM exhibited an immune-suppressive skew. Consequently, these factors limit the efficacy of CAR-T, CAR-NK, and CAR-M therapies, as shown in the figure below.

3.1 High Glucose Inhibits Immune Cells in the TME

High blood glucose promotes glycolysis in tumor cells [43, 44]. Recent studies have indicated elevated glycolysis levels in tumor cells can suppress T-cell function via the TNF-α pathway [45]. In patients with diabetes, chronic high glucose levels may directly inhibit NK cells through NAD metabolism, resulting in reduced NK cell cytotoxicity [46].

Simultaneously, high blood glucose levels induce the upregulation of calpain in the mitochondria, which leads to reduced ATP synthase activity and increased mitochondrial ROS formation[47]. Mitochondrial ROS plays a crucial role in stabilizing hypoxia-induced transcriptional profiles, as it can activate pathways that support tumor angiogenesis [48] and promote myofibroblast deterioration[49]. Additionally, ROS contributes to the generation of diabetes-specific “ox-inflammation”[50]. This “ox-inflammation” includes the downregulation of Bcl2 expression, which leads to T cell apoptosis[51], and the downregulation of TCRζ-CD16ζ-chain expression in NK cells and T cells. This downregulation reduces NF-κB activity, resulting in decreased secretion of interferon-γ, TNF-α, and IL-2, ultimately impairing the efficacy of T-cell[52, 53] and NK cell therapies[54, 55].

In tumor cells, high glucose levels can promote HIF-1α expression under both normoxic and hypoxic condition[47, 48], enhancing the expression of several oncogenes. This leads to increased expression of angiogenic factors such as VEGF and HIF-1 and the inhibitory factor PD-L1 [49]. Furthermore, high glucose levels contribute to macrophage M2 polarization [50], reduce T cell activity and infiltration [51], promote regulatory T cells (Treg) differentiation [52], and reduce cytotoxic T cell activity [53], thereby decreasing the efficacy of T cell therapy. Additionally, high glucose, in synergy with hypoxia, sensitizes macrophages to cytokine stimulation [54] and generates an M2-skewed M1/M2 cytokine spectrum [55]. Hypoxia-induced VEGF activates VEGFR, leading to phosphatidylserine exposure on

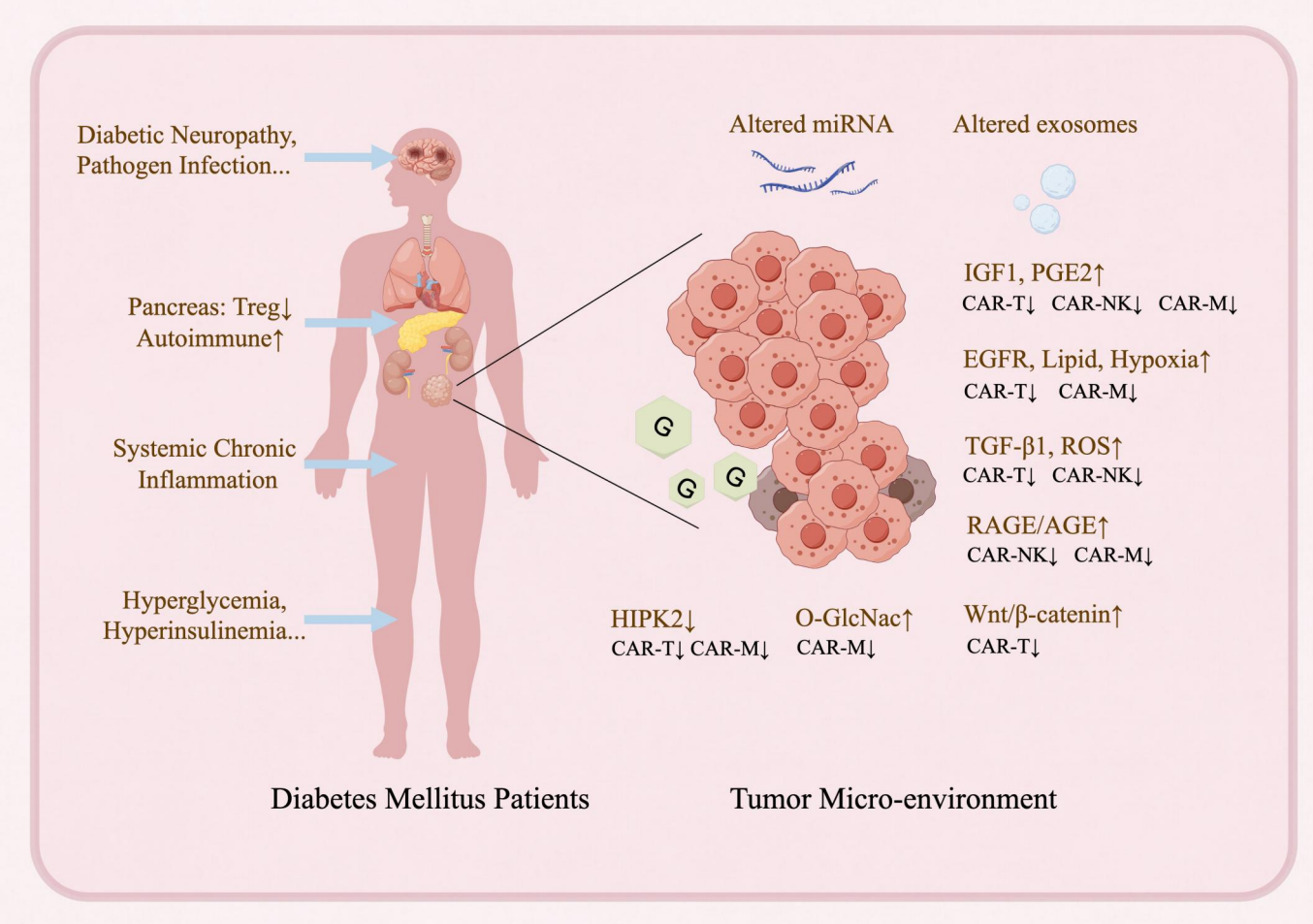

Fig. 1: Influence of DM on Immune cell therapy in Anti-tumor response, G refer to higher Glucose level in the patients with DM.

exosomes and cell membranes, which results in an immune-suppressive microenvironment by recruiting MDSCs, T-regs, and blocking the functions of NK, NKT, CD8+, and CD4+ cells [56].

3.2 High Glucose Upregulates O-GlcNAc Modification

O-GlcNAc modification is a dynamic post-translational modification that influences various proteins involved in cell cycle regulation and is a major contributor to the harmful effects of high blood glucose[66]. This modification includes adding an N-acetylglucosamine molecule to the hydroxyl residue of serine or threonine via O-GlcNAc transferase. In a high-glucose environment, this process leads to the O-GlcNAcylation of oncogenic factors and other cell cycle regulatory factors in tumor cells[67-69]. Recent studies have reported that high blood glucose increases the flux of the hexosamine biosynthesis pathway in tumor-associated macrophages (TAMs), resulting in upregulation of O-GlcNAc, activation of macrophage p56 and IκB, which leads to decreased macrophage activity[70], and induction of M2 polarization[71]. Upregulated O-GlcNAc reprograms active macrophages into TAMs[72-74] and reduces anti-tumor immunity[73].

3.3 Chronic High Glucose Accelerates RAGE/AGE Accumulation

Chronic high glucose is a hallmark of diabetes. It accelerates the formation of AGEs, a heterogeneous group of compounds formed by non-enzymatic reactions between carbohydrates and amino groups of proteins, lipids, and nucleic acids [57, 58]. All cellular components of tumor cells and the tumor stroma express RAGE. Increasing evidence supports the role of the RAGE/AGE axis in promoting tumor growth, with high glucose significantly enhancing RAGE expression. Consequently, the behavior of various cell types in the TME is influenced by diabetes or hyperglycemia. Patients with diabetes exhibit high rates of AGE formation, leading to overexpression of RAGE and overactivation of the RAGE/AGE axis [59]. Activation of this signaling pathway is a significant factor in inflammation-related tumorigenesis through mechanisms such as hypoxia, apoptosis resistance, anti-tumor immunity, angiogenesis, and tumor invasion [60, 61]. Specifically, the RAGE-HMGB1 pathway is believed to decrease the activity of monocytes, macrophages, and NK cells [62, 63]. At the same time, the RAGE-DAMPs/PAMPs axis interacts with the gut microbiota, promoting acute immune reactions in patients undergoing immunotherapy and leading to additional complications [64, 65], which may be more severe in patients with diabetes. Therefore, the upregulation of RAGE/AGE and its downstream pathways threaten the efficacy and safety of innate immune cell therapies for patients with diabetes.

Moreover, activating the RAGE/AGE axis in diabetic tissues and cells significantly increases the expression of COX-2 mRNA and protein and the levels of PGE2 [66]. The COX-2/PGE2-mediated signaling pathway is a key factor in diabetes-related complications such as hypertension and atherosclerosis [67]. This pathway also plays a crucial role in the inflammatory niche of gastric and colorectal cancers [68]. Downstream pathways mediated by PGE2 support tumor growth, metastasis, and neovascularization [69]. Additionally, PGE2 can directly inhibit NK cell anti-tumor activity [70, 71] and suppress T cell activity via dendritic cells, leading to the failure of CAR-T therapy [72], recruitment of MDSCs cells [73] and reduced macrophage activity [74, 75].

3.4 High Glucose Upregulates the Wnt/β-Catenin Pathway

Increasing evidence highlights the significant role of the Wnt/β-catenin pathway in the onset, progression, and metastasis of gastric cancer [76]. High glucose levels can affect the Wnt/β-catenin pathway in cancer cells by continuously enhancing the activity of histone acetyltransferase p300 or suppressing the activity of sirtuin-1, which leads to increased expression of Wnt target genes [77-79]. Consequently, high blood glucose results in elevated levels of β-catenin acetylation, allowing for nuclear accumulation and transcriptional activation of Wnt target genes [80]. This process ultimately leads to decreased T-cell infiltration and limits the efficacy of CAR-T therapy [81].

3.5 High Glucose Promotes TGF-β1 Activity

The TGF-β1 signaling pathway is excessively active in patients with diabetes[100, 101], and its role as a key fibrosis-promoting factor in the progression of diabetic nephropathy is well-documented[101-103]. Extensive research has demonstrated that TGF-β plays a crucial role in gastrointestinal cancer biology, influencing tumor progression; evasion of growth inhibitors; and resistance to apoptosis, angiogenesis, invasion, and metastasis[100, 104, 105]. TGF-β1 can induce T cell dysfunction[106], decrease CD8+ T cell infiltration[107], recruit MDSCs[108], and inhibit NK cell activity[109]. These factors contribute to the potential failure of cell therapies in a high-glucose environment.

3.6 High Glucose Activates the Epidermal Growth Factor Receptor (EGFR) Pathway in the TME

In vivo studies demonstrate that post-translational modifications of the ECM occurring during high blood glucose periods favor the invasion of cancer cells by activating the EGFR signaling pathway [82]. This mechanism is similar to that observed in diabetic nephropathy, a common microvascular complication of diabetes. The interaction between glycated ECM and increased EGFR activity may be a key factor in enhancing cancer cell invasion in patients with DM. Activation of the EGFR signaling pathway promotes cell proliferation, inflammation, and ECM remodeling, all associated with progressive cancer in patients with DM [83]. Notably, several ligands or other biological mediators can activate these signaling pathways, such as ROS[84,85], TGF-β[86], and PKC[87], all upregulated in DM. Studies have shown that upregulation of downstream EGFR

pathways, such as ERK and AKT, leads to upregulation of cell surface CD47, resulting in tumor cell resistance to macrophages and T cells [88-90].

3.7 High Glucose Downregulates HIPK2

Desmoplasia, or connective tissue hyperplasia, is common in patients with diabetes due to hyperglycemia, which activates the fibrotic pathway by directly stimulating the synthesis of ECM components and triggering the transformation of epithelial and endothelial cells into myofibroblast-like phenotypes. HIPK2 has been identified as a critical negative regulator in this process; its downregulation promotes tumor progression [91][118]. Hyperglycemia leads to the sustained degradation of HIPK2 [92], promoting the differentiation of epithelial and stromal cells into cancer-associated fibroblasts (CAFs). CAFs are known for their immunosuppressive properties, significantly enhancing epithelial-mesenchymal transition in hyperglycemia [93]. HIPK2 also exerts an “anti-inflammatory” effect by inhibiting NF-κB activation and phosphorylating HDAC3 in macrophages [94, 95]. Its downregulation has been reported to inhibit DC cells directly, regulate T helper cell activity [96], inhibit cytotoxic T cells [95], and contribute to tumor immune escape [97]. Consequently, some studies have proposed HIPK2 as a marker for immune escape in breast cancer [98], noting its downregulation in patients with DM.

3.8 High Blood Glucose Concurrent with High Lipid Metabolism TME

High blood glucose promotes glycolysis by inducing the expression of glycolysis-related genes [43, 44], which leads to increased ATP production [99]. This effect exerts a greater inhibitory impact on immune cells than the Warburg effect and is associated with higher lipid concentrations in the TME.

Furthermore, high blood glucose enhances the expression of the carbohydrate-responsive element-binding protein (ChREBP), a known promoter of lipogenesis [100, 101]. In patients with diabetes, lipids in the TME are transported into effector T cells via lipid transporters such as CD36 and Mincle. This leads to oxidative stress in effector T cells, resulting in T cell dysfunction and ferroptosis [102, 103]. However, this high-lipid environment does not similarly affect Tregs [104, 105]. Tregs upregulate the expression of glutathione peroxidase 4, which inhibits ROS accumulation and ferroptosis [105-107]. Therefore, the high-lipid environment induced by diabetes may reduce the efficacy of CAR-T cell therapy. Additionally, the high-lipid microenvironment increases lipid intake and fatty acid oxidation in macrophages due to elevated levels of CD36, leading to ROS production. This promotes M2 polarization of macrophages and prolongs the survival of M2 macrophages while shortening the lifespan of M1 macrophages via the JAK1-STAT6 pathway, potentially impacting the efficacy of CAR-M therapy [108].

3.9 Hyperinsulinemia Directly Inhibits the Immune Response in TME

Hyperinsulinemia is closely associated with type 2 diabetes [109]. Emerging data suggest insulin may be a key regulatory factor in certain human tumors, leading to tumor immune escape in gastric cancer[110], breast cancer[112,115,116], prostate cancer[113,114]. This process enhances tumor proliferation[111] and anti-apoptotic programs [117]. Upon binding, insulin-like growth factor 1 receptor activates the PI3K pathway [118], which results in the downregulation of CD8+ T cell infiltration [119], recruitment of MDSCs [120], TAMs [121], and inhibition of NK cell activity [122, 123].

3.10 High Glucose Induces Changes in miRNA Expression Profiles

miRNAs are small, non-coding RNAs that act as post-transcriptional regulators of gene expression [124]. They are involved in various cellular processes such as cell growth, differentiation, development, and apoptosis across many cancer types [125] including leukemia[126], cervical cancer[127,128] and so on. Hypoglycemia and hyperinsulinemia in patients with DM patients lead to significant changes in miRNA expression profiles, which can possess tumor-promoting characteristics. Tumor suppressor miRNAs, such as miR-497, miR-495p, and miR-203, are downregulated, potentially inhibiting tumor cell proliferation and migration, thereby suppressing immune cell activity in the TME [129, 130]. Additionally, the downregulation of the Let-7 miRNA family is associated with malignancies [131]. Let-7 miRNAs are downregulated under hyperglycemic conditions and insulin resistance [129], leading to the upregulation of PD-L1 and other immune inhibitory factors [132], which may adversely affect immune cell therapy.

3.11 Exosome Skewing Promotes Inflammation in the TME of Patients with Diabetes

Exosomes are submicron-sized extracellular vesicles involved in intercellular and interorgan communication [133]. They participate in the pathogenesis of various diseases, including inflammatory diseases and cancer [134, 135], and can inhibit immune cell activity in cancer [136]. Evidence indicates that chronic hyperglycemia or hyperinsulinemia alters the molecular cargo of exosomes and changes their secretion levels. These alterations induce significant changes in exosome function, enhancing crosstalk between tumor and non-tumor cells [137]. Recent studies have shown that exosomes released by patients with diabetes exhibit pro-inflammatory cargo skewed characteristics, which reduce the activity of relevant immune cells in the microenvironment. This pro-inflammatory shift may contribute to the reduced efficacy of cell therapy in patients with diabetes [137].

4.Potential Adjuvants for Immune Therapy in Patients with DM

The targets mentioned above may contribute to the poor prognosis observed in patients with diabetes undergoing immune cell therapy. Based on these findings, we have identified several drugs that could be combined to improve the precision of immune therapy for patients with diabetes. Notably, these targets and pathways are derived from literature and primarily offer ideas and directions for future research. Additional molecules and clinical mechanisms remain to be explored.

To address glucose and ROS upregulation in the TME of patients with diabetes, nanoenzymes such as copper nanoparticle-based POD-mimicking nanozymes have gained attention for their effectiveness in clearing ROS from tissues [138]. These nanozymes can significantly reduce ROS levels in the TME, enhancing CAR-T efficacy [139]. Additionally, silicon dioxide nanoparticle-encapsulated CaO2 and MnO2-based nanozymes (combined iron-manganese-based nanozymes) are believed to help downregulate tumor hypoxia, M2 macrophage polarization, and Treg activity, while activating T cells [156]. For CAR-NK cell therapy, IL-15 co-treatment may mitigate ROS-induced damage to NK cells, thereby improving CAR-NK therapy efficacy in patients with diabetes [140]. Furthermore, drugs targeting SLC1A5, SLC3A2, and SLC7A5 (e.g., IGN523 [141], JPH203 [141], V-9302 [157]) have shown significant potential in strengthening anti-tumor immunity in the TME [158].

In cases of hyperlipidemia induced by hyperglycemia in the TME, recent studies indicate that the ChREBP inhibitor SBI-993 can effectively reduce lipid content and enhance T cell activity, improving the efficacy of PD-L1 monoclonal antibody therapy [142]. GLUT inhibitors such as BAY-876 and fasentin can also achieve similar effects [143]).

For severe hypoxia and highly activated HIF pathways in the TME of patients with diabetes, studies have shown that the hypoxia-activated agent TH-302 can significantly enhance the efficacy of anti-PD-L1 and anti-CTLA4 therapies [144]. Additionally, HIF-1α inhibitors can serve as adjuvants to improve immune cell therapy efficacy [144, 145, 159].

Regarding the highly activated RAGE/AGE pathway in the TME of patients with diabetes, 4'-methoxyresveratrol can inhibit the inflammatory microenvironment induced by RAGE/AGE activation, potentially serving as an effective adjuvant to enhance immune therapy efficacy in patients with diabetes [146, 160, 161]. However, its clinical safety, dosage, and other aspects require further validation.

For the downregulated HIPK2, anti-tumor drugs such as cisplatin, adriamycin, and roscovitine have been reported to activate the HIPK2/p53Ser46 apoptotic signaling pathway and upregulate HIPK2 concentration in the TME, which could be beneficial for treating patients with diabetes with immune cell therapy [147].

In the case of upregulated O-GlcNAc in patients with diabetes, studies suggest that OGT and OSMI-1 can alleviate this process [148, 162]. However, whether these adjuvants can enhance immune therapy efficacy remains to be further investigated.

For the upregulation of the Wnt signaling pathway in patients with diabetes, the highly specific Wnt pathway inhibitor ICG-001 has effectively enhanced T cell infiltration and cytotoxicity[149,150], thus improving immune therapy efficacy [81, 163].

Regarding the upregulation of the TGF-β signaling pathway, various mature TGF-β inhibitors may enhance immune therapy efficacy in patients with diabetes [164]. Additionally, compounds such as Cu(sal)phen [151] and ST80 [152] targeting TGF-β could be potential adjuvants [153].

Tab1. DM may deteriorate the TME and inhibit immune therapies

pathways	DM patients	Innate immune therapy			potential adjuvants	Ref.
		CAR-T	CAR-NK	CAR-M		
Glucose & ROS	↑	↓	↓		Nanoenzymes, IL-15, JPH203, IGN523	[138] [139] [140] [141]
Fatty acid	↑	↓	↓	↓	SBI-993, BAY-876, fasentin	[142] [143]
HIF1&VEGF	↑	↓		↓	TH-302, HIF1a inhibitors	[144] [145]
RAGE/AGE	↑		↓	↓	4'-Methoxyresveratrol	[146]
HIPK2	↓	↓		↓	cisplatin, roscovitin, adriamycin	[147]
O-GlcNAc	↑			↓	OGT, OSMI-1	[148]
Wnt/β-catenin	↑	↓			ICG-001	[149] [150]
TGF-β1	↑	↓	↓		Cu(sal)phen, ST80	[151] [152]
EGFR	↑	↓		↓	DRD1	[153]
PGE2	↑	↓	↓	↓	DP1, DP2, EP4	[154]
IGF1	↑	↓	↓	↓	CT102	[155]
miRNA	alterned					
Exosomes	alterned					

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expression of EGFR associated with diabetes, DRD1 can inhibit its activity, improving the efficacy of cell therapy [153].

In response to high PGE2 concentrations in the TME induced by hyperglycemia, various anti-inflammatory drugs, including aspirin and COX2-specific inhibitors, are commonly used. Additionally, analogs of PGE2, PGF2α, and PGI2, TP antagonists, and antagonists of DP1, DP2, and EP4 are undergoing clinical evaluations for various indications [154, 165].

Finally, for upregulated IGF in patients with diabetes complicated by hyperinsulinemia, studies have shown that CT102 can serve as an adjuvant to promote tumor therapy by reducing the expression of inhibitory signals such as PD-L1 on tumor cell membranes and enhancing the prognosis of CAR cell therapy [155].

5. Conclusion and Future Directions

High glucose levels in patients with DM not only promote chronic inflammation, increasing cancer prevalence but also exacerbate immunosuppression within the TME. This results in the upregulation of various factors, including ROS, HIF-1 & VEGF, O-GlcNAc, TGF-β1, EGF, PGE2, IGF1, and fatty acid levels, alongside the downregulation of HIPK2 levels. Additionally, high glucose promotes a pro-inflammatory bias in miRNA and exosome expression profiles, potentially leading to the failure of immune cell therapy.

The targets and drugs discussed have shown potential to enhance the efficacy of immune cell therapy in patients with DM by mitigating the anti-immune effects of the high-glucose TME. However, due to the limited data available on CAR cell therapy, specific adjuvants targeting metabolic disorders have not yet been developed despite their significant potential to improve the efficacy of immunocytes. A successful treatment might yield poor outcomes simply due to the patient's underlying metabolic disease.

The efficacy of CAR therapy has improved significantly since its inception by Steven A. Rosenburg in the 1990s. The next step in advancing CAR therapy may involve the development of adjuvants tailored for the precise treatment of patients with specific metabolic disorders. Given that over 11% of the population develops DM, there is a pressing need for further research to identify effective and safe adjuvants for immune cell therapy. Such advancements are crucial for creating successful tumor treatments in heterogeneous patient populations.

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