Harnessing the Anti-Tumor Mediators in Mast Cells as a New Strategy for Adoptive Cell Transfer for Cancer

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The emergence of cancer immunotherapies utilizing adoptive cell transfer (ACT) continues to be one of the most promising strategies for cancer treatment. Mast cells (MCs) which occur throughout vascularized tissues, are most commonly associated with Type I hypersensitivity, bind immunoglobin E (IgE) with high affinity, produce anti-cancer mediators such as tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and generally populate the tumor microenvironments. Yet, the role of MCs in cancer pathologies remains controversial with evidence for both anti-tumor and pro-tumor effects. Here, we review the studies examining the role of MCs in multiple forms of cancer, provide an alternative, MC-based hypothesis underlying the mechanism of therapeutic tumor IgE efficacy in clinical trials, and propose a novel strategy for using tumor-targeted, IgE-sensitized MCs as a platform for developing new cellular cancer immunotherapies. This autologous MC cancer immunotherapy could have several advantages over current cell-based cancer immunotherapies and provide new mechanistic strategies for cancer therapeutics alone or in combination with current approaches.

Keywords: mast cells, adoptive cell transfer, cancer immunotherapy, FcεRI, IgE

ADOPTIVE CELL TRANSFER FOR CANCER IMMUNOTHERAPY

The use of autologous cells that can be targeted to tumors and induce apoptosis is an emerging therapeutic option to treat malignancies (1). From 2017 to 2018, there was a > 112% increase in the number of cell-based active agents in the global cancer immunotherapy pipeline. Most cells being investigated for autologous cancer immunotherapy have both pro- and anti-tumor mediators,

Abbreviations: MC, Mast Cell; MCs, Mast Cells; ADMC, Adipose-Derived Mast Cells; IgE, Immunoglobin E; TNF-α, Tumor Necrosis Factor Alpha; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; AMCT, Autologous MC Cancer Immunotherapy; ACT, Adoptive Cell Transfer; CAR, Chimeric Antigen Receptor; CAR T, Chimeric Antigen Receptor T Cells; TIL, Tumor-Infiltrating Lymphocyte; CRS, Cytokine Release Storm; EFS, Event-Free Survival; ORR, Overall Response Rate; PFS, Progression-Free Survival; OS, Overall Survival; ADCG, Antibody-Dependent Cellular Cytotoxicity; FDA, US Food and Drug Administration; NK, Natural Killer Cells; DC, Dendritic Cells.
their elevated numbers correlated with positive or negative patient outcomes, and strategies investigated to either inhibit their presence in tumors or utilize them for their anti-tumor properties. This strategy of adoptive cellular transfer (ACT) is typified by the use of autologous, peripheral T cells engineered ex vivo to express a transmembrane chimeric antigen receptor (CAR) composed of an extracellular, antigen-specific single-chain antibody and an intracellular T cell signaling domain (CAR T) (2). The use of CAR T-cell therapies has been approved by the Food and Drug Administration for children with acute lymphoblastic leukemia and adults with advanced lymphomas (3). Other T-cell based strategies, such as tumor-infiltrating lymphocyte (TIL) and engineered T cell receptor therapies are also being investigated (4). Several non-T immune cells also have potential anti-tumor activity. For example, dendritic cells (DC) modified in vitro with specific tumor-associated antigens to generate an immune response for cancer-cell elimination has led to clinical trials testing their safety and efficacy (5). Natural killer cells (NK) can eliminate cancer cells with surface markers associated with oncogenic transformation and have been investigated in clinical trials in patients with hematological malignancies or solid tumors (6). Peripheral blood eosinophils and neutrophils, containing potent mediators utilized by the immune system for pathogen destruction, have recently been demonstrated to have antitumorigenic activity (7, 8). As mentioned above, strategies to control tumor macrophages have resulted in numerous clinical trials in cancer patients to eliminate them alone or in combination with other therapies (9–11). Strategies to deplete macrophages are typified through inhibition of the CSF-1/CSF-1R signaling pathway. In general, depleting strategies have had limited success as unwanted removal of beneficial macrophages in non-tumor sights is a challenge (12). Conversely, other studies have hypothesized the anti-tumor capabilities of macrophages could be exploited and thus examined employing them as a form of ACT (13). While cytotoxic macrophages proved effective in animal models, this observation did not translate to humans (14). Recent strategies using CAR are intended to polarize pro-tumor and immunosuppressive M2 phenotype to a M1 phenotype with phagocytic functions, target cancer specific biomarkers, and induce an adaptive immune response (15, 16). In short, most cells being investigated as new platforms for cancer immunotherapy exert both pro- and anti-tumor effects. Therefore, the challenges moving forward in utilizing these cells is to remove the pro-tumor activity and/or enhance their anti-tumor functions. A summary table on the history of cell types being explored or used as cancer immunotherapy is shown in Table 1.

**Challenges with Cell-Based Cancer Immunotherapies**

While the numbers of autologous cells to target and inhibit cancer cell growth in vivo continues, so do the unanticipated roadblocks and challenges emerge. One challenge associated with CAR T cell therapies is the potentially life-threatening side-effect loosely defined as cytokine release syndrome (CRS). The CRS is induced by a systemic release of inflammatory cytokines associated with the T cell infusion and proliferation (and other T cell stimulants) (29). Also, the overwhelming majority of unique tumor antigens reside inside tumors, out of the reach of cells targeting them. This has led to efforts to identify and optimize delivery methods such as “in situ vaccination” at the tumor site hypothesized to release the inner tumor-associated antigens (30–33). Relatedly, most tumor antigens are promiscuous being found in and on cancerous and non-cancerous cells. This off-target phenomenon can result in serious or even fatal outcomes. An example of this is relates to an early trial in which T-cells were targeted to melanoma-associated antigen 3 (MAGE-A3) on metastatic cancers. Nervous system cells also express a similar MAGE-A12. As a result, T cells also invaded patients brain tissue resulting in the death of 2 out of 9 patients (34). The CAR T cell target CD19 is found on normal and malignant B cells. This can lead to lower immune cell numbers and side effects, such as a higher risk of infection when healthy cells are destroyed (35). Cancer cells are readily accessible to immune cells in blood as they circulate as individual cells or small clumps of cells compared to much larger solid tumors. Thus, another consideration in ACT development is the ability of the targeted cells to enter inside the tumor and release their anti-tumor mediators and killing at multiple locations.

**Allergy, Cancer Risk, and the Emergence of Tumor Targeting IGE’s for Cancer Immunotherapy**

Epidemiological studies investigating a correlation between atopic disease (e.g. serum IgE levels) and several types of cancer have demonstrated either a protective role or as a risk factor depending on the location (36–38). The retrospective, epidemiological observations that dominate the literature in general evaluated self-reported allergy histories, total IgE measurements, and/or skin prick tests and risks of cancer. An emerging area of research that suggests that patients with “ultralow” IgE serum levels have an associated with high rates of new malignancies not observed in mice (39–41). Specifically, patients with IgE deficiency and negative skin prick tests had a higher rate of malignancy than patients who had IgE deficiency with positive skin tests (41). This is important as a hallmark of IgE mediated functional responses of tissue mast cells (MCs) is the skin prick test which would support the possibility that IgE bound to MCs may have a role in tumor surveillance. As the epidemiological evidence linking atopic status to cancer risk continues to evolve (increased, decreased, or no association) so have the proposed hypotheses attempting to relate the possible mechanism linking allergy to cancer (37).

The development of atopy is initiated by the generation of IgE which binds FcɛRI on MCs and basophils to induce allergic
mediator release which induces allergy inflammation when encountering allergen. Tumor targeting IgE’s are being developed in an attempt to harness the diverse acquired responses mediated through IgE (e.g. parasite expulsion), the success of targeting cancer tumor markers with humanized IgG as a therapeutic strategy (42), and the epidemiological evidence suggesting a protective role for atopy against some malignancies (43). The IgE isotype has several potential advantages over IgG antibodies approved by the FDA on the market to treat various cancers such as the low serum levels of IgE (generally 100,000 fold lower than IgG) that result in less competition for FcγR occupancy, lack of inhibitory FcγR, and induces a different anti-tumor immune response compared to IgG (44, 45). Currently, there are over 10 IgE antibodies derived from patients or

| Cell type | Year | Clinical trials | Strategy for targeting | Mechanism of action | Targeted cancer | Refs |
|-----------|------|-----------------|------------------------|---------------------|----------------|-----|
| **Bacteria cells** | 1891 | n/a | Injection of heat-killed cultures of bacteria into tumors to stimulate immune response. | Coley’s toxins released through the stimulation of TLRs on immune cells | Sarcoma, lymphoma, testicular carcinoma, etc. | (17) |
| **T cells** | 1974 | n/a | T cells exposed to histocompatible, virus-infected target cells lysed lymphocytic choriomeningitis-infected cells in vitro and in vivo. | T-cell activation and release of perforin and granzymes | Lymphocytic choriomeningitis | (18) |
| **NK cells** | 1975 | n/a | Endogenous type-C viruses in tumor led to immune cells reactivity in mice. | Tumor cell lysis with NK cells by secretion of IFN-γ, TNF-α, GM-CSF, and chemokines | YAC-1 lymphoma cell line | (19) |
| **Mycobacteria** | 1990 | FDA approved | Attenuated live culture of bacteria injected in tumors to stimulate the innate immune response. | Macrophages phagocytosis | Non-muscle invasive bladder cancer | (20) |
| **Cytolytic T lymphocytes (CTLs)** | 1991 | n/a | Melanoma cells transduced with MZ2-E were recognized and killed by CTLs. | CTL activation and release of perforin and granzymes | Human melanoma | (21) |
| **T cell targeted immunomodulators** | 1996-2019 | FDA approved | Anti-FO-1/L1, anti-CTLA-4, Bispecific T-cell Engager (BiTE) antibodies, etc. | T-cell activation and release of perforin, granzymes, etc. | Colon carcinoma, fibrosarcoma, melanoma, bladder cancer | (22) |
| **Antigen presenting cells (APC)** | 2010 | FDA approved | GM-CSF/PAP fusion proteins induce APC activation and mobilized anti-PAP T cells. | Stimulation of T-cell immune response against PAP and release of perforin and granzymes | Prostate Cancer | (23) |
| **Dendritic cell (DC) vaccine** | 1989-present | FDA approved | Immunization of mice with DC pulsed with unfractionated tumor proteins induced protective immunity against subsequent in vivo tumor cell challenge. | Antigen presentation by MHC I and CD8+ T cell secretion of perforin, granzymes, etc. | Malignant lymphomas stages III and IV, Breast cancers, etc. | (24) |
| **Dendritic cells** | 2010-2020 | Phase II completed | DC pulsed with melanoma specific peptides or tumor cell lysate stimulate response to melanoma cells. | Antigen presentation by MHC I and CD8+ T cell secretion of perforin, granzymes, etc. | Brain tumors | (25) |
| **CAR T cells** | 2010-present | FDA approved 2017 and 2018. | T cells with chimeric antigen receptor to B cell CLL19. | T-cell activation and release of perforin, granzymes, etc. | CD19+ B cell acute lymphoblastic leukemia | (26) |
| **Neutrophils** | 2010-present | n/a | The anti-tumor activity of alemtuzumab was shown to be primarily dependent on the ADCC mediated by neutrophils in vivo. | G-CSF GM-CSF | B-cell lymphocytic leukemia | (9) |
| **Macrophages** | 2011-present | Used in several clinical trials as a combinatorial immunotherapy | Macrophages manipulated with antibodies or reprogrammed with metabolic/epigenetic substances to repolarize towards an anti-tumor phenotype | Downregulation of pro-tumor cytokines; Upregulation of anti-tumor cytokines | Pancreatic, melanoma, ovarian cancer, etc. | (27) |
| **Oncolytic viral particles** | 2015 | FDA approved | Viral particles modified to express GM-CSF for patients with melanoma | GM-CSF | Metastatic melanoma | (28) |
| **Eosinophils** | 2019 | n/a | Adoptive transfer and cytokine neutralizations. | IL-5 INFγ Phagocytosis, MHC II, TNF, INFγ | Colorectal cancer | (7) |
| **CAR Macrophages** | 2020 | n/a | Macrophages with chimeric antigen receptor to HER2/neu induced anti-tumor activity. | HER2+ ovarian cancer, CD19+ leukemia | (15) |

*ORR: overall response rate.
**PFS: progression-free survival.
***OS: overall survival.
n/a, not applicable.
produced to target tumor-specific that have been assessed using in vitro and in vivo cancer models (Tables 2 and 3) For example, Fu et al. investigated the serum levels of IgE in patients with pancreatic cancer and revealed the cytotoxic effect of the purified IgE against this type of cancer cells (49). The synthesized human tumor-specific IgE’s such as MOv18 IgE for ovarian carcinoma (47), Trastuzumab and C6MH3-B1 IgE’s for breast (50), colon (58), and ovarian (47) cancers, Cetuximab IgE for breast and epidermoid carcinoma (52), anti-hCD20 for human B-cell lymphoma (53), anti-PSA for human prostate cancer (55), have been investigated by many research groups (Tables 2 and 3). Of note, the MOv18 IgE specific for the folate receptor alpha (FRα) was demonstrated to have anti-tumor effects in vitro and in vivo and is in phase 1 clinical trials testing with early data demonstrating demonstrated safety and efficacy in ovarian cancer patients (64). The survival of FRα-positive xenograft-bearing mice was increased in the presence of monocytes (48). Systemic treatment with MOv18 IgE induced TNF-α and IL-10 upregulation in tumors and significantly upregulated TNF-α, MCP-1 and IL-10 levels in bronchoalveolar lavage fluid using an in vivo xenograft model (65). Further in vitro studies examined the anti-tumor mechanism of IgE and demonstrated pro-inflammatory signals and tumor cell killing by human monocytes (66). An IgE targeting the tumor-associated antigen SLC3A2 induced FcRI-mediated degranulation using a rodent cell line transfected with human receptor and triggered with SLC3A2-positive cell lines (58). The antibody did not trigger human basophil activation using unfractuated peripheral blood from cancer patients. In each of these studies, the mechanistic emphasis was on IgE-monocyte-mediated anti-tumor effects via IgE Fc-mediated ADCC.

**MC IN CANCER; EVIDENCE FOR BOTH ANTI- AND PRO-TUMOR ROLES**

As mentioned above, MCs are the final tissue effector cell in FcεRI-IgE allergic responses through the release of histamine and other noxious mediators. Their ability to release these mediators is also controlled by non-IgE and non-receptor mechanisms that are less common and include hypoxia, adenose, and certain chemokines within the tumor milieu (67). MCs possess both pro-tumor and anti-tumor mediators, are found in large numbers in and around many types of tumors, and studies have variously suggested MCs should be targets for inhibition/depletion or exploited as an anti-tumorigenic strategy (67). There are various studies that showed MCs have an anti-tumorigenic role in ovarian cancer (68), clear-cell renal cell carcinoma (ccRCC) (69), B cell lymphoma (70), skin cancer (71, 72), renal cancer (73), oral squamous cell carcinoma (OSCC) (74, 75), non-small-cell lung cancer (NSCLC) (76, 77), intestine cancer (71, 78), lung cancer (79), melanoma (80–82), prostate cancer (83–85), colorectal cancer (86), and breast cancer (57, 87–92) (Figure 1A). Patients with elevated MC counts had a significantly better event-free survival (EFS) compared to those with fewer MCs in several tumor types. Several unique phenotypic characteristics of MCs could contribute mechanistically to anti-tumor effects. Human MCs are unique in that they have prestored, releasable (through FcεRI) tumor necrosis factor alpha (TNF-α), histamine, and tryptase within their granules. The biggest impediment to using TNF-α as an anti-cancer agent is its systemic toxicity and strategies that limit its systemic distribution through local administration in patients have been investigated (93). Histamine induces the

| Year | Recombinant IgE | Name | Effector cells against cancer cells | Target cancer | Ref. |
|------|----------------|------|-----------------------------------|---------------|-----|
| 1991 | Anti-HIV gp120 | n/a  | Human blood basophils and using IgE pathway for cancer immunotherapy | H2712 mouse mammary carcinoma | (46) |
| 1999 | Anti-FRα | MOv18 IgE | Human basophils and platelets against IGROV1 cell line | Ovarian carcinoma | (47) |
| 2003 | Anti-FRα | MOv18 IgE | Monocytes, eosinophils against human ovarian carcinoma cell line IGROV1 | Human ovarian cancer | (48) |
| 2008 | IgE from patient | n/a | Peripheral blood mononuclear cells against HPAC cell line | Human pancreatic cancer | (49) |
| 2009 | Anti-HER2/neu | Trastuzumab IgE | Monocytic cell line U937 against SKBR3; Rat basophilic leukemia MC (RBL-SX38) expressing human FcRI, against murine colon adenocarcinoma cell line CT26-HER2/neu | Human HER2/neu positive breast and colon cancers | (50) |
| 2011 | anti-FRα | MOv18 IgE | RBL-SX-38 against ovarian carcinoma IGROV1 cell line | Ovarian carcinoma | (51) |
| 2012 | Anti-EGFR | Cetuximab IgE | Purified human monocytes and MC, U937 and RBL-SX38 cell lines against EGFR epidermoid and breast cancer cell lines | Human breast cancer and epidermoid carcinoma | (52) |
| 2012 | Anti-hCD20 | n/a | Primary human MC and eosinophils derived from umbilical cord blood against VU-3C6 hybridoma and OCI-Ly8 lymphoma cancer cell lines | Human B-cell non-Hodgkin lymphoma | (53) |
| 2012 | Anti-HER2/neu | C6MH3-B1 | MC of transgenic mice strains that express human FcRI against murine mammary carcinoma cells that express human HER2/neu (D2F2/E2) | Breast and ovarian cancer | (54) |
| 2013 | Anti-PSA | AR47.47 IgE | RBL-SX-38 cells sensitized with anti-PSA IgE and challenged with PSA or artificial molecules containing multiple epitopes of PSA | Human prostate cancer | (55) |
| 2017 | Anti-FRα | rMOv18 IgE/IgG2b | RBL-2H3 targeting WAG adenocarcinoma and ovarian tumor | FFα+ cancers | (56) |
| 2019 | Anti-HER2/neu | Trastuzumab IgE/C6MH3-B1 IgE | Human primary skin/adipose derived MC against breast cancer cell lines | Breast cancer | (57) |
| 2021 | SF-25 | SLC3A2 | RBL-SX-38 cell, basophils, cancer cell lines and in vivo xenograft models | Colon cancer (others) | (58) |

n/a, not applicable.
differentialation of immature myeloid cells and suppresses their ability to support the growth of tumor allografts (71). Increased histidine decarboxylase (which produces histamine) gene expression is associated with better relapse-free and overall survival in breast cancer patients and histamine treatment reduces tumor growth and increased apoptosis in xenograft breast cancer models (94). Mast cell tryptase alters the morphology and reduces the proliferation of human melanoma cells (82). We and others have demonstrated human MC release copious amounts (2,500-4,000 pg/ml from 10^5 cells) of granulocyte-macrophage colony-stimulating factor (GM-CSF); also, an anti-tumor mediator investigated in over 50 clinical trials (95). Mast cells showed direct antitumor effects in vitro and decreased angiogenesis and recruitment of NK and T cells in vivo (80).

In contrast, other studies have suggested a pro-tumorigenic role of MCs in different cancers (Figure 1A) with increased MC populations in certain tumor microenvironments associated with poor patient prognosis (96–106). These studies investigated the expression of MC markers (e.g. chymase/tryptase expression, FcεRI, c-KIT, etc.) in tumor tissues using immunohistochemistry, flow cytometry, immunoblotting, or RT-PCR techniques (67, 107, 108). In general, most published studies that attribute a pro-tumorigenic role for MC rely on correlations with increased MC numbers at a single time point, dependent on the tumor type, stage, and cancer microenvironment-and patient outcomes (Figure 1B). A “snapshot” analysis demonstrating an increase or decrease in MC numbers based on immunohistochemistry and subsequent association with a specific prognosis cannot be relied on to predict if these cells have a beneficial or deleterious effect.

Observing an increase in MC numbers paralleled by a poor prognosis (or vice versa) demonstrates a correlation, not a causation between numbers and prognosis. Studies are needed to assess the effects selectively knocking down (i.e. CRISPR) the pro-tumorigenic and/or upregulation of anti-tumorigenic mediators from human MCs. Nonetheless, MCs are one of the first cells to infiltrate the tumor microenvironment and possess such a wide range of receptors and molecules with diverse functions that mediate tumor responses that adds to the controversial role they play in the disease (109).

Another issue surrounding the analysis of the MCs role in cancers relates to conclusions drawn from MC knockout studies, with constraints in results observed depending on the model (110–112). In some cases, a pro- and anti-tumor effect was observed in the same tumors (67, 113, 114). In addition, differences in MC phenotypic and functional responses between mice and humans have been well documented (111, 115–123). For example, Fcγ receptor expression and functional responses mediated by them on mouse and human MCs and monocytes are vastly different (124–126). Further, mouse MCs have a diverse range of various proteases (127) while human MCs principally express three proteases (tryptase, chymase, and carboxypeptidase-A) (128). Histamine is released from human MCs, while both serotonin and histamine are liberated in reasonable amounts from MCs in mice, and both contribute to the physiological effects in anaphylactic reactions, respectively in these species. Interleukin-3 has a profound effect on murine MC differentiation and function not observed with human MCs. Of course, cancer therapeutic strategies require animal models to determine efficacy of drug targets, safety, biodistribution, etc.
But caution must be taken when extrapolating data from mouse models of cancer, especially when focused on MC numbers and MC Fc-specific mechanisms.

**COULD MCS MEDIATE THE EFFICACY OF ANTI-TUMOR IgE’S AND IN IgE TUMOR SURVEILLANCE?**

The mechanisms underlying the anti-tumor effects of therapeutic IgE’s are mostly attributed to monocyte and macrophage infiltration and subsequent IgE-mediated activation of these cells around tumors (56, 65, 129, 130). This hypothesized mechanism seems counter-intuitive to current evidence that demonstrates tumor-infiltrating myeloid cells promote, rather than inhibit-cancer progression (10). FcεRIα-positive macrophages have been identified as critical infiltrating cells that induce tumor progression in squamous cell carcinoma (131) [although evidence is presented that the anti-FcεRI antibody used in this study was not specific for FcεRI on macrophages (132)]. As is the case with MC, macrophages may initiate, promote, or suppress the development of cancer, possess both pro (e.g. VEGF, EGF, and TGF-β) and inhibitory (e.g. nitric
oxide), and have been implicated to mediate angiogenesis, invasiveness, metastasis, and acquired resistance to therapeutic strategies largely based on correlations between cell numbers and patient outcomes (133–135).

The hypothesis that monocytes/macrophages mediate anti-tumor efficacy to tumor IgE’s is also premised on the surface expression of FcεRI on monocytes/macrophages that controls their effector functions. However, the expression of FcεRI on primary human monocytes has been reported to be low (<10% in non-atopic patients), or not at all, compared to primary human macrophage and the expression level on monocytes is 10 to 100-fold less than observed for peripheral blood basophils from the same subjects (136, 137). While human monocytes can be manipulated to increase FcεRI expression in vitro (66) it is unknown if primary, tissue macrophages express FcεRI to any degree in humans. It also cannot be assumed the expression of IgE receptors will stay the same after entry and maturation in the tissues as monocytes undergo phenotypic changes upon tissue entry as they mature into macrophages (138). Others have shown human tissue macrophages do not express FcεRI (139–141). Here, another difference between species relates to reports in rodent studies that support the conclusion that macrophages can mediate anaphylaxis in mice; a phenomenon not described in humans (142, 143). One study showed that the responses of human alveolar macrophages involving IgE in vitro (144, 145) was most probably mediated by FcεRII (CD23) which has lower affinity for IgE, is distinct functionally from FcεRI (146, 147), and would help explain the RBC-rosetting most of these older studies used to determine IgE binding (148, 149). Lastly, other tissue cells besides MC have been reported to express FcεRI (e.g. Langerhan cells) and the low affinity receptor for IgE (150). Human basophils (and in some cases eosinophils) express FcεRI they are not normally found in tissue but are recruited following certain pathological mechanisms (151). Human eosinophils have demonstrated FcεRII expression (and have anti-tumor properties (7)) but only from donors with eosinophilia and lymphomas (152). Thus, the likelihood of tumor specific IgE binding to human monocyte-derived, tissue macrophages with unknown FcεRII expression to mediate effects seems less likely given many other IgE binding cells are present. MCs [with almost 100% FcεRII expression (57)] are as abundant or more abundant in the tumor microenvironment than macrophages depending on the tumor type. For example, the rodent form of IgE MOv18 reduced lung metastases in a syngeneic rat tumor model expressing human FRα which was attributed to TNFα, IL-10, and MCP-1 released by MOv18-triggered monocytes (56). However, the cytokine profile induced in BAL by MOv18 (TNFα, MCP-1, and IL-10) could very likely include a contribution from lung MCs which we and many others have shown produce such cytokines upon FcεRII stimulation (57, 153–156). We thus propose the binding of tumor targeted IgE Fc to human MC FcεRI and subsequent triggering of this receptor upon tumor engagement mediate the anti-tumor effects of therapeutic IgE’s given the demonstrated high amounts of FcεRI on primary human MCs in the tumor milieu (157), the high numbers of FcεRI (>1 x 10^6/cell) that require only ≈100 receptors for full activation (67, 158), the affinity of this interaction (159), the juxtaposition of MCs with cancers cells (67), and the anti-tumor mediators released from MCs (160). Infusion of IgE into patients is hypothesized to increase surface expression of MC FcεRI as this receptor is dependent on serum IgE levels (158, 161).

### STUDIES USING TUMOR TARGETING IgE’S AND MCs

Attempts to utilize anti-tumor mediators from MCs for cancer cell targeting was first examined using a mouse–human chimera IgE specific for CD20 and the epithelial antigen MUC1. Cord blood-derived MCs sensitized with anti-hCD20 IgE are cytotoxic to CD20 tumor cells in vitro (53). We used adipose-derived mast cells (ADMC) sensitized with human anti-HER2/neu IgE which bound to and released MC mediators when incubated with HER2/neu-positive human breast cancer cells (SK-BR-3 and BT-474) resulting in TNF-α mediated, tumor cell apoptosis (57). Importantly, monomeric (shed) HER2/neu and sera from HER2+ breast cancer patients did not induce ADMC degranulation, suggesting that such an interaction will not trigger systemic anaphylaxis.

### WILL MC BE ADDED TO GROWING LIST OF TUMOR TARGETING CELLULAR IMMUNOTHERAPY?

As discussed above the variety of cell types being investigated as new strategies for cancer immunotherapy continues to increase. MCs are similar to tumor associated macrophages as discussed above in that both have both pro- and anti-tumor capabilities and correlative studies led to assumptions regarding their role in various cancers (16). Because of this, initial efforts were aimed at depleting or repolarizing these cells as a therapeutic, anti-tumor strategy. MCs are presently at the apparently contradictory position in which rationale arguments could be made for inhibiting their numbers in the tumor milieu or increasing their numbers and harnessing their natural associated anti-tumor mediators within them. Yet from our perspective informed decisions as to deplete, increase, or repolarize MCs cannot be made until more studies assess their functional role in cancer models. As with human macrophages, human MC may need to be “repolarized” from a Type I hypersensitivity-associated cell type to an anti-cancer cell through up or down regulation of certain mediators. To this end, transfection/transduction of primary MCs has only recently been achieved using human peripheral blood derived MCs (162). The conditions that will now allow us to manipulate MC so that maximal anti-tumor activity is conferred and/or potential deleterious mediators can be deleted are being explored in our laboratory.

We propose human MCs as another cell type to be used in ACT for cancers in which tumor specific IgE’s are available or...
could be made. To do this, autologous MCs could be obtained from adipose tissue or cultured from peripheral blood and expanded *ex vivo*. Anti-tumor capabilities could be increased or deleterious mediators downregulated during expansion. FcɛRI-positive MCs are then sensitized with IgE targeting antigens found on tumors. The tumor targeting MCs would then injected into the patient and become active upon FcɛRI-IgE crosslinking. This autologous MC cancer immunotherapy (Figure 2) would result in the release of anti-tumor mediators within the tumor milieu (see graphical abstract). Recently we have demonstrated up to $6 \times 10^6$ human ADMC can be injected i.v. into mice with no toxicological effects. The ADMC, sensitized with human IgE recognizing the breast cancer antigen HER2/neu, shrink HER2/neu-positive tumors *in vivo* using a xenograft mouse model (manuscript submitted). Since human GM-CSF is not active in mice (163) the anti-tumor effects we have observed are expected to be stronger in humans in which GM-CSF would be fully active (164). This approach may enhance anti-tumor immunity through epitope spreading of cancer antigens. Importantly, this strategy may spurn new areas of research through transformation or manufacturing of tumor-targeted IgE’s. Harvesting adipose tissue from patients is not difficult, commonly performed, and increasingly being used for a wide variety of clinical applications (165, 166). Recently, we have demonstrated peripheral blood, CD34-positive stem cell derived MC also have anti-tumor activity providing a second source of autologous MCs (data not shown).

**ADVANTAGES OF AMCIT AS A NEW CANCER IMMUNOTHERAPY APPROACH**

There is a growing list of human IgE antibodies targeting cancer antigens that have been fully characterized which provide the targeting needed to transport the MCs to the tumor sites (43). It should be noted with caution when examining anti-tumor effects experimentally that the use of certain tumor targeted IgE’s is limited as human IgE does not bind mouse FcɛRI receptors (167). Second, the *in vitro* incubation of MCs with IgE for targeting is extremely stable (168) and allows for the saturation of FcɛRI binding, thus maximizing the effect while preventing patient IgE binding. IgE also stays bound to MCs for several months *in vivo* (169–173). Third, the adipose stem cells may be cryopreserved, reconstituted, and differentiated into ADMC while retaining expression of introduced genetic modules (data not shown). This is an important characteristic, as it greatly enhances the “logistics” of the potential therapy in that patient cells could be transduced, cryopreserved for shipping, and reconstituted when needed for therapy. Fourth, MC activation is hypothesized to induce acute inflammation and destruction of cancer cells in the tumor microenvironment due to the release of multiple mediators. The presence of dead tumor cells would allow uptake and presentation of tumor antigens by antigen presenting cells as with dendritic cells that elicit an adaptive, long lasting immune response not only to the targeted antigen but also to other tumor antigens due to epitope spreading. This would increase due to the local release of GM-CSF from MCs (174, 175) and the release of regulatory T-cell function suppressors (176). Of course, the use of tumor IgE’s alone or using tumor IgE-sensitized MCs as proposed here has the obvious potential to induce a systemic allergic response. Strategies to delete select mediators in human MCs are underway but with caution as it is simply not known if those with potential “toxic” side effects also have potent anti-tumor effects. Lastly, this strategy has the potential to circumvent challenges associated with current ACT strategies in which hyperactive T cells create a cytokine storm (177), reduced chances of off-target binding (not expressed on normal cells; e.g. CD19) (178), and avoid the lack of expansion and/or persistence of autologous cells (as with NK cells) (179).

**FIGURE 2** | Autologous MC cancer immunotherapy: a potential new platform for cancer therapy. We propose using MCs as a new cell type for adoptive cell transfer for cancers in which tumor-specific IgE’s are available. MC progenitors are obtained from patient, MCs expanded and polarized to enhance cytotoxicity and/or minimize systemic toxicity, and re-polarized MCs reinfused into patient.
CONCLUSIONS AND FUTURE DIRECTIONS

While the role of MCs in all cancer pathogenesis is still unclear, future studies are needed to examine if ex vivo-derived MCs possess anti-tumor capabilities. Questions remain regarding the possibility of systemic MC activation, although this issue can be overcome as discussed above with prophylactic anti-histamines, as is common practice (180–183). An alternative clinical strategy could be to first add IgE, followed by the MCs. Antigen levels on target cells may vary in patients, which could minimize cell targeting and activation. It is not anticipated that high levels of antigen will be needed, as human MCs require >100 FcεRI receptors to aggregate for a full activation response (158) and all FcεRI will be saturated so that patient IgE binding will not occur. Shed antigen in serum may also “mask” the MC-bound IgE without inducing degranulation, however blocking future binding. That said, this remains unlikely given the in vivo studies using IgE antibodies to tumor antigens do not suggest masking (50, 58, 184, 185).

There are myriad reasons to speculate on the many potential roadblocks that could arise during the development of the AMoIT as a new cancer immunotherapy strategy. But it is important to highlight similar misgivings, inaccurate predictions regarding toxicity, and major setbacks in the early years of CAR T-cell therapy (177, 186, 187). The emergence of CAR-T immunotherapy was met with skepticism and progressed only incrementally based on incremental insights over many years. Even though unexpected toxic effects in Phase 1 studies can quell any new therapy, the unfortunate reality is that it can take time to distinguish toxic effects as was the case in the first CART-19 trials (186, 188, 189). The point is that it is impossible to predict what, if any, side effects might occur in vivo with ADMC until studies to assess their role are performed. We believe the need for novel therapies that bring new mechanisms to combat cancer pathologies are important to investigate given the continued morbidity and mortality associated with this disease.

AUTHOR CONTRIBUTIONS

Conceptualization: CK. Methodology: MF, MM, EA, KD, TK, and CK. Investigation: MF, MM, EA, KD, TK, DM, and CK. Writing-original draft: MF and CK. Writing-review and editing: MM, MF, EA, KD, TK, DM, and CK. Funding acquisition: CK and TK. Resources: DM, TK, and CK. Supervision: DM, TK, and CK. All authors contributed to the article and approved the submitted version.

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