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Role of Mesenchymal Cells and Immunosuppressive Cells within Inflammatory Tumor Microenvironment

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Abstract

In recent years, cancer microenvironment comprises of several kinds of immune factors associating to the group of tumor environment. The role of mesenchymal stem cells (MSCs) and regulatory T cells (Tregs) play a vital factor in the immune environment. Mesenchymal stem cells are multipotent adult stem cells with immunomodulatory chattels, Recently MSCs are found to be promising candidates for cell based immunosuppression and immuno tolerance. The regulatory T cells or the suppressor T cells are a subpopulation of T cells modulating the immune environment and maintain tolerance to self-antigens. The mechanism intricate in MSCs to inhibit proliferation of proinflammatory T lymphocytes responsible to instigating autoimmune disease have to characterised but the mechanism behind this is the MSCs knack to generate Tregs cells and has been found to enrol foxp3 in maintaining immune homeostasis along with Natural killer cells and dendritic cells.

Keywords: Immunosuppression; Mesenchymal stem cell; T-regulatory cells (Tregs); Foxp3; Inflammation; Natural killer cells

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Introduction

The progressive growth and metastatic phase of the cancer is associated with the help of host cells like the immune cells, mesenchymal stem cells, fibroblast and other immune infiltrates. The equilibrium of the cellular interaction determines and influences the response to the cancer immunotherapy which relates to the tumor host dynamics resulting the tumor microenvironment. It is a key factor for the diagnosis of the cancer and provides therapy. Several evidences showed that unresolved chronic inflammation play a critical role in initiation and promotion of tumor leading to the establishment of the inflammatory tumor microenvironment around the tumor. The tumor microenvironment controls cancer progression, development and metastasis. Till recent years the cancer therapy has been based on the targeting the cancer cells with radiotherapy and chemotherapy and nowadays the therapies are focused based on the disruption of signalling pathways like the angiogenesis inhibitor (bevacizumab) [1]. HER-2 specific monoclonal antibody (Trastuzumab) [2]. BRAF enzyme inhibitor for melanoma (Vemurafenib) [3]. These therapy including traditional therapies with combinational drugs result in a better treatment and cure for the cancer [4]. The host cells associating the tumor microenvironment form a complex pathways resulting in a barrier for the treatment of cancer. Understanding the cell signalling with resultant host cells and adopting the infiltrates can provide a picture for the approach of the cancer therapeutics. Now with the efficacy of modulating tumor microenvironment, drugs are made with microenvironment modifier (Check point inhibitors, Depletion of tregs and inhibiting their suppressive effects, modifying the chemokine profile, Inflammatory mediators and toll like receptor agonists and manipulating cytokines) [5]. Along with additional immunotherapy are used as cancer therapeutics. The bone marrow derived stromal cells with disease favourable condition is found in several group of subpopulation are mostly found and involved in tumor expansion through homing. An inflammatory environment appears to be vital to encourage their influence and various inflammation associated molecules such

as TNF-α and IFN-γ might be connected. It has been detected that Mesenchymal Stem Cells (MSC's) recruit Regulatory T- lymphocytes (Tregs) to both lymphoid organs and graft [6]. MSC's are virtually found in all organs and tissues, it remains dormant and primitive. They are multipotent and differentiate into various lineages composing adipocytes, pericytes, chondrocytes, neurons, osteocytes, mainstay stromal cells, including fibroblasts and endothelial cells. They have high plasticity and have a capability of tissue regeneration [7]. MSC's migrate towards the site of the tumor and form a major component of the tumor microenvironment [8]. Studies using mouse models have been shown with inflammation induced tumors, which recruit MSCs, cytokines and chemokines [9]. The MSC's arbitrated immunosuppression may hinder with the anti-tumor immunity and assist the tumor escape immunological surveillance [10]. HLA-G5 secreted by MSCs stimulates FoxP3+ CD25Hi CD4+ Tregs proliferation and preserves the immunosuppressive activity by plummeting T lymphocytes and NK functions for a prolonged period upon co-culture in vitro [11,12]. Instead of research intention into T regulatory cells (Tregs), limited information is known about the mechanism regulating their recruitment and function. MSCs exert an immune regulatory function and suppress T-cell proliferation

Inflammatory Tumor Microenvironment

Tumor acts like an aberrant growth of cells resulting in a tumor microenvironment associating host cells, T-regulatory cells, cytokines and interleukins allied with inflammation. Many evidence show unsolved inflammation results in to initiation of tumor and promote the tumor progression with the formation of tumor microenvironment. The environment is a cellular microenvironment where various cells and factors connected with signalling molecules help tumor cells to progress and proliferate. This environment helps and shields the tumor cells from the body repair mechanism leading to act like a separate organ which further encourages the tumor angiogenesis and leading to accumulation of immune cells in tumor microenvironment [13]. The immune cells fabricate a major role in controlling the development and progression of cancer, this further leads to down regulation of anti-tumor functions in the tumor microenvironment. Vivacious understanding is necessary to understand the factor associating the tumor microenvironment and the structure of the microenvironment through the pathways connecting it. This would be highly helpful in understanding and developing the effective future approach [14,15]. However, approaches of using antibodies or adoptive cell transfer can arbitrate tumor regression in patients [16]. The tumor microenvironment can inhibit immune response progressing to futile responses of immunotherapy. The tumor microenvironment increases the change in the immunosuppressive microenvironment by the use of Immuno modulators. Anti-tumor immunity can be inhibited by variety of cells like the tumor infiltrating leukocytes, regulatory T cells, myeloid derived suppressor cells, macrophages, natural killer cells, and other immune infiltrates [17-19]. Contrivance employed by this cell types suppress the immune system with IL-10 and TGFβ, The TGFβ secretion in the tumors suppresses the anti-tumor activities in the tumor microenvironment. Various factors have been used to block TGFβ and lift immunosuppression, simulating other immunotherapies eradicating the tumor [20], and expression of CTLA-4, PD-L1 inhibitory receptors and amino acid depleting enzymes like arginase and IDO in the microenvironment can produce a negative impression on tumor environment. Malignant cells can block T cell function through secretion of soluble forms of ligands like NKG2D, MICA, MICB,[21] and galectins impede T cell activity and survival [22]. The Inflammation of tumor microenvironment Influences outcome by changing the stability of suppressive responses in tumor microenvironment [23]. The other factors that alter the tumor environment are blocking, differentiating and recruitment of the tregs. Blocking immunosuppressive enzymes like the arginine and tryptophan degradation present in the tumor microenvironment [24]regulatory cell depletion with the depletion of M2 macrophages [25]. Modifying the chemokine profile of the tumor microenvironment [26]. Chemokines can be a potent way of altering the composition of tumor microenvironment along with Toll like receptors (TLR) inviting and employing several leucocyte composition and trigger the changes in the microenvironment. The TLR agonists can start wide inflammatory responses provoking innate immunity and activating adaptive immunity [27] John LB et al., has shown the enhanced inhibition of tumor growth and survival of mice when oncolytic vaccinia virus along with intra peritoneal delivery of anti CD137 injected in tumors of mice has shown in increased tumor infiltrates by Natural killer cells, neutrophils and CD8+ effector cells and manipulating cytokines, results in manipulating the tumor microenvironment [28]. Although various immune cells are recruited to tumor site many anti-tumor signals and effects are down regulated with response to tumor glean signals, inflammatory cells and its infiltrates present in tumor niche are enhanced with Tregs, Myeloid derived suppressor cells MDSCs and other immune cells promote tumor growth. Constant stimulation of the NF-κB pathway in the tumor locale represents the mechanism that seems to help tumor existence and retard the activation of immune cells. The result is tumor escape from the host immune system. Tregs have been associated to play dual role in inflammatory tumor microenvironment [29]. Tregs has shown a tendency to upregulate and downregulate inflammation and are also linked with tumor progression [30]. Tregs have also been associated with controlling inflammation and also supress anti-tumor activities by promoting cancer progression. The normal function of Tregs is to regulate and suppress negative and critical immune responses and they attain anti tumorigenic properties [31]. In CRC, the FoxP3 Tregs have been found in abundance with positive prognosis of disease resulting in control of excessive inflammation [32].

Immuno surveillance of cancer

In 1950 burnet and Thomas proposed a hypothesis with cancer immunosurveillance [33]. The immune system involves in the recognition and suppression of the budding transformed cells [34]. The malignancies have been an intensive problem to understand [35]. The concept of immunosurveillance has progressed into a bigger and more multifaceted. Ikeda, Old and Schreiber has proposed the concept of cancer Immunoediting [35]. Where the three key elements are Elimination, Equilibrium and Escape. The concept of the immune system destroying the transformed cells by cancer immunosurveillance was first coined by burnet and Thomas. This process is basically elimination of the tumors and sculpturing the phenotype of the tumor and the renaissance of the cancer immunosurveillance was started after the discovery of the NK cells by Heberman & Holden [36] and later on the specific subsets of T lymphocyte cells were found to be vital in the immuno surveillance [37]. The cancer immunosurveillance starts with the Elimination phase where the cancer cells are detected and destroyed by the immune response of the mechanism. Second is the Equilibrium phase, the cancer cells and the immune system play accordingly and

result in the compromise of the system for the tumor to develop into next phase. The last is the Escape phase where the tumor escapes the immune environment and then immune system helps in the growth of the tumor to progress, sculpturing the further growth of the tumor. Basically the existence of the immunosurveillance is that it can form a component of eliminating and sculpting the tumor. The tumor which escapes from the immune surveillance leads to form the tumor environment associating various factors forming a prominent tumor microenvironment [38]. The tumor microenvironment is very crucial for the suppressing the host immune surveillance system with hypoxia tumor microenvironment allowing the cancer cells to escape from the immune surveillance of cytolytic T cells and NK cells, where the myeloid derived suppressor cells and mesenchymal stem cells play a role in the suppression of the T cells and Nk cells targeting malignant tumor cells [39-41]. The development of severe metastases at distant organs needs the incursion of primary tumors through the basement membrane and distribution. Epithelial cells at the invasive end of carcinoma triumph this physical blockade by obtaining aggressive properties through Epithelial Mesenchymal Transition (EMT) [39,42] showed the cross talk between the tumor cells, MDSCs and MSCs and other cells in regulating the tumor proliferation. Stromal cells recruitment to the site of tumor by the increase in the tumor infiltrates like tregs and the metastasis of the tumor with the formation of the tumor microenvironment. EMT is greatly associated with inflammatory tumor microenvironment [43] showed the association of EMT with inflammatory lung adenocarcinoma, there by identifying the markers for epithelial and mesenchymal lung adenocarcinoma and EMT is associated with wider inflammatory vicissitudes in the tumor microenvironment, associating multiple targets in immune checkpoints. Nk cells and dendritic cells play a major role in regulation of the immunosurveillancein regards to the EMT associating with subsets of T cells along with its associated soluble factors.

Activity of NK cells and dendritic cells with regulatory T cells and MSCs in immune surveillance

NKT cells are part of the innate immune system, and link the adaptive immune system with the innate immune system. These cells when activated can perform functions indorsed to both Th and Tc cells [44]. Natural killer (NK) cells were known as lymphocyte of the innate immune system that can kill tumor. NK cells can find numerous stressed cells that have or have not been opsonized by antibodies by producing cytokines and by playing a part in adaptive immune response leading to cell lysis of infected and damaged cells. CD1d Dependent NKT cells are a subset of innate lymphocyte that help in mediating anti-tumor immunity [45]. Various studies have shown that NKt cells can mediate immune suppression and are also responsible for immune suppression [46]. Zimmer et al., found the association of NK cells with Tregs based with TGFβ factor and found that mechanism of suppression, TCR Treg stimulation is crucial for suppression [47]. Spaggiari GM et al., indicated that MSCs impede IL-2 induced proliferation of unactivated NK cells [48]. Selmani Z et al., described MSCs inhibited NK cells expansion in transwell system [11]. In vitro co-culture studies have shown that allogenic Tregs with NK cells show a decrease in the natural killer cell cytotoxicity and cytokine production [49]. It is clear that decrease of Treg cells leads to increased NK cell functions and proliferation, various groups have depleted tregs to restore NK cell functions [50]. Another group has shown the effect of IL-2 activated NK cells have shown blocking iTregs in humans and mice [51]. CTLA-4 and PD-1 are responsible to block the Tregs [52]. Pomalidomide and lenalidomide have shown to inhibit the proliferation of Tregs function and also have shown to promote NK cell activity [53]. Also Roy S et al has shown that FoxP3 cells conversion was inhibited during a NKG2D response with microbial antigen in healthy individuals [54]. Interaction between Natural Killer cells and Treg cells in hematopoietic stem cell transplantation was demonstrated by Beziatet al., [55]. He demonstrated the ability of CB HSCT early NK cells have shown to kill leukaemia cells. These studies show that the environment created by Tregs have an influence on NK cells. Mesenchymal stem cell natural killer cell interfaces suggests that activated NK cells are capable of killing Mesenchymal stem Cells, whereas Mesenchymal stem cells inhibit IL-2 induced NK-cell proliferation during graft versus host disease in bone marrow transplant [48]. MSC promote T lymphocyte survival [56] and help in stimulating, activating and proliferating CD4+ T cells [57]. Although T cells are activated by MSC, they contain an increase in CD4+CD25+FoxP3+ Tregs that shows the suppressive activity [58] the MSC interact with the immune cells and metabolically control the immune cells with their adaptation to inflammatory conditions [59] MSCs inhibit the maturation, activation and antigen presentation of dendritic cells (DCs) [60,61] DCs are the main Antigen Presenting Cells in the immune system. Their function is to present antigen material on the cell surface to the T cells. These cells affect the balance between Th cells and Tregs and create tolerance to self-antigen [62]. Co-culture of MSCs with DCs ensued in abridged expression of CCR7 stimulated by DCs [63]. Presented that MSCs impede the up-regulation of CD1a, CD40, CD80, CD86 and HLA-DR through DCs differentiation and avert an increase of CD40, CD86 and CD83 expression during DCs maturation.

Activity of Mesenchymal stem cells with regulatory T cells in immune suppression

Mesenchymal stem cells (MSCs) epitomise a diverse population of adult fibroblast-like multipotent cells. These cells have produced huge attention in the field of regenerative medicine for their differentiation potential into various cell types and also for the production of soluble factors, chemokines, cytokines and other associating molecules. Mesenchymal stem cells (MSCs) are multipotent stem cells they differentiate into a variety of cell types and cell lineages, including adipocytes, osteoblasts, chondrocytes, myocytes and neuronal cells. In addition to their differentiation potential, MSCs have been reported to regulate the immune response in many diseases [64]. In addition to these factors these cells are said to migrate to the site of inflammation. MSCs have a great potential of immuno modulatory and anti-inflammatory effects. MSCs and T lymphocytes associate to produce various soluble factors which indeed help in the formation of the tumor microenvironment [65]. MSCs are also known to produce immuno protective cytokines which help in the repair mechanism and tissue regeneration. The Treg-inducing action of MSCs is equal to their ICOSL expression so ICOSL expression in human MSCs plays an vital role in contact-dependent regulation of MSC-mediated Treg induction [66]. Micro environmental cues enhance mesenchymal stem cell-mediated immunomodulation and regulatory T-cell expansion [67]. Interaction between MSCs and immune cells has influenced the adaptive and innate immune response. T cells are primarily targeted by MSCs immunosuppressive effect affecting the immunomodulatory properties. Sakaguchie et al., classified and characterized CD4+, CD25+FoxP3+Tregs, this helps in the maintenance of the immune tolerance and homeostasis [68]. Le blanc et al have shown that MSCs

inhibit the proliferation of the immune cells and hinder their maturation their by suppressing their in vitro and *in vivo* immune reactions in non MHC circumscribed mode [69]. The MSCs which were expanded in *ex vivo* condition have shown to supress the activity of various immune cells like T cells, NK T cells, dendritic cells, neutrophils, macrophages and monocytes. Various evidences have shown that adult MSCs can affect the immune T- and B- cell response, adult MSCs suppress T-cell proliferation, control the stability of Th1/Th2 and regulate the function of Tregs and cytokine secretion [11]. MSCs inhibit T cell proliferation and suppress allogenic T- cell response [65]. They are capable of suppressing the T – lymphocyte population induced by the mitogens [70] MSCs modulate immune responses with the introduction of the Regulatory T cells (Tregs) maintaining self-tolerance and immune homeostasis and also initiate the formation of Tregs and increase in population of Tregs [71]. In spite of abundant research into T regulatory cells (Tregs), little is known about the mechanism regulating their recruitment and function. MSC exert their immuno modulatory function through the inhibition of CD4+ and CD8+ T-cell proliferation. It is unknown that MSC impair the immunosuppressive function of regulatory Tcells (Treg) [72]. Mesenchymal Stem Cells Increase T-Regulatory Cells and Improve Healing Following Trauma and Hemorrhagic Shock [73]. Molecules associated with the tolerogenic and suppressive functions of Treg partially overlap with those involved in MSC-mediated immunomodulation. As mesenchymal stromal cells (MSCs) employ immune regulatory function and suppress T-cell proliferation and also possess the immuno regulatory and immunosuppressive properties, they recruit, regulate, maintain and suppress Tregs proliferation *in vivo* and in vitro [12,70,74]. Even though considerable importance in MSCs, data on interactions between MSC and Tregs are infrequent and contrary. In an in vitro MSC T-cell co-culture model, T cells presented a regulatory phenotype and tregs recruitment [75]. Di ianniet al., showed that, in both naïve and memory derived Tregs, MSCs regulate and maintain Treg function over time [76]. Though the mechanism behind Treg upregulation in the presence of MSCs remains unclear. MSCs regulate the innate and adaptive immune system by suppressing the T cells and by promoting the generation of Tregs through soluble factors [77]. They also regulate the maturation of the dendritic cells and also diminish B-cell activation and proliferation and hinder the cytotoxicity of NK cells. Yan Z et al., testified that MSC with Tregs are proficient of more immunosuppressive than Tregs without co culturing with MSCs showed that PD-1 receptor and IL-10 can be liable for the better suppressive capability of MSC- exposed regulatory T cells but depletion of tregs had no effect on suppression of T cells by MSCs [78]. MSCs are found to induce regulatory T cells via modulating miR-126a [79]. Han Z et al. showed Bone Marrow derived MSCs decreased the survival and proliferation of T cells by cell-cell contact-dependent mechanisms also they indicated increase in the percentage of Tregs [80]. English et al., reported that MSCs showed inhibitory effects on T cells in the presence of MSC and T- cells contact and also showed that MSCs and T-cells are required for the Tregs induction. In malignancies, the regulatory Tregs sponsor cancer cell survival and outcome [81]. Tumor derived exosomes (TDEs) transmit a pro-EMT (epithelial–mesenchymal transition) pathway including hypoxia-inducible factor 1 alpha (HIF1a), transforming growth factor beta (TGFβ), caveolin-1,and b-catenin. This enhances the invasive and nomadic abilities of recipient cells. This contributes to stromal remodelling and pre metastatic niche formation [42]. Chen et al., suggested that MSCs may alleviate SLE through upregulating Treg cells, which was partly dependent on sHLA-G [82]. By identify a possible mechanism in which MSCs convert conventional T cells to iTreg through strong modifications of mRNA of genes that are involved in Runx complex of Foxp3 [83]. TDEs have powerful immuno modulatory function that help tumor escape from immunosurveillance. EMT is not associated with the tumor mutational burden presenting independent factors mediating an inflammatory tumor microenvironment [84]. Both MSC and Treg were able to effect the adaptive immune system by utilizing similar and distinct mechanisms. Maccario et al., showed the autologous MSC were able to suppress the proliferation of CD4+ T cells and CD8+ T cells in mixed lymphocyte culture population [6]. When resimulated with mixed lymphocyte culture, the cells secreting CD25+ increased. This shows MSC dependent differentiation into T cells with a regulatory phenotype. IL-2 stimulation of PBMC in the presence of MSC showed increased population of CD4+CD25+ cells [85]. Co-culture of MSC with immune selected cells such as CD4+CD25+cells, CD4+CD25+CD45RA+cells and CD4+CD25+CD45RO+ cells maintained FOXP3 expression, CD127 down regulation and the immunosuppressive activities of Treg for about two weeks. In the absence of MSC the Treg populations lost their suppressive capacities during this period [12]. Engela et al., showed that majority of cells in the induced tregs had been found to have methylated Foxp3 gene and were found to be of some other origin of tregs [86]. Many evidences show PGE2, IDO, HGF, TGF–β and IFN-γ soluble factors play a vital role in MSCs suppressive activity. The maintenance and the initiation of FoxP3 expression is regulated by TGFβ, and the production of IL2 and T cell mitogenesis is inhibited by an immunosuppressant called PGE2. This TGFβ and PGE2 are produced by the mesenchymal stem cells. In the case of *in vivo* interaction between tregs and mesenchymalstem cells, *In vivo* studies have shown many discrepancies with regards to the immunomodulatory effects of MSCs. These studies have been premeditated to examine the efficiency of MSC therapy. Crosstalk between mesenchymal stem cells and Tregs is critically important for the attenuation of acute liver injury [87]. The prevention of allograft rejection and the ability to suppress abnormal immune response in autoimmune and inflammatory diseases. Kavanagh and Mahon, 2011 demonstrated the importance of Tregs induction by the MSCs with an inflammatory airway allergen driven mouse model. The administration of the allogenic mouse MSCs reduced the pathologies with the secretion of mucus in the airway and the IgE and the allergen directed lung eosinophilia were diminished resulting in an increase of the CD4+Foxp3+ cells in both the lungs and spleen of mesenchymal treated mouse model. Another study by Ge et al., showed that Generation of Tregs by mesenchymal stem cells helps in graft survival of the kidney allograft mouse model [88]. With the intravenous administration of MSCs after renal transplantation for 24 hours showed the inhibition of T cell proliferation. It was shown that significant increase of CD4+CD25+FoxP3+ T cells after MSC treatment intra graft FoxP3 + cells were found to recruit Tregs to the renal allograft. Then depleted Tregs using anti CD-25 monoclonal antibody reversed the effect of MSC causing graft rejection. Perico et al., showed the MSC therapy in transplantation confirming that MSC mediated the induction of Tregs *in vivo* [89, 90]. The autologous MSC were administered intravenously for 7 days to 2 patients with kidney grafts. Both patients received induction therapy with standard immunosuppression. Immunomodulatory plasticity of mesenchymal stem cells: a potential key to successful solid organ transplantation [91]. In the first 30 days of induction regime consisting Basiliximab

and low dose of rabbit anti thymocyteglobulin caused depletion of CD4 + and CD8+ T cells in both MSC treated and non-MSC treated patients peripheral blood. Later the patient with MSC treated was found to have CD4+ T cell was found to be lower when compared with non-MSC treated patients and many evidences show that inflammatory environment changes and can change the immuno modulatory effects of MSCs.

Conclusion

Currently, there are many promising clinical trials using MSCs based with tregs in cell-based therapies of numerous diseases. MSCs suppress T-cells, B cells and DCs function and represent a promising strategy for cell therapy of immune-mediated diseases. The immunomodulatory activities of MSCs provide a rational basis for their application in the treatment of immune-mediated diseases. MSCs have become a subject of clinical research interest due to their easy isolation and *in vitro* large scale cultivated amplification, attractive potential for multi-lineage differentiation, supporting, growth factors production and cytokines secretion and potential immunomodulatory capacity. In addition, MSCs is definitely safe and well-tollerated for use in cell therapy, which provide a striking candidate for degenerative diseases and immune mediated diseases. Increased clinical evidence suggests that MSCs may have great potential along with tregs in the treatment. Expanding our understanding of the molecular mechanisms governing immunomodulatory properties of MSCs with tregs will enable us to greatly improve their clinical efficacy. Most importantly, further well-designed, randomized and controlled. We suggest that we should determine the MSCs cell dose according to the biological effectiveness of the MSCs and also understand the principle and functioning of tregs. Meanwhile, it is really urgent to develop the biological effectiveness of tregs with MSCs biological functions. Meanwhile with Tregs there is growing evidence that tumor cells can induce the expansion of immuno suppressive cells. Cumulative proofs advise that a variety of chemokines, cytokines are produced by cancer cells as well as by cells of the tumor microenvironment. Phenotype and function of Treg subsets in peripheral blood and tumor infiltrates has to be fully characterized using different relevant and novel markers along with the markers of MSCs. Associating MSCs and Tregs we could built up a mechanism to control the immune cells system and clearly understand the immune metabolism and prevent the defect in the immune system and we could understand the missing link in the immune system to control inflammation and also understand the migrating and homing capability of immunosuppressive cells with MSCs such that we could understand the missing link to cure auto immune diseases and inflammatory disorders.

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