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Original Article

Exploring the Dynamic Role of Gamma-Delta T Cells in Clinical Pathology: A Systematic Review of Current Knowledge and Future Perspectives

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Gamma-Delta T Cells, Multiple Sclerosis, Immunoregulation, Pathogenesis, Immunotherapy, Malignant Cells, Major Histocompatibility Complex.

ABSTRACT

Gamma-delta [γδ] T cells are a significant subset of T cells with ability to recognize many antigens without the guidance of major histocompatibility complex (MHC) molecules. A lot of studies have been conducted on them ever since they were discovered 36 years ago. Advances have been made about their structure and function. Thus, there is a need for an up-to-date review about their significance as well as their roles in Multiple Sclerosis. The study aimed to provide an up-to-date knowledge concerning gamma delta T cells in pathogenesis of Multiple Sclerosis (MS). A systematic review methodology was used to scope information from recent studies about gamma delta T cells. The review was carried out in PubMed database and it followed the PRISMA guidelines. The computerized review yielded 60 peer-reviewed articles published between 2011 and 2020. The results showed that gamma delta cells play a critical role in protection against infections and the fight against malignant cells. Most of the reviewed studies highlighted recent advances in research. It was noted that the subset of T cells plays a role in pathogenesis of MS**.** Several studies have highlighted the protective and detrimental effects of γδ T cells. On the one hand, the cells contribute to the pathogenesis of MS, while, on the other hand, they also help in immunoregulation. However, there is a dearth of literature on their specific role and their mechanism of action. Therefore, further studies are needed about γδ T cells in both human and animal model studies. Based on the findings of the reviewed studies, there is great promise in the use of γδ T cells for MS immunotherapy.

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INTRODUCTION

T-cells (also known as thymocytes or T lymphocytes) are part of the cellular immune system that originate from the bone marrow's stem cells and protect the body from infections and cancer. Gamma-delta [γδ] T cells are a significant subset of T cells with the ability to recognize many antigens without the guidance of major histocompatibility complex (MHC) molecules [1]. They work either directly by using their cytotoxic activity to attack target cells or indirectly by activating other immune cells [2]. They induce their functional responses upon stress antigen recognition, which stimulates the production of cytokines and regulates the clearance of pathogens, tissue homeostasis, and inflammation [3-5]. Nonetheless, it is not yet well understood about the various parameters of the function of the human γδ T-cell, which, therefore calls for an updated knowledge about them [6, 7]. Consequently, there will be a better understanding of what can be done in the future and how they can be used to improve clinical outcomes [8].

γδ T cells provide rapid, innate reactions to antigens, thus serving in the afferent phase of the immune response [8]. As such, they are responsible for surveillance, detecting and responding to infections and other stresses without clonal expansion. It is due to this that they play a critical role in tumour surveillance [9], infectious diseases [1, 4, 5], autoimmunity [8], and inflammation [3, 10]. Besides, some studies have shown that γδ T cells play a role in the development of some clinical conditions, including inflammatory diseases such as dermatitis, hepatitis, psoriasis, and inflammatory bowel diseases [11, 12]. Recent studies based on animal models [such as mice] have also shown that they facilitate the growth of tumours by stimulating angiogenesis [9, 10-13]. In contrast, other studies have shown that mice without γδ T cells are more susceptible to inducible tumours. However, the role of cancer-related inflammation in humans has not been extensively explored [14- 16, 25, 27, 31]. In recent years, some studies have looked at the role of Gamma Delta T cells in disease and health [12, 17-30], but there is a lot of heterogenicity in the findings. This systematic review, therefore, aims to provide updated knowledge about γδ T cells and clinical diseases.

This systematic review provides a comprehensive synthesis of existing knowledge and research pertaining to γδ T cells, with a specific emphasis on their functions within distinct clinical conditions such as cancer, autoimmune, and inflammation. Through the provision of a comprehensive and contemporary amalgamation of existing scholarly works, this research endeavour serves to enhance

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the depth of understanding pertaining to the functionality and prospective therapeutic utilities of γδ T cells. It further aims to highlight the areas where inconsistencies and gaps in knowledge exist, setting a direction for future research.

METHODOLOGY

The study methodology was a systematic review that followed the PRISMA guidelines [32]. The PRISMA is an evidence-based set of items used for reporting systematic reviews, which standardizes the review writing process [32]. A systematic review has a high level of evidence, as exhibited in the evidence-based pyramid, and so a well-conducted review is a feasible solution for contemporary evidence-based practice. In the present study, the protocol used was not registered a priori in PROSPERO, although a search was conducted according to PROSPERO to ensure that the title of the present study is not reserved for a future project.

To attain the objectives of the current systematic review, a computerized search was carried out in February 2021 in the PubMed database. The main reason why this database was selected is its comprehensiveness, reputation, and specificity to the subject. The process was facilitated by a framework that identified concepts related to the study objective. Besides, there was a search of references in the retrieved articles. The query included terms such as “gamma-delta-T-cells”, as well as “gamma delta lymphocytes”, as well as “T-lymphocytes gamma delta”, as well as “clinical diseases”, and similar terms and combinations from these terms.

The inclusion criteria focused on articles that were published in the English language and from the last 10 years (2011-2021), with special emphasis on those conducted within the past three years. Articles were excluded because they were not peer-reviewed or published in a language other than English. Besides, case reports and conference abstracts were not considered. The researcher conducted the data extraction by following a pre-specified data collection form. The information obtained includes author, objective, design, and major findings.

RESULTS

Figure 1 shows a total of 221 documents were retrieved. However, the inclusion criteria led to the identification of 60 studies based on the quality of the articles.

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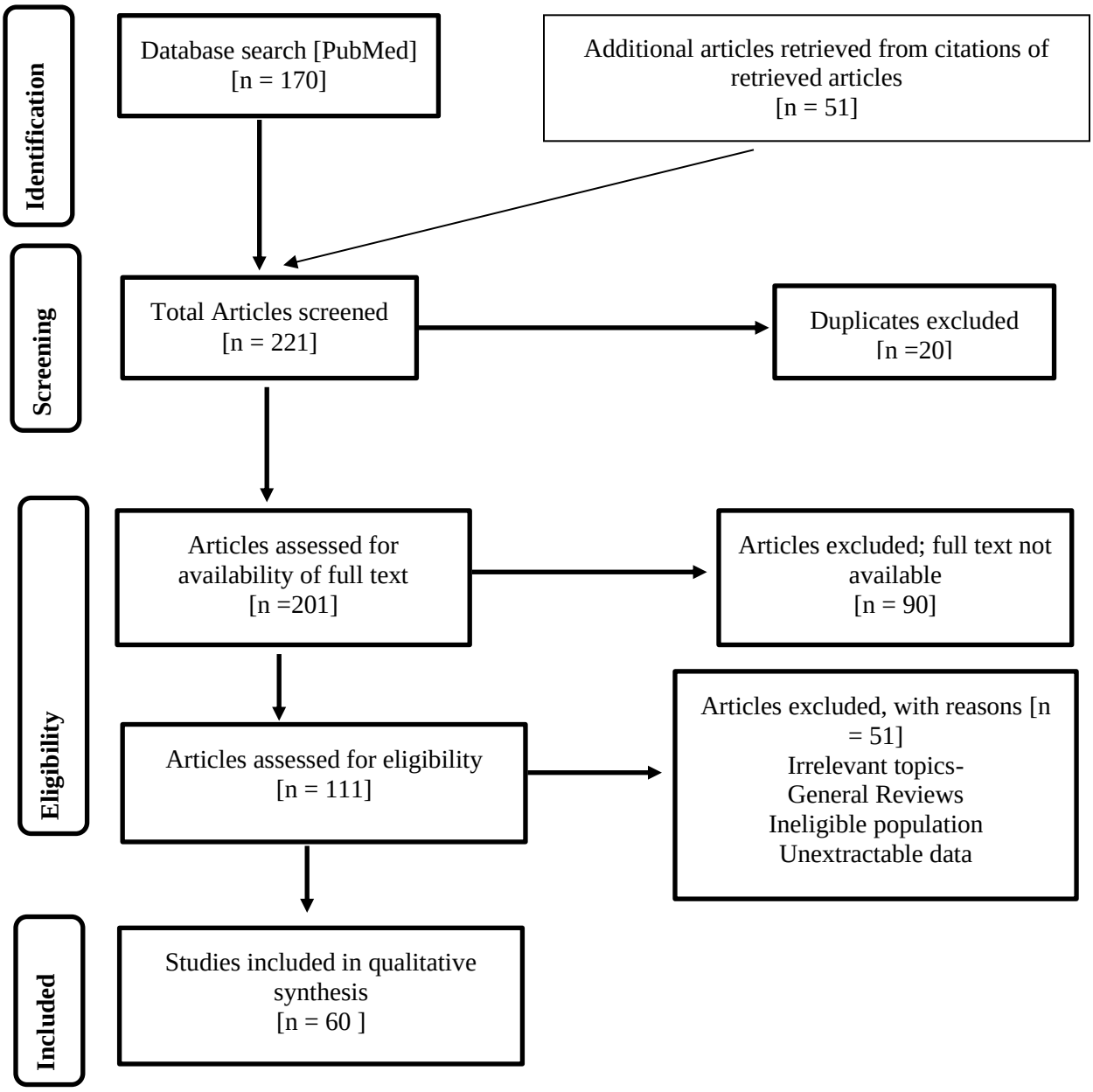
Figure 1: Prisma flow chart for selection of articles



The inclusion criteria led to the identification of 60 papers that addressed the study objective. They consisted of clinical trials, retrospective studies, randomized studies, systematic reviews, and experimental studies. A summary of the studies and their key findings is given in *Table 1*.

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Table 1: Summary of the studies and their key findings

Author	Study objective	Design	Major findings
Fonseca et al. [19]	Quantification of total γδ Tc and Vδ2/Vγ9 and Vδ1 Tc in the blood of 30 healthy individuals	A cross Sectional study	There was a high variation of γδ Tc among study subjects.
Karunakaran et al. [34]	To explore TCR ligands that potentiate BTN3A1	Experimental design	butyrophilin-2A1 [BTN2A1] was identified as critical to recognition of Vγ9Vδ2 T cell.
Rigau et al. [18]	To explore the role of Butyrophilin 2A1 in γδ T cells' phosphoantigen reactivity.	Experimental	γδ T cells recognize pAg differently from other immune cells
Harly et al. [33]	Examine the role of CD277/BTN3A in activation of Vγ9Vδ2 T cells	Experimental	B7-like molecules play a novel role in γδ T-cell antigenic activation in humans.
Fichtner et al. [36]	To discuss current understanding of human γδ TCR repertoires	Review	Non-Vγ9Vδ2^{+} TCR repertoire serve as log-file, which show the immunological history of the individual antigen challenges.
Kabelitz et al. [20]	To discuss recent developments in γδ T cell-based immunotherapy	Review paper	Recent developments include optimization of in vitro expansion, in vivo activation of γδ T cells that target tumours, and design of gene-modified T cells.
Melandri et al. [35]	To explore how γδTCR combines with adaptive and innate immunity	Experimental	Responsiveness to BTNL (human) or Btnl (mouse) us mediated by germline-encoded motifs in the variable y-chains of TCR.
Nussbaumer and Thurnher [24]	To provide a summary of current knowledge of Vγ9Vδ2 T cell functional phenotypes	Review	Vγ9Vδ2 T cells play a critical role in stress surveillance. They respond even to DC-derived IL-12 and IL-18. Vγ9Vδ2 T cells that express GPR56, CD56, and CD161 can be used for immunotherapy purposes.
Johnson et al. [39]	To explore current knowledge on the functions of γδ T cells that are tissue resident in adipose tissue, intestinal epithelium, and epidermis.	Review	Tissue-resident gamma delta T cells play significant roles in tissue repair and homeostasis.
Witherden et al. [38]	To examine the role of the interaction of CD100 receptor with plexin B2 in epithelial repair	Experimental/ animal model	Plexin B2 serves as a functional ligand for CD100 in the skin of a mouse. The interaction between CD100 and the plexin is critical for the activation of γδ T cells.
Hermann et al. [22]	To provide an update on the molecular basis of phosphoantigen recognition by gamma delta T cells	Review	Recent discoveries include the identification of genes that are important for pAg recognition encoding for gamma delta T cells and the role played by BTN2A1.
Bank [40]	To examine the role of Gamma Delta T cells in Rheumatic diseases	Review	γδ T cells are implicated in the development of scleroderma, systemic lupus erythematosus, ankylosing spondylitis, juvenile idiopathic arthritis, and rheumatoid arthritis.

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Author	Study objective	Design	Major findings
Clohosey et al. [41]	To present evidence of Vδ2 cell functional responses in people living with HIV.	Randomized Controlled Trial	The use of Antiretroviral therapy [ART] promotes recovery of Vδ2 polyfunctionality.
Xu et al. [21]	To develop a new formula for improving peripheral gamma delta cell expansion from healthy donors.	Clinical Trial	Expanded γδ T cells have improved immune effector functions, including cancer cell killing, differentiation, and proliferation.

Characteristics of Gamma Delta T cells

All the reviewed studies explored γδ T cells, a unique class of T lymphocytes with a characteristic distribution that is different from alpha beta T cells. The discovery of these cells occurred about three decades ago [17, 39]. Ever since scientific interest and research in the area have been increasing. The cells are categorized into two classes depending on their variable region types: V2V9 and V1 [19]. They mostly occur in mucosal tissue and epithelial tissue, whereas in blood, they only account for less than 5% of T lymphocytes [59]. Since they serve as a bridge between innate and adaptive immunity, they have different roles, including antitumor, anti-infection, and autoimmune responses [1, 3, 4]. Recently, it was discovered that the cells differ from other T cells in that they do not recognize antigens that are presented to them by the Human Leukocyte Antigen (HLA), but they rather detect some molecules secreted by pathogens, which are phosphorylated and non-peptic [17]. These molecules are not exclusive to bacteria but occur even in cells of eukaryotic organisms, as is the case for the cholesterol synthesis pathway. Thus, the activation of tumour-reactive T cells occurs when there is an overproduction of cancerous cells caused by a dysfunction in the mevalonate pathway [18]. It was not clear how the phosphoantigens have been recognized for a long time, but the recent study by Harly et al. [33] has helped to explain the role of molecules referred to as butyrophilin (BTN), and the findings have been corroborated by more recent researches [18, 20, 34].

In recent years, studies have explored the action mechanism of transmembrane molecules. Consequently, it is now known that the BTN3A1 molecule plays a more significant role than BTN2A1 [22]. Furthermore, recent studies have helped to develop an understanding of the inhibition and activation of γδ T cells, thereby contributing to their therapeutic application. The study by Serrano et al. [23, 26] has advanced scholarship in this area by investigating the costimulatory effects of Toll-like receptors (TLRs ligands. Various studies have discussed the signalling pathways that govern γδ T cell differentiation and activation [44, 51, 56, 57]. One study has discussed control of gamma delta T cell differentiation and activation [8, 12] by using classes of cell surface receptors such as inhibitory, NK, cytokine, costimulatory, and T-cell receptors. Further, this study has summarized how TCR controls gamma T cell activation.

How γδ T cells interact with other Immune Cells

Many of the reviewed studies explored the interaction of γδ T cells with other components of the immune system [1, 4, 7-10]. It is noted that generally, the main role of T cells is to provide signals that help to activate B cells, which in turn produce antibodies that help to fight against infections [17]. B and T cells interact through various

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costimulatory pathways, which include CD86.CD28, inducible T-cell costimulatory, and CD40/CD40-ligand [18, 44, 58]. They also produce cytokines, which help to differentiate B cells into plasma cells for the production of antibodies. Nonetheless, research also shows that the interaction is reciprocal, as t-cell activation can be promoted by B cells [28, 33-35]. Additionally, they help in the regulation of autoantibody response, which is critical in the development of autoimmune diseases [37].

Role in Immunosurveillance, Health, and Disease

A lot of recent research focus has emphasized the role of γδ T cells in immunosurveillance against diseases and cancers [53]. Kabelitz and colleagues [17] have explained the importance of these cells being localized in tissues through empirical studies conducted in both mice and humans. As local agents, they exert immunosurveillance through constant monitoring of the tissue integrity. For example, the mice epidermis has been shown to contain dendritic T cells, which express γδ TCR [38], which helps in wound healing. One study [39] has provided an insightful review of the role played in adipose tissue, internal epithelium, and the epidermis. Human T cells that are phosphoantigen-reactive also mediate stress surveillance because only transformed and stress cells produce high levels of isopentenyl pyrophosphate (IPP), which is necessary for activation of γδ T cells [24].

Some researchers have explored how the gamma delta cells can be used for immunotherapy. They are also involved in viral infections and the development of autoimmune diseases. For instance, Rampoldi et al. [37] have a role played in the production of autoantibodies. The findings are corroborated by Ilan Bank [40], who has examined the role that these cells play in autoimmune conditions that include ankylosing spondylitis, systemic lupus erythematosus, as well as rheumatoid arthritis [54]. During viral infections, such as HIV, there are alterations that occur in the compartment of gamma delta cells. Besides, recent evidence from studies shows that Vδ2 T cell proportion reduces in HIV-infected donors. Since they play a significant role in anti-microbial immunity, their reduction could be a result of exposure to multiple microbes, including some that are not pathogenic [59]. It is for this reason that anti-retroviral therapy helps in reconstituting the gamma delta T cells' functional activity [41]. Some studies reported that γδ T cells affect adipocyte function [39]. For instance, they negatively regulate adipogenesis, which protects mice against obesity [48, 49].

Role of the γδ T cells in Cancer Immunity

Many of the reviewed studies explored how gamma delta cells contribute to the protection against tumours [1, 2, 5-7]. Due to their role in immunosurveillance, a lot of focus has been put on developing ways for their use in cancer immunotherapy [21]. For instance, one recent study has described how these cells are abundant in cases of tumours at the transcriptomic level [42]. Other studies have shown that there are various elements in the tumour microenvironment that have tumour-suppressing responses [45]. Moreover, many others have examined various mechanisms that the gamma delta T cells use for cancer immunity so that developments can be done to apply them to patients treating cancer [29, 46, 47]. In the current review, there are some studies that have explained how the cells contribute to the tumour, leukaemia, and lymphoma destruction, especially through the production of anti-tumour cytokine, IFNy [8, 56, 57]. Therefore, they are involved in the immune surveillance against solid tumours and haematological neoplasms [15, 19].

DISCUSSION

The current study has used a systematic review approach to provide up-to-date knowledge on the present status of research concerning γδ T-cell. Notably, most of the contributions have focused on cancer immunity and immunosurveillance.

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Evidence from literature has shown that ligands derived from tumours are recognized by gamma delta cells, which makes them significant in the control of cancer [2, 53]. The field of immunotherapy continues to experience exciting developments, and several companies have started to explore how this class of T cells can be used to control some conditions, such as cancer. Generally, it has been established that gamma delta is an unconventional T cell [40, 50-52]. This unconventionality is evidenced by the broadening of the scope of antigens that T cells can recognize. Therefore, γδ TCR does not follow the classical MHC process for recognizing antigens [1, 18, 40]. Instead, their TCRs permit the direct recognition of molecules that are non-peptide [59, 60].

In summary, the role of γδ T cells in immunology is summarised into six properties based on the insights obtained from the reviewed studies. One, γδ TCRs recognize a broad range of antigens. However, today, only a few ligands have been identified [53], belonging to diverse families of autoantigens and exogenous molecules [2]. Two, the rapid response of γδ T cells is because they develop fully in the thymus, thus not needing additional peripheral maturation or clonal expansion for them to act (60). Besides, their localized distribution makes them fit for the provision of primary defence. Third, they are pre-programmed during developmental stages, and so they differ from alpha beta T cells. Fourth, they reside in specific tissues, with their distribution impacted by the expression of unique chemokine receptors. Fifth, they contribute broadly to immune responses, and they have the potential to regulate major immune cell subsets. Finally, they mediate essential responses to pathogens, and they are particularly effective against *Plasmodium falciparum, Mycobacterium tuberculosis,* and cytomegalovirus [2, 55].

Finally, the review has enhanced my understanding of γδ T cells, which will be crucial in their application in therapies and vaccination. For instance, their ligands' monomorphic nature and independence from MHC are critical in vaccine development [52]. However, presently, there are only a few defined ligands with clinical relevance. Nonetheless, the review has shown that multiple fronts exist for future development and optimization aimed at making gamma delta T cells clinically useful.

CONCLUSION

In sum, the aim of the present review was to provide updated information about γδ T cells. The review identified 60 studies authored between 2011 and 2021. Evidence from these studies shows that this class of T cells is critical in the control of infections, malignancy, and tissue homeostasis. A lot of progress has been made in understanding the biology and physiology of the cells, which has helped in their development for application in clinical medicine. The collection of original papers and review articles in the present review has provided an up-to-date overview of the current state of research. It is expected that in the future, the cells will serve significant roles in clinical medicine. Finally, γδ T cells are involved in immune surveillance against cancers, in immune response to infection, and for initiation of autoimmune diseases.

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