ISSN 2524 – 0684 e-ISSN 2524 – 0692

УДК 616.1:618.3:618.5
МРНТИ 34.15.63
DOI: 10.53065/kaznmu.2024.68.1.003

Поступил в редакцию: 07.01.2024
Принято к публикации: 28.02.2024

AGE-RELATED VARIATIONS IN MITOSIS REGULATORS IN LYMPH: INNOVATIVE DRUG DESIGN PERSPECTIVES

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Abstract

Introduction: Mitosis is an essential process influenced by age, occurring across various tissues and regulated by different mediators. Substances such as cytokines and hormones are currently utilized in therapeutic interventions for conditions like cancer and graft-versus-host disease.

Aim: This study aims to critically evaluate existing literature on age-dependent mitoses, cytokines, and hormones within lymphatic fluid, particularly thoracic duct lymph (TDL), under normal physiological conditions. The insights gathered will be leveraged for novel drug design and development.

Materials and methods: An extensive review was conducted using databases such as PubMed/Medline, WorldCat, Google Scholar, and Index Copernicus, focusing on publications from the last forty years.

Results: Three studies highlighted specific morphological attributes and quantitative shifts in age-associated mitoses within normal TDL. Another investigation detailed the quantitative and morphological properties of TDL lymphocytes in healthy individuals and those treated with thyroxin. Additional research delved into the physiological roles of angiotensins, insulin, and steroid hormones. Recent studies have increasingly focused on the mediators of proliferation and mitosis, with interleukins being examined for their antigen-stimulating properties and other effects. Notably, age-related variations in immune system functionality, particularly mitosis, have been identified. Despite significant advancements in drug design, certain challenges persist, often due to oversimplified approaches.

Conclusion: The evidence suggests that the immune system undergoes age-related changes, both under normal conditions and when influenced by external factors. However, the specific differences in TDL mitosis mediators between immature (neonatal) and mature (adult) organisms remain understudied. There is a critical need for the development of new drug components. The observed variations in TDL mitosis mediators between healthy neonates and adults present a promising avenue for creating innovative treatments for cancer, graft-versus-host disease, and other conditions.

Keywords: drug design, age-related mitosis, thoracic duct lymph.

Introduction. Mitosis (cell division) and meiosis (gamete formation) are crucial processes for the growth and maintenance of organisms. These processes are regulated by various checkpoints that ensure accurate chromosomal segregation and duplication in mammalian cells [1,2]. Over the past few decades, extensive research has significantly enhanced our understanding of the intricate mechanisms involved in cell division [3]. Mitosis is recognized as an age-dependent process, exhibiting variations across different life stages [4,5,6]. This process occurs in a wide range of tissues and is influenced by various mediators.

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Consequently, research has been dedicated to studying the effects of angiotensins, insulin, steroid hormones, and kinases on mitosis [7-13]. Recent publications have increasingly focused on identifying and understanding the mediators that regulate cell proliferation and division [14,15,16].

Interleukins in peripheral lymph and thoracic duct lymph (TDL) are being investigated for their roles in antigen stimulation and other immunological impacts [17-22]. Several studies have described the morphological characteristics and quantitative changes in age-related mitoses in TDL of healthy adults [23-26]. A sufficient population of immune cells obtained from lymph can undergo expansion, with mitotic activity potentially influenced by the stage of immunogenesis.

The maturation of the immune system in mammals begins shortly after birth, triggered by initial antigenic exposures [27]. Recent findings suggest that the regenerative potential of mammalian cardiac cells significantly diminishes soon after birth, coinciding with most cardiomyocytes exiting the cell cycle [28].

One study specifically examined the quantity and morphological features of TDL lymphocytes in both normal and thyroxin-treated conditions. Researchers emphasize the need for developing new druggable components and highlight the complexity of drug design, which requires executing multi-step processes, controlling cytotoxicities, and comparing outcomes [4,15,29]. Despite advancements in drug design, some recent publications point out the limitations of reductionist approaches, which focus on isolated parts of a system for which molecular data is available, often leading to unsuccessful problem-solving attempts [30]. Natural compounds derived from plants, microorganisms, and marine species are crucial in discovering new components for various biomedical applications, including anticancer therapies [31].

Our preliminary (unpublished) data indicate a potential negative correlation between the number of mitoses and lymphocytes in the TDL of healthy rabbits across different age groups (from immature to mature). The objective of this review is to critically assess existing research on age-related mitoses, cytokines, and hormones in lymphatic fluid, particularly in TDL of neonatal (immature) and adult (mature) subjects. Furthermore, this review aims to explore new pathways for drug design and development based on these findings.

By mapping out the age-related differences in mitotic regulators within lymph, this study seeks to pave the way for innovative drug design strategies. These strategies may address complex diseases such as cancer and graft-versus-host disease by leveraging the unique characteristics of mitotic mediators in different age groups.

Materials and methods.

Data Sources and Search Strategy

To conduct a comprehensive review of the existing literature, we systematically searched multiple electronic databases, including PubMed/Medline, WorldCat, Google Scholar, and Index Copernicus. The search focused on identifying relevant articles published over the past forty years.

The goal was to gather data pertaining to age-related mitoses, cytokines and hormones in lymphatic fluid, and specifically in thoracic duct lymph (TDL) in both neonatal (immature) and adult (mature) populations.

Inclusion and Exclusion Criteria

Inclusion criteria for the articles were as follows:

Studies examining age-related variations in mitoses.

Research focused on cytokines and hormones present in lymph.

Investigations into the characteristics of mitoses, cytokines, and hormones in TDL of healthy newborns (neonatal, immature).

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Studies exploring mitoses, cytokines, and hormones in TDL of healthy adults (mature).

Articles were excluded if they:

Did not focus on the specified age groups (neonatal and adult).

Lacked detailed data on mitoses, cytokines, or hormones in lymphatic fluid or TDL.

Were review articles without original research data.

Search Terms and Keywords

We employed a combination of the following keywords and medical subject headings (MeSH terms) to conduct our search: "Mitosis", "Age-related mitosis", "Cytokines in lymph", "Hormones in lymph", "Thoracic duct lymph"

"Neonatal lymphocytes"

"Immature lymphocytes"

"Adult lymphocytes"

"Lymphatic fluid"

Boolean operators (AND, OR) were used to refine the search queries and ensure comprehensive coverage of relevant studies.

Data Extraction and Analysis

A total of 445 articles were initially identified through our database searches. These articles were then subjected to a multi-step screening process:

Title and Abstract Screening: Two independent reviewers screened the titles and abstracts of all identified articles to exclude studies that did not meet the inclusion criteria.

Full-Text Review: The full texts of the remaining articles were reviewed to confirm their eligibility based on the predefined criteria. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Data Extraction: Relevant data from each included study were extracted using a standardized data extraction form. Extracted data included:

Study characteristics (author, year, journal, study design)

Population details (age group, health status)

Key findings related to mitoses, cytokines, and hormones in lymph and TDL

Methodological quality and limitations

Quality Assessment

The methodological quality of the included studies was assessed using criteria adapted from established guidelines for observational studies and clinical trials. These criteria included:

Study design and methodology

Sample size and population representativeness

Measurement techniques and data reliability

Statistical analyses and result interpretation

Data Synthesis

Extracted data were synthesized qualitatively and quantitatively where applicable. Trends and patterns in age-related mitoses, cytokines, and hormones in lymphatic fluid and TDL were identified and analyzed. The synthesis aimed to identify gaps in the current knowledge and propose potential avenues for future research, particularly in the context of drug design and development.

Ethical Considerations

This study did not involve any primary data collection or direct interaction with human or animal subjects, thus ethical approval was not required. All reviewed studies were assumed to have followed appropriate ethical guidelines as per their respective institutions and publication standards.

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The analysis of 445 articles provided a comprehensive overview of age-related differences in mitoses and the roles of cytokines and hormones in lymph and TDL. The findings underscore the need for further research to develop innovative drug design strategies that leverage the distinct characteristics of mitotic mediators across different age groups. This methodological approach ensures a thorough and unbiased review of existing literature, contributing valuable insights to the field of biomedical research.

Results.

Overview of Research Findings

Our comprehensive review of 445 articles yielded several key insights into the age-related variations in mitoses, cytokines, and hormones in thoracic duct lymph (TDL). The findings can be categorized into several thematic areas based on the nature and focus of the studies.

Morphological and Quantitative Changes in TDL Mitoses

Three studies specifically investigated the morphological properties and quantitative changes in mitoses within TDL under normal physiological conditions. These studies provided detailed descriptions of the cellular structures and variations in mitotic activity across different age groups, highlighting significant age-related changes in TDL mitoses.

TDL Lymphocytes: Quantitative and Morphological Features

One particular study focused on the quantitative and morphological characteristics of TDL lymphocytes in both normal and thyroxin-treated conditions. This research provided valuable insights into how thyroxin treatment affects lymphocyte morphology and quantity, contributing to a better understanding of hormonal influences on lymphatic cells.

Physiological Studies on Angiotensins, Insulin, Steroid Hormones, and Kinases

Several studies examined the physiological roles of various mediators, including angiotensins, insulin, steroid hormones, and kinases. These studies highlighted the intricate regulatory mechanisms these substances have on cell proliferation and mitosis. The results underscored the complexity of hormonal regulation in lymphatic fluid and its implications for cellular growth and division.

Mediators of Proliferation and Mitosis

A significant portion of recent publications focused on mediators of proliferation and mitosis. These mediators, particularly interleukins, have been extensively studied for their roles in antigen stimulation and other immune responses. The research demonstrated that interleukins in lymph can significantly influence mitotic activity, particularly in response to antigenic stimulation.

Age-Related Influences on the Immune System

Numerous studies have established the impact of age on the immune system, with a particular emphasis on mitotic activity. The findings indicated that immune function and mitotic processes undergo substantial changes with age, affecting overall immune competence and responsiveness. These age-related variations were found to be critical for understanding disease progression and treatment outcomes in different age groups.

Challenges in Drug Design and Development

Despite significant progress in the field of drug design, several articles discussed the ongoing challenges associated with current methodologies. There is a consensus that reductionist approaches, which focus on isolated components of a system for which molecular information is available, often fail to address complex biological problems effectively. The development of new drugs requires intricate, multistep schemes that can control cytotoxicity and ensure comprehensive evaluation of results.

Need for Innovative Drug Design Approaches

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The review highlighted the necessity for innovative approaches in drug design that move beyond traditional reductionist methods. There is a clear need for holistic strategies that consider the complex interplay of various biological factors. These approaches should leverage the distinct age-related differences in mitotic mediators to develop more effective and targeted therapies.

In summary, the review of existing literature provided valuable insights into the morphological and quantitative changes in TDL mitoses, the effects of various mediators on cell proliferation, and the age-related influences on the immune system. These findings underscore the need for advanced, multifaceted approaches in drug design and development. By understanding and utilizing the unique characteristics of mitotic regulators across different age groups, researchers can pave the way for more effective treatments for complex diseases such as cancer and graft-versus-host disease.

Discussion. Despite analyzing a comprehensive set of 445 articles, only the most relevant studies were included to align with the objectives of this article. The findings demonstrate that cell division (mitosis) and gamete production (meiosis) are essential processes for the normal development of organisms. The mammalian cell cycle is meticulously regulated by various checkpoints, ensuring accurate chromosomal segregation and duplication. Over the past decades, extensive research has provided unparalleled insights into the complex process of cell division. There is an ever-expanding catalog of proteins that orchestrate, participate, and coordinate the intricate processes of spindle formation, chromosome dynamics, and the formation and regulation of kinetochore-microtubule attachments.

Role of Classical Microtubule Poisons and Need for Novel Drug Targets

Classical microtubule poisons have been widely and effectively used to combat various cancers. However, their non-selective interference in crucial physiological processes necessitates the identification of novel druggable components specific to the cell cycle and division pathways. Research has extensively studied interleukins in peripheral lymph and TDL for their roles in antigen stimulation and other impacts [32,33]. Several articles have documented the morphological properties and quantitative changes in age-related mitoses within TDL of normal adults.

Development of New Druggable Components

Some authors emphasize the need for new druggable components and highlight that drug design requires executing several complex multistep schemes, controlling cytotoxicities, and then comparing the outcomes [32,33,34]. Flow cytometry revealed increasing levels of various suppressive myeloid cells in lymphoid organs: MDSCs dominated bone marrow (BM) and spleens, M2 macrophages dominated tumor-draining lymph nodes (DLN), and a mixed IL-10(+) TNF-α(+) CD206(–) CX3CR1(+) M1/M2 (M3) macrophage subset dominated the mesothelioma microenvironment. Ki67 staining and cell cycle analysis showed that tumor-associated M1 and M3, but not M2, macrophages were proliferating in situ, with M1 cells arrested in the G1 phase while M3 cells progressed to mitosis.

Age-Related Processes in Immune System Components

Mitosis is an age-related process, similar to other components of the immune system [35,36,37]. It has been suggested that a combination of adjuvant systems could provide enhanced immune activation, typically developed without considering the target population's age [38]. Distinct combinations of TLRAs and C-type lectin receptor agonists may enhance Th1 responses of newborn dendritic cells (DCs) [39]. Neutrophils, monocytes/macrophages, and dendritic cells, which are the first to recognize and respond to infection, exhibit age-related impairments in functions relevant to antiviral responses [40]. Natural killer cells, which control many viral infections, also show age-related changes in phenotype and

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functional responses [41]. Researchers continue to explore the reduced response of aged DCs to RA, which enhances mucosal inflammation in the elderly, increasing their susceptibility to mucosal diseases [42-44].

Experimental Methods and Findings

To obtain mitoses, an original method of collecting central lymph from the cisterna chyli of the thoracic duct was employed. TDL sampling was performed using original glass micropipettes (similar to injection needles). Mitoses were observed in TDL of anesthetized intact rabbits “Chinchilla”: 50 adult rabbits (group 1) and 15 immature rabbits (group 2). The cell specimens were transferred as smears to microscopic slides, stained with Giemsa, and studied under a light microscope. Various stages of mitosis were observed in TDL of immature rabbits (16-25 mitoses per smear). However, asymmetric mitoses and the stages of prophase, metaphase, anaphase, telophase, and cytokinesis were not observed in TDL of adult rabbits. These findings confirm the existence of a mitotic factor in TDL [45]. The observed quantitative differences in age-related mitoses in TDL introduce a new approach to investigating the physiological function and regulation of mitosis [46]. Mitosis has a recurring character, and the study's results suggest a new approach to developing cancer vaccines and other drugs [26].

Implications for Drug Design and Plant-Derived Compounds

Similar changes have been observed in plants. Natural compounds from various plants, microorganisms, and marine species play a crucial role in discovering novel components that can be successfully used in numerous biomedical applications, including anticancer therapeutics [31]. Researchers continue to search for combinations of adjuvant systems to provide immune system correction [47-50].

]. Despite the progress in drug design, there is a prevailing view that reductionist methods, which focus on parts of the system with available molecular information, often fail to solve some complex problems effectively [30].

In summary, the analysis of these studies highlights the importance of a multifaceted approach in drug design, considering the complex interactions within biological systems and the need for age-specific strategies to enhance therapeutic efficacy.

Conclusion. The data reviewed highlight significant changes in the immune system with aging, both under normal conditions and under various impacts. Notably, the differences in thoracic duct lymph (TDL) mitosis mediators between healthy mature and immature organisms remain largely unexplored. This gap underscores the necessity for developing new druggable components that target these specific mediators.

The precise mechanisms underlying age-related changes in mitosis and the associated mediators in TDL of immature and mature organisms under normal conditions are not fully understood. However, it is suggested that the differences in TDL mitosis mediators between healthy newborns (neonatal, immature) and adults (mature) could provide crucial insights for the novel design of drugs aimed at treating cancer, graft-versus-host disease, and other conditions.

Furthermore, the natural age-related changes and differences in mitoses and TDL mediators between healthy immature and mature organisms present a promising predictive model. This model can serve as a foundational strategy for developing new therapeutic approaches across a broad spectrum of biological and medical fields. By leveraging these insights, researchers can enhance the effectiveness of treatments and potentially develop more targeted and age-specific therapeutic interventions.

Conflict of interest

We declare no conflict of interest**.**

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Authors' contribution

Development of the concept, processing of results, interpretation of the results, writing the article- A. Kuznetsov. I declare that this material has not been previously published and is not under consideration by other publishers.

Funding: None.

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ЛИМФАДАҒЫ МИТОЗ РЕТТЕУШІЛЕРІНІҢ ЖАСҚА БАЙЛАНЫСТЫ ӨЗГЕРІСТЕРІ: ИННОВАЦИЯЛЫҚ ДӘРІЛЕРДІ ӘЗІРЛЕУ ПЕРСПЕКТИВАЛАРЫ

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Түйіндеме

Кіріспе: Митоз жас әсерінен болатын, әртүрлі ұлпаларда жүретін және әртүрлі медиаторлармен реттелетін маңызды процесс. Цитокиндер мен гормондар сияқты заттар қазіргі уақытта қатерлі ісік және трансплантаттың иесіне қарсы ауруы сияқты жағдайларды емдеуде қолданылады.

Мақсаты: Бұл зерттеу қалыпты физиологиялық жағдайларда лимфа сұйықтығының, әсіресе кеуде түтік лимфасының (TDL) құрамындағы жасқа байланысты митоздар, цитокиндер және гормондар туралы бар әдебиеттерді сыни тұрғыдан бағалауға бағытталған. Жиналған түсініктер жаңа дәрі-дәрмектің дизайны мен дамуы үшін пайдаланылады.

Материалдар мен әдістер: Соңғы қырық жылдағы жарияланымдарға назар аудара отырып, PubMed/Medline, WorldCat, Google Scholar және Index Copernicus сияқты дерекқорлар арқылы кең шолу жүргізілді.

Нәтижелер: Үш зерттеу қалыпты TDL шегінде жасына байланысты митоздардағы нақты морфологиялық атрибуттарды және сандық ығысуларды атап көрсетті. Басқа зерттеу сау адамдарда және тироксинмен емделгендерде TDL

ISSN 2524 – 0684 e-ISSN 2524 – 0692

лимфоциттерінің сандық және морфологиялық қасиеттерін егжей-тегжейлі сипаттады. Қосымша зерттеулер ангиотензиндердің, инсулиннің және стероидты гормондардың физиологиялық рөлдерін зерттеді. Соңғы зерттеулер пролиферация және митоз медиаторларына көбірек назар аудара бастады, интерлейкиндер олардың антигенді ынталандыратын қасиеттері мен басқа әсерлері үшін зерттеледі. Атап айтқанда, иммундық жүйенің, әсіресе митоздың жасына байланысты өзгерістері анықталды. Дәрілік заттарды жобалаудағы елеулі жетістіктерге қарамастан, көбінесе тым жеңілдетілген тәсілдерге байланысты белгілі бір қиындықтар сақталады.

Қорытынды: Дәлелдемелер иммундық жүйе қалыпты жағдайда да, сыртқы факторлардың әсерінен де жасқа байланысты өзгерістерге ұшырайтынын көрсетеді. Дегенмен, жетілмеген (неонаталдық) және жетілген (ересек) организмдер арасындағы TDL митоз медиаторларындағы ерекше айырмашылықтар әлі де зерттелмеген. Дәрілік заттардың жаңа құрамдас бөліктерін әзірлеуге аса қажеттілік бар. Дені сау жаңа туған нәрестелер мен ересектер арасындағы TDL митоз медиаторларының байқалған өзгерістері қатерлі ісікке, трансплантатқа қарсы ауруға және басқа да жағдайларға инновациялық емдеу әдістерін жасаудың перспективалы жолын ұсынады.

Түйін сөздер: дәрілік дизайн, жасқа байланысты митоз, кеуде түтігінің лимфасы.

ВОЗРАСТНЫЕ ИЗМЕНЕНИЯ РЕГУЛЯТОРОВ МИТОЗА В ЛИМФЕ: ПЕРСПЕКТИВЫ РАЗРАБОТКИ ИННОВАЦИОННЫХ ЛЕКАРСТВЕННЫХ СРЕДСТВ

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Аннотация

Введение: Митоз является важным процессом, на который влияет возраст, он происходит в различных тканях и регулируется различными медиаторами. Такие вещества, как цитокины и гормоны, в настоящее время используются в терапевтических вмешательствах при таких состояниях, как злокачественное новообразование и реакция «трансплантат против хозяина».

Цель: Это исследование направлено на критическую оценку существующей литературы о возрастных изменений в митозе, цитокинах и гормонах в лимфатической жидкости, особенно в лимфе грудного протока (TDL), в нормальных физиологических условиях. Собранные данные будут использованы для проектирования и разработки новых лекарственных средств.

Материалы и методы: Обширный обзор был проведен с использованием таких баз данных, как PubMed/Medline, WorldCat, Google Scholar и Index Copernicus, с упором на публикации за последние сорок лет.

Результаты: Три исследования выявили специфические морфологические признаки и количественные изменения в возрастных митозах в пределах нормального TDL. Другое исследование детализировало количественные и морфологические свойства лимфоцитов TDL у здоровых людей и тех, кто получал тироксин. Дополнительные исследования углубились в физиологическую роль ангиотензинов, инсулина и стероидных гормонов. Недавние исследования все больше внимания уделяют медиаторам пролиферации и митоза, при этом интерлейкины изучаются на

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

предмет их антигенстимулирующих свойств и других эффектов. Примечательно, что были выявлены возрастные изменения в функционировании иммунной системы, особенно в митозе. Несмотря на значительные достижения в разработке лекарств, определенные проблемы сохраняются, часто из-за слишком упрощенных подходов.

Заключение: Имеющиеся данные свидетельствуют о том, что иммунная система претерпевает возрастные изменения как в нормальных условиях, так и под влиянием внешних факторов. Однако специфические различия в медиаторах митоза TDL между незрелыми (неонатальными) и зрелыми (взрослыми) организмами остаются недостаточно изученными. Существует острая необходимость в разработке новых компонентов лекарств. Наблюдаемые различия в медиаторах митоза TDL между здоровыми новорожденными и взрослыми открывают многообещающий путь для создания инновационных методов лечения злокачественных новообразований, реакции «трансплантат против хозяина» и других состояний.

Ключевые слова: дизайн лекарств, возрастной митоз, лимфа грудного протока.