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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CHRONIC INFECTION WITH SCHISTOSOMA HAEMATOBIUM LEADS TO THE DEVELOPMENT OF SQUAMOUS CELL CARCINOMA OF THE BLADDER

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Abstract.

Schistosoma haematobium (S. haematobium) infection is a significant global health concern, impacting over 200 million individuals worldwide. Chronic infection with *S. haematobium* is closely associated with the development of squamous cell carcinoma (SCC) of the bladder. This pathological link arises from the intricate interplay of molecular pathways and cellular processes, including persistent inflammation, deoxyribonucleic acid (DNA) damage, altered signaling pathways, and epigenetic dysregulation. Chronic immune responses to *S. haematobium* infection, combined with environmental carcinogen exposure, create a pro-inflammatory environment that drives DNA damage, mutagenesis, and epigenetic alterations in urothelial cells. These changes culminate in uncontrolled cell proliferation, angiogenesis, and tissue remodeling, which collectively promote tumorigenesis. This study investigates the molecular and inflammatory mechanisms underlying SCC development in chronic *S. haematobium* infection, providing insights into its complex pathogenesis.

Key words. Schistosoma haematobium, squamous cell carcinoma, chronic infection, DNA damage, inflammation and carcinogenesis.

Introduction.

Schistosoma haematobium (S. haematobium) is a parasitic flatworm that causes urogenital schistosomiasis, a debilitating disease affecting millions worldwide, primarily in the Indian subcontinent, the Middle East, and Africa. In this infection, adult worms reside in the blood vessels surrounding the urinary bladder, laying eggs that are excreted in the urine. This leads to inflammation, tissue damage, and potentially life-threatening complications [1]. Schistosomiasis is an ancient health complication, and despite global efforts, it remains a significant public health burden in many developing countries, with over 240 million people affected. Notably, more than 90% of these cases are reported in Africa.

There are five main species of the Schistosoma parasite that cause serious infections: *S. haematobium*, *S. mansoni, S. japonicum, S. intercalatum*, and *S. mekongi*. Of these, *S. haematobium* is primarily responsible for chronic urogenital schistosomiasis, leading to severe complications such as bleeding, anemia, renal failure, and tumor formation [2]. The infection is particularly associated with squamous cell carcinoma (SCC) of the bladder, a form of cancer that has been epidemiologically linked to schistosomiasis, although the precise mechanisms behind this connection remain unclear.

The relationship between schistosomiasis and bladder cancer (BC) is thought to involve a complex interplay of molecular mechanisms. The interaction between the parasite and the host's immune system, combined with environmental factors and carcinogenic agents such as cigarette smoking, contributes to the neoplastic transformation of bladder cells [3]. Studies have shown that the risk of BC increases by 2–14 times in individuals with schistosomiasis, particularly those infected with *S. haematobium* [4]. This infection is considered a major health risk, directly correlating with the development of BC.

Infection with *S. haematobium* and the Immune Response to Infection.

Upon infecting the host, *S. haematobium* cercariae transform into schistosomulae, the juvenile form of this blood fluke. The schistosomulae then migrate through the bloodstream to the liver, where they mature into adult schistosomes [5]. The male and female schistosomes subsequently reach the urogenital veins, where sexual maturation occurs, and the female begins egg production. This process of chronic schistosomiasis begins several weeks or months after the entry of cercariae into the host. The severity of the infection largely depends on factors such as the extent of worm infestation, the rate of egg deposition, and the location where parasitic eggs are trapped in granulomas. In the chronic stage of infection, a smaller number of eggs enter the bloodstream and travel to various organs, as opposed to being excreted through the stool. Most eggs remain trapped in liver tissues, causing symptoms of hepatic schistosomiasis [6].

The immune response to *S. haematobium* infection is predominantly driven by a T helper 2 (Th2) response, with associated cytokine profiles and activation of certain immune cells [7]. However, the role of the T helper 1 (Th1) response and its cytokines, as well as the balance between Th1 and Th2 responses, plays a crucial role in determining the course of infection. An overly strong or rapid immune response from either Th1 or Th2 cells may result in severe tissue damage. Initially, during the acute phase of infection, the immune response is Th1-mediated, targeting schistosomulae and involving cytokines such as interleukin-1 (IL-1), interleukin-1 (IL-12), Tumor Necrosis Factor-alpha (TNF-α), and interferon [5]. As the infection progresses, typically 6–8 weeks after initial exposure, the immune response shifts towards a Th2-mediated response, particularly as egg deposition begins. This phase is characterized by the release of cytokines like interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13, and immunoglobulin (Ig) E. Over time, the Th2 response contributes to the formation of granulomas and tissue fibrosis, which can become irreversible. The egg, therefore, plays a central role in the pathogenic process, initiating granuloma formation and a cascade of events that set the stage for chronic infection [8].

Acute Infection and Immune Response.

Acute schistosomiasis manifests shortly after *S. haematobium* cercariae penetrate the skin and begin their migration. During this acute phase, circulating immune complexes play a

significant role in determining the severity and intensity of symptoms. Eosinophil poisoning is a key factor in this process [9]. If the infection becomes severe, elevated eosinophil levels are often observed. When eosinophils are activated, they release major basic protein and eosinophil cationic protein, which may exacerbate disease severity through direct toxicity to major organs [5]. The acute phase is also associated with a distinct cytokine profile, including increased levels of proinflammatory cytokines such as IL-1, IL-6, and TNF-α, alongside a suboptimal Th2 response marked by IL-4 and IL-5. This cytokine imbalance helps explain the altered medical state during the acute phase, which may resolve through immune system action. However, in some cases, the parasite may overwhelm the immune response, preventing resolution and leading to chronic infection [6].

Chronic Infection and the Immune Response.

Chronic schistosomiasis is primarily driven by granulomatous inflammation, which results from the accumulation of eggs released into the tissues. Research has shown that the deposition of *S. haematobium* eggs in the bladder causes significant alterations in proteins and pathways that contribute to pathology [10]. These eggs travel through the portal venous system and may embolize in the liver, spleen, or, in severe cases, the lungs, brain, or spinal cord before reaching other tissues [11]. The secreted proteins and carbohydrates from eggs trapped in tissues activate the host's Th2 immune response, leading to an eosinophilic granulomatous reaction [12].

In the granulomatous response to infection, several immune cells are activated, including thymus- and bone marrow-derived cells, neutrophils, eosinophils, macrophages, myofibroblasts, and epithelioid cells, initiating a cascade of inflammatory events. The initiation of the Th2 immune response is largely dependent on IL-4, which is produced by various sources other than dendritic cells. Additionally, interleukin-10 (IL-10), produced by dendritic cells, plays a crucial role in suppressing IL-12 production and curbing the development of Th1 responses. IL-4 further limits the Th1 response and acts as a growth factor to strengthen Th2 activity [13].

As the granulomas mature, collagen and fibrosis begin to form around the trapped eggs, leading to irreversible tissue damage. This fibrosis, especially around the portal region, can result in periportal and hepatic fibrosis, obstructing blood flow and causing complications like portal hypertension and esophageal bleeding [14]. While granulomas prevent excessive inflammation and protect the host from egg-related toxins, such as Omega-1 and immune protective secreted enzyme (IPSE)/alpha-1, they also represent the primary pathological feature of schistosomiasis. In the chronic phase, granuloma formation remains crucial for the parasite's life cycle, although it causes significant immune responses and infection-related complications [15].

Chronic infection leading to development of SCC of the bladder.

Mechanisms of chronic infection:

Chronic infection caused by *S. haematobium* is primarily believed to contribute to BC through indirect mechanisms rather than direct ones. The adult worms deposit eggs in tissues, resulting in a prolonged inflammatory response that triggers the production of various growth factors and carcinogenic biochemical compounds [16]. Furthermore, chronic inflammation alters the host's local immune system, promoting co-infections with bacterial and viral agents that contribute to malignant transformation of the bladder epithelium [17].

During chronic infection, two key proteins—IPSE and Omega-1 ribonuclease—are secreted by the live embryos. These proteins exhibit strong immunogenicity, which is linked to their glycan moiety, and facilitate the egg's passage through the bladder wall without inducing fibrosis, which would otherwise cause egg trapping. However, the entrapped eggs inside the bladder wall produce oxygen-derived free radicals, exacerbating the inflammatory response [18]. These free radicals are capable of inducing deoxyribonucleic acid (DNA) damage and generating multiple carcinogenic substances, including polycyclic aromatic hydrocarbons and N-nitrosamines. Normally, the urothelial (transitional) epithelium serves as a protective barrier, preventing the passive entry of toxic substances into the bladder wall. However, in the case of chronic infection, this barrier can become compromised, allowing for the increased penetration of carcinogens. The continuous deposition, retention, and movement of eggs through the urothelium and bladder wall lead to tissue damage. Additionally, the toxic substances produced by the eggs promote cell proliferation, further exacerbating urothelial damage and eventually leading to the formation of BC [19].

Moreover, during the chronic phase, the inactivation of cyclin-dependent kinase inhibitors (such as p27) and the upregulation of B-cell lymphoma 2 (Bcl-2) expression contribute to an increased rate of cell proliferation and suppression of apoptosis. These changes also impact the G1 phase of the cell cycle by inhibiting the activation of cyclin D and cyclin-dependent kinase 4 [20]. This combination of inactivation and upregulation promotes uncontrolled cell proliferation and blocks the action of certain pro-apoptotic proteins. Consequently, the proliferative response aimed at repairing tissue damage becomes amplified, disrupting the regulatory processes of oncogenes (through upregulation) and tumor suppressor genes (through downregulation) [15].

Role of immune response.

The chronic inflammatory response induced by *S. haematobium* eggs remains central to the development of SCC of the bladder. This inflammation is marked by the release of cytokines, chemokines, and reactive oxygen species (ROS), all of which contribute to tissue damage and genomic instability. Cytokines such as TNF-α, IL-6, and IL-10 are elevated during chronic infection, driving the recruitment of immune cells to the bladder [21]. This persistent immune cell infiltration promotes the release of ROS and reactive nitrogen species, which interact with DNA to create mutagenic lesions [22]. Moreover, oxidative stress exacerbates cellular damage, altering key signaling pathways involved in apoptosis, cell proliferation, and differentiation.

The chronic inflammatory milieu not only induces cellular damage but also supports tumor progression by fostering an immunosuppressive microenvironment. Regulatory T cells and myeloid-derived suppressor cells become prominent within the bladder tissue, suppressing cytotoxic T lymphocyte activity and enabling tumor cells to evade immune surveillance [23]. These

immune alterations underscore the dual role of inflammation as both a driver of mutagenesis and a facilitator of tumor immune evasion.

The interaction between chronic inflammation and DNA damage is further compounded by oxidative stress-induced mutations. These mutations often target oncogenes and tumor suppressor genes, creating a microenvironment conducive to malignant transformation. Prolonged exposure to inflammatory mediators not only damages DNA but also disrupts cellular homeostasis by altering critical signaling pathways, such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Signal Transducer and Activator of Transcription 3 (24). These pathways play pivotal roles in regulating immune responses, apoptosis, and proliferation, and their dysregulation significantly contributes to carcinogenesis. The NF-κB pathway, in particular, is implicated in promoting chronic inflammation and resistance to apoptosis, thereby enabling the survival of malignant cells [24].

Genetic and epigenetic modifications.

Regardless of the tumor stage, the most frequent genomic alteration observed is the absence of heterozygosity on chromosomes like 9p and 9q [25]. This lack of heterozygosity does not differentiate squamous cell bladder carcinoma (SA-BC) from Schistosoma-non-associated BC. However, given that BC is cytogenetically diverse, the pathogenesis may vary across individual cases [26]. It was found that squamous cancers, but not urothelial cancers, showed increased Bcl-2 gene overexpression in patients with SA-BC. This suggests that Bcl-2 amplification may contribute to the predominance of SCC in SA-BC [27]. Bcl-2 upregulation impairs genomic stability, suppresses programmed cell death, and cooperates with several proto-oncogenes to promote carcinogenesis. In 32% of tumors, Bcl-2 overexpression was identified; in 73% of tumors, abnormal tumor protein 53 (TP53) mutations were discovered; and in 13% of tumors, both Bcl-2 and TP53 were present [28]. Additionally, SA-BC showed amplification of the cyclooxygenase-2 (COX-2) gene, which plays a critical role in the multistage, complex process of SA-BC-linked carcinogenesis. Other notable variants included harvey rat sarcoma virus oncogene homolog, p16 deletion, p15 enhancing epidermal growth factor receptor, TNF-α, and cellular erythroblastic leukemia viral oncogene homolog 2. Overproduction of prostaglandins upregulates COX-2, decreases killer T cell activity, and increases Bcl-2 and glutathione-S-transferase levels [29]. These mutations may enhance carcinogenicity by inhibiting cell apoptosis, inducing immunosuppression, downregulating adhesion molecules, degrading the extracellular matrix, and promoting angiogenesis. Furthermore, kirsten rat sarcoma viral oncogene homolog gene mutations have been identified in bladder abnormalities, suggesting a link between the emergence of this mutation and SA-BC [17].

Emerging evidence highlights the role of epigenetic modifications in the pathogenesis of SCC of the bladder. DNA methylation and histone acetylation are significantly altered in patients with chronic *S. haematobium* infection. Hyper-methylation of tumor suppressor genes, such as cyclin-dependent kinase inhibitor 2A and ras association domain-containing protein 1, has been observed, leading to their silencing and subsequent loss of function [30,31]. These epigenetic changes are thought to be driven by chronic inflammation and the release of parasitic antigens [32]. Targeting these epigenetic alterations offers a potential therapeutic avenue for mitigating the progression of bladder cancer in endemic regions.

Dysfunction of the tumor suppressor gene *TP53* leads to the accumulation of the p53 protein in tumor cells, which is associated with the histological grade of the tumor [33]. Both pre-malignant and malignant lesions are linked to schistosomiasis and are characterized by elevated p53 levels. These increased p53 levels in pre-malignant lesions likely contribute to the TP53 alterations observed in bladder lesions caused by Schistosoma infection [29]. Additionally, nitrosamines become carcinogenic when combined with the eggs trapped in the bladder, as both the eggs and the cancer-causing nitrosamines are introduced to the bladder mucosal lining. Apart from this, epigenetic modifications in the host genome may also play a role in the development of SA-BC. DNA extracted from individuals with urinary Schistosoma infection shows hypermethylation of several genes. Moreover, in bladder tissue treated with agents that suppress DNA methylation, urothelial hyperplasia is reduced, indicating the importance of these epigenetic changes [15].

Environmental factors.

Environmental factors, including smoking and exposure to industrial chemicals, synergize with *S. haematobium* infection to exacerbate bladder carcinogenesis. Cigarette smoke contains polycyclic aromatic hydrocarbons and nitrosamines, which interact with oxidative stress induced by chronic inflammation to further damage DNA [34]. Smoking also impairs DNA repair mechanisms and enhances the expression of genes involved in epithelial-mesenchymal transition (EMT), a process critical for tumor invasion and metastasis [35]. Industrial chemicals, such as aromatic amines and chlorinated hydrocarbons, exacerbate the pro-inflammatory state within the bladder, compounding the carcinogenic effects of chronic infection [36]. Diet, in this regard, is a significant factor that may induce systemic and/or local inflammation, further promoting tumorigenesis.

These immune processes, in combination with environmental factors such as tobacco use, diet, and exposure to industrial chemicals, contribute to the rapid progression of invasive squamous cell bladder carcinoma [25]. Environmental factors induce multiple genetic mutations and modify the tumor microenvironment, including immune cells and fibroblasts. Cigarette smoking, in particular, is a major environmental factor that damages DNA structure and impairs DNA repair mechanisms. Smoking also induces morphological changes, activates EMT, and stimulates the mitogen-activated protein kinase pathway [27]. Some chemical agents, such as 2-naphthylamine, toluene, 4-aminobiphenyl, 4,4′-methylenebis polyaromatic hydrocarbons, and perchloroethylene, have been implicated in triggering or enhancing bladder tumor development, although the detailed mechanisms behind their involvement remain unclear. These agents likely exacerbate inflammation, which is directly linked to tumor initiation and growth. In addition, dietary factors may further contribute to

systemic or local inflammation, promoting the progression of BC [19].

Conclusion.

In conclusion, the persistent presence of *S. haematobium* infection initiates a multifaceted cascade of events, involving genetic, immunological, and environmental factors, which together contribute to the development of SCC of the bladder. The deposition of parasite eggs in the bladder tissues induces a chronic inflammatory response, stimulating the production of growth factors and carcinogenic substances. This inflammatory environment, along with concurrent bacterial and viral co-infections, further exacerbates the transformation of the bladder epithelium. Moreover, the dysregulation of cell cycle control, coupled with the inactivation of cyclin-dependent kinase inhibitors and the upregulation of Bcl-2 expression, leads to uncontrolled cellular proliferation. This results in significant tissue damage, ultimately culminating in the formation of BC. Overall, the complex interplay of immune responses, genetic alterations, and environmental factors is central to the pathogenesis of SCC of the bladder in the context of chronic *S. haematobium* infection.

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