Xia & He Publishing Inc.

Instruction for Manuscript Preparation

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I. Article-specific Formatting Requirements

A. Original Research Articles

The manuscript, excluding the Abstract but including the References, must not exceed 5000 words and have no more than 50 references.

i. Abstract

The Abstract will be written as a complete but succinct summary of the study, its main objectives, results, key findings, and implications for the field or specialty. The Abstract may not exceed 275 words, will be structured with the following section headings: Background and Objective(s), Methods, Results, and Conclusions. Acronyms and abbreviations must be defined the first time they appear. Abbreviations will only be used if the abbreviated term appears 3 or more times in the Abstract. Footnotes and references are not permitted.

Abstract Headings

Background and objective(s): The Background statement supports the importance of the study's objective(s). The Objective states the question(s) addressed by the study, from which the study design was determined.

Methods: This section briefly describes the basic study design and techniques used to fulfill the objective(s) of the study.

Results: The Results section reports the main data obtained by the study, including statistical values (e.g. confidence intervals or P-values). The results of each experiment described in the Methods should be stated. The appropriate values and statistical differences will be reported so that readers can determine the absolute as well as the relative impact of the results.

Conclusions: The Conclusions section should state only the logical interpretations that can be drawn from the data that was reported in the Results, and how the study contributes to the knowledge of the research or medical community.

Keywords: Three-to-four keywords should be selected from the Medical Subject Headings (MeSH) descriptor terms listed in the National Library of Medicine's controlled vocabulary database. These terms can be searched using the MeSH browser at: http://www.nlm.nih.gov/mesh/MBrowser.html. The keywords will be presented in the row-list style and written in lowercase, separated by semicolons, with no period at the end of the list.

ii. Main Body of the Manuscript

The sections of the main body of the manuscript should be arranged in the following order: Introduction, Methods, Results, Discussion, Conclusions, Acknowledgments, References, Figure legends, Tables, Figures.

INTRODUCTION

The Introduction should focus on the rationale for conducting the study—why it was performed, and why the objectives were formulated as they were. The Introduction should succinctly convey the authors' depth of understanding of the problem(s) addressed by the study, and the work of other investigators in this area. The objective(s) is then succinctly stated in the final paragraph. The statement of the objective is the most important sentence of the paper, since it determines all that follows after it. A brief outline of the study design is optional, but sometimes highly recommended if the design is not immediately clear from the objective or to entice the reader to read further. The Introduction is not divided into subsections. The results and conclusions of the study should not be included in the Introduction.

METHODS

The Methods section should provide all the details that would be required for another investigator to repeat the work *as it was performed by the authors*. A beginning subsection "Study design" is highly recommended, that gives an overview of how the study satisfied the objectives of the study (as stated in the

last paragraph of the Introduction). Subsequent subsections should be presented *in the order in which the protocols were performed*.

It is highly recommended that each subsection begin with a sentence explaining the reason for the protocol, that is, how the protocol contributed to satisfying the objectives of the study. The steps taken for each protocol discussed in each subsection should be presented *in the order in which they were performed*. The results of an experiment should not be included in the Methods section, unless the results determined the direction of further experiments.

By convention, the last subsection should discuss the methods used to perform statistical analyses.

Methods that have been published previously and used without significant alteration may be described briefly, with the appropriate reference. When significant changes have been made to a method, however, those changes should be described in detail, with citations as appropriate. Do not have a separate subsection for listing materials or equipment; but do list the materials and equipment within the protocols if they influenced the data (see below). No materials or methods should be presented outside of the Methods section. Do not state or repeat the steps of an experimental procedure in the Results section or in the Figure Legends.

For human trials, the type of study should be indicated from the following list: randomized controlled trial, cross-sectional study, cohort study, case series, or survey. In addition, the following study-relevant information should be presented: participating institutions, number of subjects, method of selection, recruitment, enrollment, randomization, withdrawal and completion, and assignment to interventions, method of administration, and duration of the intervention. The authors will provide declarative statements that (a) informed consent in writing was obtained from each patient prior to enrollment; (b) the study protocol was approved by the appropriate institutional review committee (IRB), with the name of the committee and institution being clearly stated; and (c) the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. No information that could identify a patient can be shown without express written permission from the patient.

For animal studies, it will be clearly stated that approval was obtained from an institutional animal care committee and that all animals received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and

published by the National Institutes of Health (NIH publication 86-23 revised 1985).

All experimental methods described in the Methods section must have accompanying data presented in the Results section or additional materials, and vice versa (all data presented must have the experimental procedures described in the Methods section). The complete names and locations (city, state/province and country) must be provided for the manufacturers of drugs, tools, instruments, software, reagents and equipment.

RESULTS

The subsections of the Results should correspond to the subsections of the Methods, as much as practical. Reasons for performing an experiment or protocol may be summarized, but not to replace explanations that more properly belong in the Methods section.

There should be data reported for each experiment described in the Methods section. The Results section should objectively present the *data* in a straightforward manner, noting the degree of significance in differences when appropriate. The Results section should not include interpretations of the data or conclusions, unless they redirected the investigation. Where data is presented in a table or figure, the data should be summarized in the text and the reader referred to the table or figure. Each table or figure should be referred to, and in numerical order.

The Results section usually does not include any background information or discussion of results from previously published studies. Therefore, in general, no references are present in the Results text.

Citing “data not shown” is discouraged; however, if unavoidable the term will be presented at the end of the sentence containing the description of the findings and written in parentheses as “…(data not shown)…”

DISCUSSION

It is highly recommended that the Discussion section begin with a very brief summary (1-3 sentences) of the study’s objectives, the methods used to

achieve the objectives, and the results. Repetitions of information that was already provided in the Introduction, or information in support of the study's importance or objectives, is misplaced and discouraged.

Remaining paragraphs of the Discussion should focus on interpretations of the data of the study, with thoughtful comments on the novelty or unexpected features of the results, and references to relevant past studies.

The paragraph before the final summary and conclusions should discuss the limitations of the study. Limitations of the study are only those features that weakened the statistical power of the data, or prevented the full realization of the study's objectives (as stated in the Introduction).

New data (that is, that was not in the Results section) should not be presented in the Discussion section. The data presented in the Results section, including figures, tables and supplemental materials, should not be repeated in the Discussion section.

CONCLUSIONS: The Conclusions section should briefly summarize conclusions that are directly supported by the evidence, and comment on the implications of the findings.

Acknowledgments

This section should acknowledge any and all personal assistance and providers of special reagents from sources that do not fulfill the requirements of authorship; individuals' names and affiliations should be provided in full. Grant support and other financial assistance should be specified, with grant numbers (if available; written as "No. ###") and the author to whom the grant was awarded (written as abbreviated given name(s) and full last name "to AZ Wang"). The names of (in full and with affiliations, if applicable) and funding sources for individuals who provided writing assistance should be given in this section.

REFERENCES

References will be cited according to the rules recommended by the International Committee of Medical Journal Editors and NLM. References are numbered consecutively in the order in which they first appear in the paper, and are formatted within square brackets, for example, “Tam et al. [3] reported that…”.

Citations with multiple references (e.g. 2,3,4,7,9) can be abbreviated as: [2-4, 7, 9]. The citation numbers within the brackets should placed after a coma and a period [e.g. ", [7-10]"; ". [2]"], and before a semi-coma and a colon and a semi-colon [e.g. " [7-10];"].

Commonly used reference styles are listed as below, or can be found at: https://www.nlm.nih.gov/bsd/uniform_requirements.html .

Reference examples

Articles in journals

List all authors up to six, and use "et al." When the number is greater than six, use the following format:

Article in print

Yi SG, Sadhu AR, Jones SL, Turner Krista, Monsour H, Donahue K, et al. The Effect of Adrenal Replacement Therapy on Rates of Fungal Colonization and Mortality in Critically Ill Patients Awaiting Liver Transplantation. J Clin Transl Hepatol. 2015; 1(1):2-8.

Issue with supplement

Kim WR. The burden of hepatitis C in the United States. Hepatology 2002; 36 (Suppl 1):S30–S34.

Issue with no volume

Ahrengart L, T?rnkvist H, Fornander P, Thorngren KG, Pasanen L, Wahlstr?m P, et al. A randomized study of the compression hip screw and Gamma nail in 426 fractures. Clin Orthop Relat Res 2002; (401):209-22.

Article published electronically ahead of the print version

Yang WJ, Wu YB, Chen L, Xu KK, Xie YF, Wang JJ. Two Chitin Biosynthesis Pathway Genes in *Bactrocera dorsalis* (Diptera: Tephritidae): Molecular Characteristics, Expression Patterns, and Roles in Larval-Pupal Transition. J Econ Entomol. 2015 Oct; 108(5):2433-42. Epub 2015 Jul 1.

Books and other monographs

Authors

Smith, B. M. Basics of Analytical Chemistry and Chemical Equilibria. Hoboken: John Wiley & Sons, Inc., 2013.

Organization as author

American Psychiatric Association. Practice Guideline for the Treatment of Patients with Eating Disorders. 3rd edition. Washington, DC: American Psychiatric Association; 2006.

Editor(s), compiler(s) as author

Dawson C., Whitfield HN, editors. ABC of Urology. 2nd ed. Oxford: Blackwell Publishing Ltd.; 2006.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter/Article in a book

Shah J. Bladder Outflow Obstruction. In: Dawson C., Whitfield HN, editors. ABC of Urology. 2nd ed. Oxford: Blackwell Publishing Ltd.; 2006. p. 6-9

E-book

Tissue, B. M. Basics of Analytical Chemistry and Chemical Equilibria [Internet]. Hoboken: John Wiley & Sons, Inc., 2013. [cited 2015 May 21]. Available from Wiley Online Library:http://onlinelibrary.wiley.com/book/10.1002/9781118647042

Conference proceedings

Marle F, Jankovic M, Maurer M, Schmidt MD, Lindemann U, editors. Risk and Change Management in Complex Systems. Proceedings of the 16th International DSM Conference; 2–4 2014 July 2-4; Paris, France. Dutch: Elsevier; 2014.

Conference paper

Ollmar S, Nicander I, ?berg I, Birgersson U. Evolution of a Diagnostic Decision Support Tool Based on Electrical Impedance. In: Hermann Scharfetter, Robert Merwa, editors. 13th International Conference on Electrical Bioimpedance and the 8th Conference on Electrical Impedance Tomography; 2007 Aug 3-Sep 2; Graz, Austria. Berlin: Springer; 2007. p. 4-7.

Dissertation

Grant, C. Grounded in your culture: the hidden key to promoting academic achievement among African American adolescent males [Dissertation]. Minneapolis:Capella University; 2010.

Patent

Cheng, DY and Wiersma SJ, inventor; International Power Technology, Inc., assignee. Composite membrane for a membrane distillation system, United States Patent US 4419242. 1983 December 6.

Unpublished Material

In press or forthcoming

Lan T, Chang L, Wu L, and Yuan YFIL-6 plays a crucial role in HBV infection. J Clin.J Clin Transl Hepatol. Forthcoming 2015.

Electronic Material

Homepage/Web site

rsc.org [Internet]. London: Royal Society of Chemistry; c2015 [updated 2002 May 16; cited 2015Oct 26]. Available from: http://www.rsc.org/.

TABLES

All tables should provide concise but detailed information without the need to reference any portion of the text in the main body of the manuscript (or elsewhere). The information provided in the table should provide additional information that is not present in the text, to avoid redundancy.

The tables should be numbered according to their sequential presentation in the manuscript. Each of the tables should be on a separate page, starting immediately after the figure legends, or immediately after the Reference list if there are no figure legends. The tables should not be submitted as a separate file.

Tables should have a clear descriptive title that includes a summary of the features or variables described in the first column and the treatment groups in the first row of the table. For example, “Table 1. Clinical features of the patients and healthy control group”, where the clinical features are listed in cells of the first column beginning with the second row, and the patients and control groups are in cells of the first row, beginning with the second column (see example below). However, if the experimental/treatment groups far outnumber the variables, it is prudent for space considerations to reverse the column/row assignments. The title is above the table; it does not constitute the first row of the table.

The table should be written using the Table function in Microsoft Word (not embedded Excel/.xls or image files). Tables should read vertically, if space allows, and have headings for each column prepared *without the use of tabs*. Abbreviations used in the table should be defined below the table in alphabetical order, unless they were defined in the main body of the paper.

Table 1. Clinical features of the patients and healthy control group

	Patients	Control	P-value
Body mass index, kg/m^2			
Systolic blood pressure, mmHg			
Diastolic blood pressure, mmHg			

FIGURES

All figures must be referred to in the main body of the paper, most often in the Results section, and numbered in the order in which they are referred to in the text.

Figure legends

Figure legends should be listed together on a separate page and located immediately after the Reference list. Figure legends and figures should not be

submitted as a separate file. The figure legends should correspond to the figures. Each of the figures should be on separate pages starting after the tables. The figure legend should begin with a single unifying title that generally describes all the panels of the figure and data presented in the figure. The title should not appear in the figure itself.

Figure legends should interpret the figure for the readers, ensuring that readers understand what the authors need them to understand about the results. The figure legends *should not repeat details given in the Methods, or details that should be stated in the Methods*. Do not redefine abbreviations that were defined in the text. The figure legend should not repeat the data values presented in the figure (including statistical values). The Figure Legend should not include any results or conclusions.

For inclusion of any copyrighted material, documentation that permission has been obtained for reproduction must be provided, and the source acknowledged in the legend. All symbols appearing in the Figure should be defined in the legend (such as asterisks and arrows). In addition, any color distinctions should be defined in the Figure Legend, unless a key has been added as an inset to the figure itself and provides the definitions. For micrographs, a scale bar within the figure is preferable to inclusion of the magnification in the legend.

Figure images

Only images that are essential to justify the conclusions stated in the manuscript should be included. The image files should be embedded in the manuscript, each on a separate page, starting immediately after the tables, or immediately after the Figure legends if there are no tables. Roman letters (A, B, C…) should be placed in the upper left corner of the image to identify the individual panels corresponding to the textual description in the accompanying figure legend. Images may be clinical, pathologic (gross or microscopic), endoscopic, or radiographic.

All images must be of high quality, with a resolution of 300 dots per inch (dpi) or greater, with all pictured evidence clearly and completely visible. The preferred formats for figure files are jpeg (.jpg) and tiff (.tif). The images should be labeled consecutively, such as "Figure 1. jpg," "Figure 2. jpg," etc., with the appropriate file extensions appended (.tif, .jpg).

Photographs

All patient identifiers must be removed from photos and radiographic studies, unless specific written permission has been obtained from the patient.

Line art and graphs

All graphs or line art files are required to be at a resolution of at least 500 dpi.

Gel electrophoresis labeling

The protein molecular weight or DNA marker sizes must be indicated on all appropriate figure panels.

Figure files

All color figures should be submitted in the CMYK color mode. All black and white figures should be submitted in grayscale While each figure may contain several labeled panels, each panel must be presented as a separate electronic file.

B. Review Articles

The manuscript, excluding the Tables, Figure Legends and References, must not exceed 6000 words. No more than 120 references are allowed; references should be limited to those seminal to the field.

The manuscript components are the same as for Original Research Articles (listed above) but the Abstract should be written in an unstructured paragraph form. A Methods section is not necessary in the main body of the manuscript, unless the focus of the article is on methodology.

C. Letters to the Editor

The manuscript may not exceed 500 words (including the References) and should be addressed to the Editor. No accompanying abstract is required. No more than 2 figures are allowed. No more than 10 references are allowed.

D. Editorials

These invited manuscripts may not exceed 1500 words (including the References section). No accompanying abstract is required. Figures are discouraged, but if necessary only 1 figure may be allowed. No more than 5 references are allowed.

Original Research

Original research manuscripts should describe experimental and/or clinical studies in hepatology, including exploratory and hypothesis-driven studies of basic or applied research. The data described in the article should have been generated exclusively from an original research study, and the results should be supported by appropriate statistical analyses.

Reviews

Review manuscripts should describe the most recent advances or challenges in a specific field or specialty of hepatology. The information should be presented as a logical summary of the current knowledge and should provide novel insights into the topic and reasoned recommendations for future research directions. Illustrations, diagrams, algorithms, tables, and other visual aids are strongly encouraged.

Letters to the Editor

Letters to the Editor should describe timely issues related to a previous publication in the JCTH. These letters should use constructive and professional comments to expand upon the issue, providing novel and reasoned insights into and/or updates on the topic under discussion. All opinions stated in the letter should be supported by the most current topically relevant literature.

Commentaries and Editorials

Commentary and Editorial articles should present reasoned opinions on a topically relevant issue that is currently trending in hepatology. It is intended to motivate readers to consider seriously the topic and its potential for affecting the field and/or specialty.

Case Reports

Case Reports should describe an individual or series of patient cases that have a timely and significant influence on the field or in a specialty of hepatology. These reports should provide novel insights into a particular pathological or physiological issue related to liver disease, supported by well-described background information for both the case(s) (from documented medical records) and disease (from the literature).

II. General Formatting Requirements for All Article Types

All manuscripts should be submitted as a single Microsoft Word document that is typed in Times New Roman, font size 11, and double-spaced. Tables are also submitted as double-spaced.

Conflict of Interest Statement

All authors are required to disclose any potential conflicts of interest (financial, professional, personal, or otherwise) within the past two years that are relevant to the manuscript, including but not limited to consultancies, ownership, equity, patent-licensing agreements, research support, major honoraria, employment or board positions involving a company whose product is mentioned in the manuscript. In the case that there is nothing to disclose, this fact should be clearly stated as: “The author(s) has (ve) no conflict of interest(s) related to this publication”.

Data Repository Accession Numbers

Accession numbers should be provided for the repository for all sequences, plasmids, expression microarrays, and amino acid sequence data that is presented, regardless of whether it has already been or should be submitted in the future to GenBank or EMBL.

Abbreviations

In general, the use of non-standard abbreviations is discouraged. Abbreviations should be defined the first time they are used in the Abstract, and also the first time they are used in the main body of the manuscript. For the Abstract, abbreviations should be used only for phrases of 3 or more words, or for treatment groups in which the abbreviation is used 3 or more times.

For the main text of the manuscript, in general abbreviations are used only for terms or phrases used 6 or more times, or for the acronyms of genes, or for terms that are known better by the abbreviation than the term.

Abbreviations in the Figures and Tables must be defined in the figure legend and table footnotes, regardless of how many times they appear. Standard abbreviations not requiring definition can be found in the AMA Manual of Style or the Index Medicus.

Author Assurances

The accompanying Publishing Agreement document must accompany all manuscripts submitted to JCTH. This agreement must be read and signed by every author. The Correspondence Author must certify that all listed authors participated significantly in the study, and that they have seen and approved the final manuscript.

Cover Letter

The cover letter should provide the title of the manuscript, the article type (Original Article, Review, Case Report, Editorial, Commentary, or Letter to the Editor), a recommendation for the preferred Associate Editor, and recommendations for three potential referees (including contact information: email address, phone, and fax numbers) who are not members of the authors' institution or have conflicts of interest with any of the authors, as well as the correspondence author's name, institution, email address, and telephone number. Authors may also list referees whom they would prefer to be excluded from the review. The final selection of an Associate Editor and referees is at the discretion of the JCTH editorial office.

Title

The title should be written as a brief but complete statement that accurately describes the content of the article. The title must not exceed 120 characters (including spaces). There should be no non-standard abbreviations.

Short Title

The running title should not exceed 45 characters (including spaces).

Authors

All authors should be identified by their first (given) name and family surname (family name). The individual's degree designation (i.e. PhD, MD, BSci, etc.) should not be listed. Each author's affiliation(s) (where the work was performed) should be provided, and the information should include the full name of the institution(s) and department(s). The affiliation should be denoted for each author using a numbering system that corresponds to that author's position in the author list. Current addresses should be indicated separately and denoted by a symbol (but not an asterisk).

Corresponding Author

The contact information for the corresponding author should include the individual's name, complete mailing address (department, institute, street and number, city, state/province, zip code, and country), e-mail address, telephone number, and fax number. The name of the Corresponding Author in the authors' list should be denoted by an asterisk (*). In the case of co-corresponding authors (no more than 2 are allowed), the person responsible for addressing reviewers' comments should be listed first.

Author Contributions

The Authors' Contributions should be provided in paragraph form following the authors' names and affiliations and the Corresponding Author(s)' information. The manner in which each author was involved with the study and/or preparation of the manuscript should be described after the author's name, as first and middle initials followed by the full last name. Contributions that are acceptable for inclusion as an author are: study design, performance of experiments, analysis and interpretation of data, manuscript writing, critical revision, statistical analysis, critical funding, administration, and technical or material support.

III. Specific Instructions for ERH Series Journals

The unique character of manuscripts published in ERHX series

Apart from the standard sections (Introduction, Methods and Materials, Results and Discussion [IMRD]), an additional section “Hypothesis”, with or without “Future Research Directions”, with no less than 100 words, is required by the ERHX series. This section is preferably accompanied by a graph that illustrates the hypothesis (e.g., proposed molecular mechanisms).

The proposed hypothesis should be derived from the results of the study, although it may be preliminary, incomprehensive, or incomplete, with direct or indirect support from previous research findings in the literature. Thus, this section should shed new light on further basic and translational research, and may provide clues to approaches to clinical application. Some examples are provided below.

Example 1, from a review article

Original review article:

Xia HH and Talley NJ. Apoptosis in gastric epithelium induced by *Helicobacter pylori* infection: implications in gastric carcinogenesis. Am J Gastroenterol. 2001 Jan; 96(1):16-26.

Statements in the original version:

Paragraph 2, Page 18:

Apoptosis in Gastric Carcinogenesis

The development of gastric cancer in humans has been shown to be a multistep process, ranging from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and ?nally invasive cancer (39).

……

It is proposed that dysplasia, especially high-grade dysplasia, might eliminate DNA-damaged or unnecessary cells by apoptosis, thus obtaining higher proliferative activity. However, when the apoptotic process fails, leading to increased survival of cells with DNA damage, gastric cancer may arise (42, 43). Therefore, apoptosis in non-neoplastic mucosa occurs in a manner that is at least partially cell cycle–dependent; but in neoplasia it is no longer cell cycle–dependent, resulting in an imbalance between cell apoptosis and proliferation (Fig. 2).

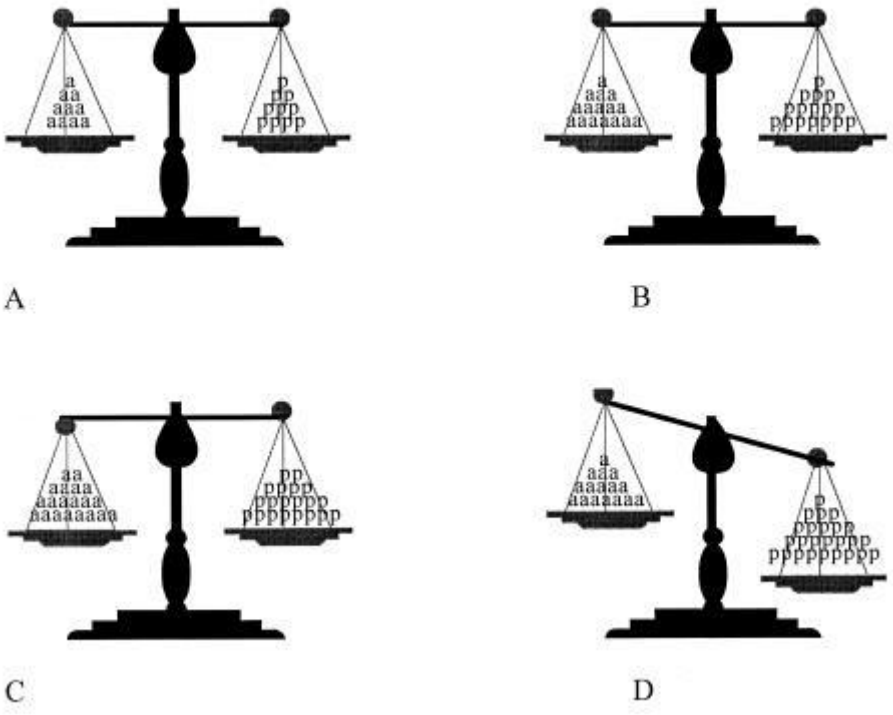

Figure 2. Balance between gastric epithelial cell apoptosis (a) and proliferation (p) in the normal mucosa (A), gastritis (B), atrophy, intestinal metaplasia and dysplasia (C) and carcinoma (D). The balance may alter following the progress from gastric atrophy (i.e., apoptosis predominant) to intestinal metaplasia (i.e., relatively balanced), then to dysplasia (i.e., proliferation predominant). In gastric cancer, the balance favors p. The numbers of a and p represent the levels of apoptosis and proliferation.

Modified Hypothesis and Future Research Directions section:

Hypothesis

The development of gastric cancer in humans has been shown to be a multistep process, ranging from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and ?nally invasive cancer (reference). We hypothesized that during the process from dysplasia to cancer, dysplasia, especially high-grade dysplasia, might eliminate DNA-damaged or unnecessary cells by apoptosis, thus obtaining higher proliferative activity. However, when the apoptotic process fails, leading to increased survival of cells with DNA damage, gastric cancer may arise. Therefore, apoptosis in non-neoplastic mucosa occurs in a manner that is at least partially cell cycle–dependent; but in neoplasia it is no longer cell cycle–dependent, resulting in an imbalance between cell apoptosis and proliferation (Figure 2).

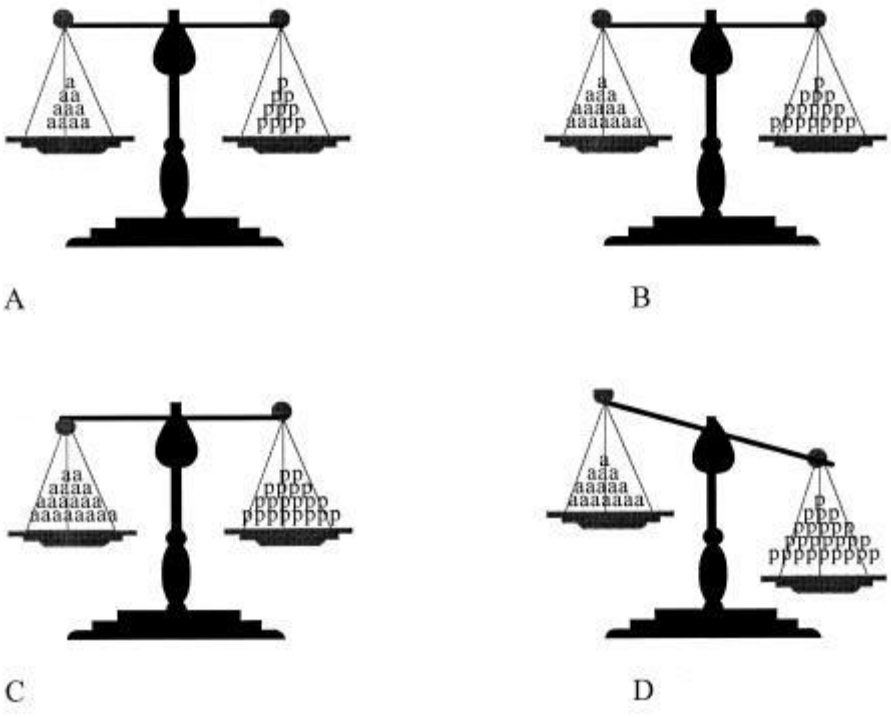

Figure 2. Balance between gastric epithelial cell apoptosis (a) and proliferation (p) in the normal mucosa (A), gastritis (B), atrophy, intestinal

metaplasia and dysplasia (C) and carcinoma (D). The balance may alter following the progress from gastric atrophy (i.e., apoptosis predominant) to intestinal metaplasia (i.e., relatively balanced), then to dysplasia (i.e., proliferation predominant). In gastric cancer, the balance favors p. The numbers of a and p represent the levels of apoptosis and proliferation, respectively.

Note: The Hypothesis section is mostly composed of sentences from the original version.

Example 2, from a clinical research article

Original clinical research article:

Xia HH, Kalantar JS, Talley NJ, Wyatt JM, Adams S, Chueng K, Mitchell HM. Antral-type mucosa in the gastric incisura, body, and fundus (antralization): a link between *Helicobacter pylori* infection and intestinal metaplasia? Am J Gastroenterol. 2000 Jan;95(1):114-21.

Statements in the original version:

DISCUSSION

Paragraph 3, Page 119

……

We hypothesize that antralization in the upper stomach may have affected local acid secretion (although it is possible that local acid secretion may also have an influence on antralization in the upper stomach). The degree of influence may depend on the severity and extent of antralization, as well as the ability of the oxyntic mucosa to compensate. It is likely that the majority of individuals with *H. pylori*-associated antralization but without duodenal ulcer may, to some extent, have reduced acid secretion, as the acid-secreting area is decreased (17, 30).

Therefore, more studies are required to elucidate the relationship between antralization and local acid secretion.

Paragraph 6, Page 119

Further histological and pathophysiological studies on populations with a high risk of intestinal metaplasia or gastric carcinoma and clinical trials evaluating the effect of eradication of *H. pylori* infection on the antralization process are now needed to further understand this condition.

Modified Hypothesis and Future Research Direction section

Hypothesis and Future Research Direction

Based on the preliminary results of the present study, we hypothesize that antralization in the upper stomach may have affected local acid secretion (although it is possible that local acid secretion may also influence antralization in the upper stomach). The degree of influence may depend on the severity and extent of antralization, as well as the ability of the oxyntic mucosa to compensate. It is likely that the majority of individuals with *H. pylori*-associated antralization but without duodenal ulcer may, to some extent, have reduced acid secretion, as the acid-secreting area is decreased (Figure 2).

More studies are required to elucidate the association between antralization and local acid secretion and the underlined mechanisms. Also, histological and pathophysiological studies on populations with a high risk of intestinal metaplasia or gastric carcinoma, and particularly, clinical trials evaluating the effect of eradication of *H. pylori* infection on the antralization process, are now needed to further understand this condition.

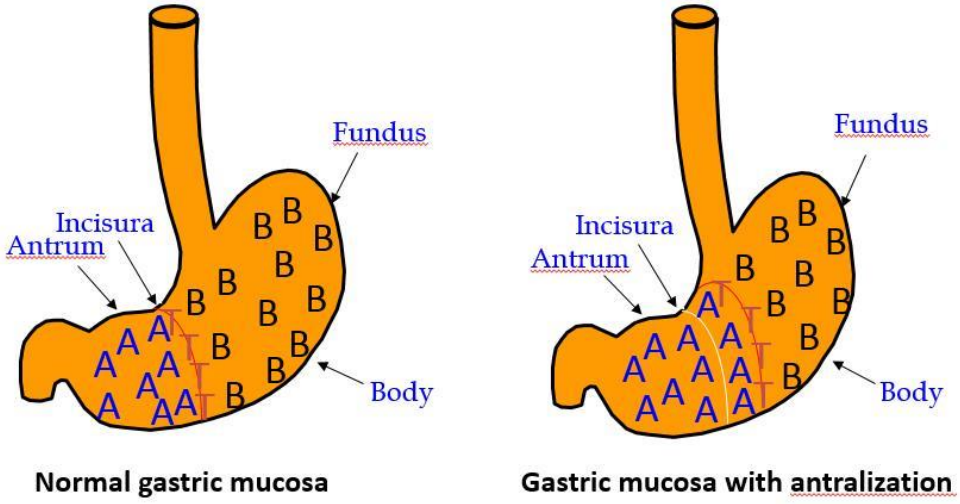

Figure 2. Proposed hypothesis regarding antralization and the local acid section of the gastric mucosa. The left and right panels illustrate the normal and antralized gastric mucosa, respectively. After replacement of the oxyntic body-type mucosa with antral-type mucosa, the local acid secretion is reduced. The red curve indicates the transitional zone in the normal and antralized gastric mucosa. The yellow curve in the right panel indicates the transitional zone that should be in the normal gastric mucosa. A, Antral-type; B, Body-type; T, transitional-type mucosa.

Note: The Hypothesis and Future Research Direction section is extracted from different parts of the Discussion section of the original manuscript. The diagram is easily drawn from the description in the main text.

Example 3, from a basic research manuscript

Original basic research article:

Zhang YY, Li JN, Xia HH, Zhang SL, Zhong J, Wu YY, Miao SK, Zhou LM. Protective effects of losartan in mice with chronic viral myocarditis induced by coxsackie virus B3. Life Sci. 2013 Jul 10; 92(24-26):1186-94.

Statements in the original version:

Discussion

Paragraph 4, Page 1191

In our present study, losartan was orally administered to Balb/c mice infected with CVB3 at a dose of 12.5 mg/kg consecutively for 28 days. We observed that losartan protected infected mice from death as shown by the decreased mortality and the survival curve. Oral administration of losartan also significantly decreased, HW/BW ratios. Moreover, we observed that losartan alleviated pathological scores and necrosis of murine hearts in mice infected with CVB3. These findings were different from that of Araki et al. (1995) who reported that none of the studied losartan doses (1.2, 12, and 60 mg/kg/day) influenced myocardial inflammation and necrosis resulting from viral infection. The difference may be attributed to different experimental conditions. Araki et al. used the encephalomyocarditis virus while CVB3 was used in the present study. More importantly, Araki et al. administered losartan from 7 days after infection, and consecutively for 14 days, whereas we administered losartan from the same day of infection, and consecutively for 28 days. It is known that virus is more prevalent in the early phase of myocarditis, and the titers are dramatically decreased in the late phase. It is accepted that myocardial inflammation and necrosis at the early phase are mainly resulted from the virus per se. However, in the later phase, myocardial inflammation and necrosis may be largely due to the production of inflammatory cytokines and autoantibodies. Indeed, in the present study, virus titers were not decreased by losartan in either in vivo or in vitro experiments, which was consistent with previous studies on encephalomyocarditis virus and herpes simplex virus (Araki et al. 1995), and indicates that protective effects of losartan were not through any antiviral mechanisms. Instead, anti-inflammatory and anti-autoimmune mechanisms may be involved in the protective effects of losartan although further extensive investigation is required to test this hypothesis. Based on the abovementioned findings, losartan may exert protective effects in the chronic phase, but not in the acute/subacute phases. However, the best time point for intervention of losartan needs to be determined.

Paragraph 2, Page 1193

The present study revealed, for the first time, the protective effects of losartan on CVM induced by CVB3 in Balb/c mice. However, limitations existed. First, we only chose one time point (i.e. day 29 as the endpoint) due to the ethic consideration and limitation of the research funding. Thus, the effects of losartan in the early phase of viral myocarditis were not determined in the present study. However, the present study mainly focused on the effect on the chronic phase, and the effect of losartan on viral myocarditis in the early phase has already been investigated in previous studies (Araki et al., 1995) Second, determination of the longer-term effects of losartan (e.g. up to 90 days after infection) would provide more clinically meaningful data. Due to the same reason, we did not include more and longer time points in the present preliminary study, and thus more extensive study with multiple and longer time points is needed. Third, although the present study clearly demonstrated protective effects in mice with CBV3-induced chronic myocarditis, the underlying molecular mechanisms of losartan regulating Th1, Th2, and Th17 cells need to be further elucidated.

Modified Hypothesis and Future Research Direction section

Hypothesis and Future Research Direction

It is hypothesized that losartan exerts protective effects in mice with viral myocarditis induced by CVB3 when it is administrated consecutively for 28 days. In other words, it exerts protective effects in the chronic phase, and not in the acute/subacute phases, although the best timepoint for intervention of losartan needs to be determined. Moreover, it is accepted that myocardial inflammation and necrosis at the early phase mainly result from the virus. However, in the later phase, myocardial inflammation and necrosis may largely be due to the production of inflammatory cytokines and autoantibodies. Therefore, we further hypothesize that losartan exerts its protective effect through anti-inflammatory and anti-autoimmune mechanisms, any not by antiviral mechanisms (Figure 5).

Further studies are required to determine the effects of losartan both in the earlier (<14 days) and later (>28 days) phases of viral myocarditis, and particularly to elucidate the underlying molecular mechanisms of

losartan, with particular attention to the regulation of Th1, Th2, and Th17 cells.

Note: The Hypothesis and Future Research Direction section is written by incorporating different parts of the Discussion section of the original manuscript. The diagram is then drawn from the generated hypothesis accordingly.

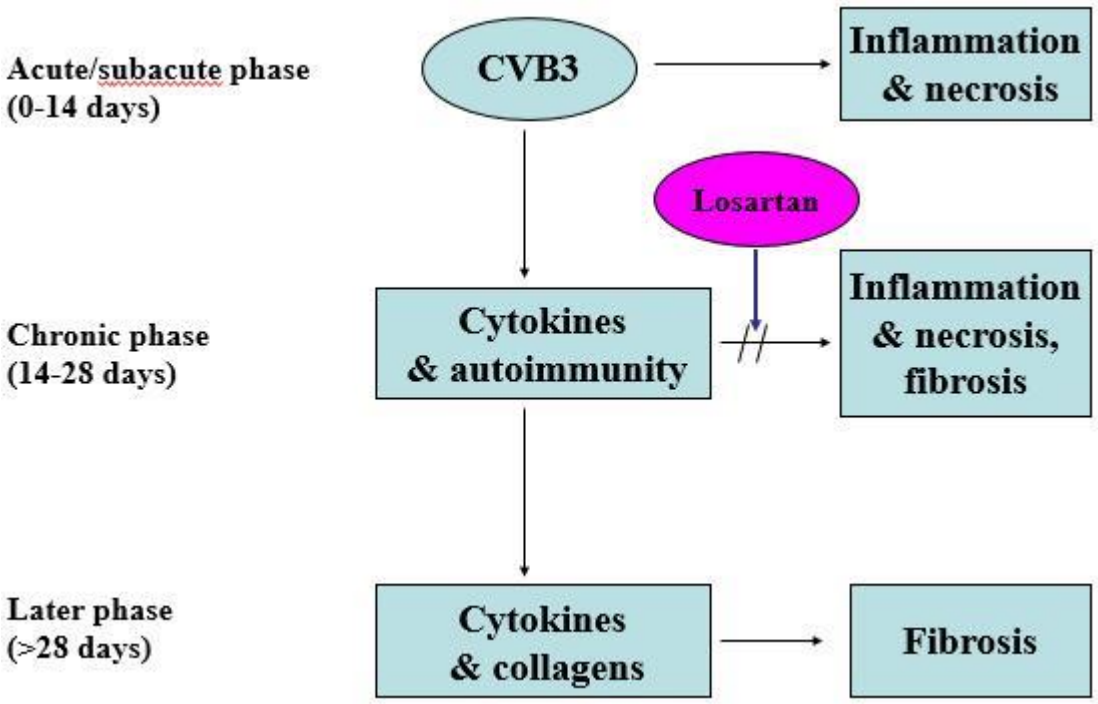

Figure 5. Losartan exerts protective effects in the chronic phase (14-28 days), not in the acute (0-4 days) and subacute (4-14 days) phases. Moreover, losartan exerts its protective effect through anti-inflammatory and anti-autoimmune mechanisms, any not through any antiviral mechanisms.

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