

REVIEW

*By Prof. Dr. Hristo Stefanov Gagov, Faculty of Biology,
Sofia University "St. Kliment Ohridski"*

Regarding the dissertation of full-time PhD student Radostina Petkova Tsvetankova, on the topic: "Influence of Specific MicroRNAs in Tumor Pathogenesis by Modulating Autophagy Processes and Innate Immune Signaling," in the professional field 4.3. "Biological Sciences," with a specialization in Immunology.

Radostina Petkova Tsvetankova's dissertation was developed under the scientific supervision of Prof. Dr. Krasimira Todorova-Hayrabedian in the Reproductive OMIC Technologies Laboratory of IBIR - BAS. The work is based on two scientific articles published in journals with impact factors (IF), where Radostina Tsvetankova is the first author. One publication is in BAS Reports (IF=0.251 for 2022, 03) and the other in Biotechnology and Biotechnological Equipment (IF=1.762, 03). The dissertation spans 160 pages, adheres to the required structure for such works, and includes all necessary sections.

The literature review is concisely written, extensive, and thorough, covering 37 pages. It provides data on the diagnosis and therapy of prostate cancer, explores the use of microRNAs as biomarkers for prostate carcinoma diagnosis from tissue biopsies, blood samples, and other body fluids, and discusses autophagy's role and mechanisms in prostate cancer, as well as the impact of innate immune signaling and chronic inflammation on cell transformation. The review synthesizes information from 280 sources. It concludes with a summary on the diagnostic and therapeutic potential of microRNA-141 and siRNA MAPK1 in metastatic prostate carcinoma cell lines.

Methods: The dissertation employs numerous modern techniques, underscoring the high quality of the data obtained and Radostina Tsvetankova's excellent experimental skills, laying a strong foundation for her future research endeavors.

Purpose and Objectives: The dissertation's aim is clearly stated, followed by nine specific and well-defined tasks focused on the effects of microRNA-141 and siMAPK1 on signaling and functions in the LNCaP metastatic prostate carcinoma cell line and the RSZ cell line, a model for bone metastases.

Results: Spanning 14 pages, the results are depicted in 31 figures (many complex, with supplementary figures such as 23.1, 24.1, 26.1, 27.1, 29.1, and 30.1), three tables, and one diagram. Although extensive, only a subset of these results is included in the two publications.

Discussion: Over 20 pages, this section elaborately discusses the regulation of autophagy and mitophagy by microRNA-141 in two metastatic prostate carcinoma models—the LNCaP and RSZ cell lines. It includes references to 100 papers (80 cited for the first time in this dissertation) and four diagrams generated with GENEMANIA. The discussion concludes with a diagram illustrating the genetic interaction and signaling pathways involving the androgen receptor gene,

TP52, and MARK1, demonstrating Radostina Tsvetankova's profound understanding of the literature and her ability to critically analyze data, indicating her creative maturity.

The literature cited is comprehensive, with 359 sources, 2 in Bulgarian and the remaining 357 in English. This, along with Radostina Tsvetanova's competent responses during her preliminary presentation, attests to her scientific prowess in the field.

The nine conclusions effectively summarize the findings, and the two contributions are specific and substantiated. The first highlights the role of microRNA-141 in mitophagy and macroautophagy regulation, and the second underscores the significance of MARK1 in prostate pathogenesis. I view the scientific and applied potential of these conclusions and contributions positively.

The summary in Bulgarian spans 39 pages, succinctly presenting the dissertation's main points and results, including 18 figures, one table, one diagram, and sections on introduction, objectives, materials and methods, results and discussion, conclusion, nine conclusions, two contributions, a list of publications, participation in five conferences related to Radostina Tsvetankova's dissertation, and more.

Remarks: When citing publications, unnecessary details like "Eric ..., PMID: PMID: ..." should be omitted for standardization with scientific publications, rather than following PubMed's format. Additionally, many abbreviations are missing from the list of used abbreviations, including those in Cyrillic (e.g., ADT, PK) and Latin (e.g., ATG, AMPK, ATG16L, DRAM, DAPK, IL-1,6,18; NLRP3,12; AIM; DRAM, etc.). While some abbreviations like IL-n, p52, MARK, and AMRC are well-known, others are not. My remarks are technical and do not detract from the substantive quality of the work.

Personal Impressions: I am not personally acquainted with Radostina Petkova Tsvetankova. My assessment is based solely on the provided materials, including her dissertation, summary, and scientific publications.

In conclusion, I believe that the objectives set forth have been successfully achieved. The dissertation and related publications fulfill the minimum national requirements as stipulated by the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation for PhD degrees, and the Bulgarian Academy of Sciences' standards. Based on the above, I positively evaluate the research presented in the dissertation, summary, publications, and the derived conclusions and contributions.

I recommend that the distinguished scientific jury award Radostina Petkova Tsvetankova the educational and scientific degree of "Doctor" in professional field 4.3. Biological Sciences, with a specialization in "Immunology."

Sofia, 03.01.2024 Prof. Dr. Hristo Gagov