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REVIEW

of the Doctoral Dissertation

'Transcriptional and epigenetic regulation in vitro adipogenic differentiation of porcine Mesenchymal Stem Cells (MSCs)'

by Mehmet Onur Aksoy, M.Sc.

prepared under the supervision of Prof. Izabela Szczerbal, Ph.D., D.Sc.

This review was prepared according to the decision of the Scientific Council of the *Biological Sciences* discipline at the Faculty of Veterinary Medicine and Animal Sciences of the Poznań University of Life Sciences (Resolution no. 1/6/2026, 18th June 2026). The basis of this review was a doctoral dissertation written in English and delivered in printed form, containing:

- a substantive part
- a list of the Doctoral Candidate's achievements, including:
    - list of publications
    - list of conference presentations
    - list of scientific projects in which the Doctoral Candidate was involved
    - information about a scientific internship
    - bibliometric summary
- copies of three papers constituting the dissertation's core
- the declaration of independent authorship
- co-authors' declarations regarding the Doctoral Candidate's contribution to each of the cycle's publications.

I. Information about the Candidate

Mehmet Aksoy, M.Sc., obtained his master's degree in biochemistry on February 13, 2020, at Anadolu University in Turkey. He had not applied for a doctoral degree previously. Since 2021, Mr. Aksoy has been a participant in the Doctoral School at the Poznań University of Life Sciences, where he was preparing this doctoral dissertation under the supervision of Prof. Izabela Szczerbal, Ph.D., D.Sc.

II. Evaluation of the scientific achievement

The Doctoral Candidate presented a scientific achievement pursuant to Article 187, 20th July 2018 on *Act on Higher Education and Science* (Dz.U. 2020, 85, as amended), in the form of a collection of three thematically related scientific publications under the joint title: *'Transcriptional and epigenetic regulation in vitro adipogenic differentiation of porcine Mesenchymal Stem Cells (MSCs)'.* All three papers are original publications published between 2024 and 2026.

The doctoral cycle comprised three multi-author original papers:

1 **Aksoy, M. O.***, Bilinska, A.*, Stachowiak, M., Flisikowska, T., & Szczerbal, I. (2024). *Deciphering the role of the SREBF1 gene in the transcriptional regulation of Porcine adipogenesis using CRISPR/Cas9 editing.* International Journal of Molecular Sciences, 25(23), 12677. https://doi.org/10.3390/ijms252312677
MNiSW 140, 5-year Impact Factor 5.7, *equal contribution

2 **Aksoy, M. O.**, Rozynek, J., Stachowiak, M., & Szczerbal, I. (2026). *The role of the CEBPB gene in porcine adipogenesis: a study using CRISPR/Cas9-edited mesenchymal stem cells.* Journal of Applied Genetics, 67, 447–486. https://doi.org/10.1007/s13353-025-01030-xc
MNiSW 140, 5-year Impact Factor 2.0

3 **Aksoy, M. O.**, Wozniak, J., Stachowiak, M., & Szczerbal, I. (2026). *Dynamic Histone Modification Patterns in Key Transcription Factor Genes During Porcine Adipogenesis.* Genes, 17(5), 521. https://doi.org/10.3390/genes17050521
MNiSW 100, 5-year Impact Factor 3.2

In all three papers, the Doctoral Candidate played a leading role, appearing as first author (papers 2 and 3) or co-first author (paper 1*). Mr. Aksoy's leading contribution was confirmed by the attached co-author declarations. His individual contribution consisted of: participation in developing the study concept (papers 2 and 3), experimental analysis and interpretation of results (1, 2, 3), selection of methodology (1, 2, 3), and preparation and editing of the manuscript at initial and later stages (1, 2, 3).

All papers have been published in journals listed in the Journal Citation Reports. The summarized 5-year Impact Factor value is 10.9, and the combined MNiSW score is 380. The dissertation papers have been cited 8 times, so far, according to Scopus (as of August 24th, 2026). In my opinion, the value of these indicators is very good relatively to the standards expected of doctoral candidates.

The dissertation starts with the wide introduction of the reader into details of the topic of the research (*Introduction*), the study's aim (*Research problem and hypothesis; Aim of the study*), characteristics of the material used and methods applied (*Material and method*), then the results obtained (*Results*) and discussion with the literature (*Discussion*). This part ends with final conclusions (*Conclusions*), a bibliography (*Bibliography*), and a list of figures (*List of figures*). The dissertation also includes a *Table of Contents* and abstracts in Polish and English. The substantive part counts for 92 pages. The dissertation's structure is classical for this type of theses.

The scientific aim of the dissertation was to investigate the molecular regulatory mechanisms of adipogenesis – a biological process crucial for maintaining energy balance and the development of obesity – with particular focus on the interactions between transcriptional and epigenetic pathways responsible for controlling differentiation during porcine adipogenesis. This aim was achieved by:

- determination of the role of *SREBF1* and *CEBP* genes in regulation of adipogenesis differentiation and their effect on the proliferative potential of mesenchymal stem cells, through analysis of changes in the expression levels of key adipogenesis markers (*PPARG, GATA2, CEBPA, CEBPD, FABP4*) induced by CRISPR/Cas9 genome editing
- determination of changes in the acetylation or methylation levels of selected histone residues (H3K9ac, H4K8ac, H4K20me3) within the promoter regions and coding sequences of four genes (*PPARG, GATA2, CEBPA, CEBPB*) during adipocyte differentiation.

The aim of the study was clearly framed. It is wort to notice that the aim concerns current scientific questions and demonstrates the potential for applying of modern genome editing technologies in livestock breeding for desired features.

In **the first paper (1)** the role of the *SREBF1* gene in the adipogenesis process has been characterized, with detailed investigation of the gene's three isoforms influence on differentiation process. The effect of each isoform on the expression levels of a range of adipogenesis-related genes was determined, demonstrating the key role of the *SREBF1c* isoform in the molecular regulation of the process. For the first time, it was shown and documented that disruption of a function of *SREBF1c* isoform leads to increased (*CEBPB*) or decreased (*PPARG, CEBPA, CEBPD, FABP4*) gene expression levels, while no changes were observed for the *GATA2* gene. As a result of the cascade of changes triggered by deletion of the studied isoform, the adipogenesis process was inhibited. A potential relationship between *SREBF1c* and *CEBPB* in regulation of the process was also suggested. Thus, in addition to elucidation and characterization of the molecular mechanisms underlying fat cell formation in pigs, the future potential of using genome editing methods to alter meat quality was suggested.

In the **paper 2** characterization of the role of the *CEBPB* gene in the adipogenesis process has been shown. CRISPR/Cas9 genome editing on mesenchymal stem cells (MSCs) was applied again. A decrease in the expression levels of marker genes related to fat cell differentiation was observed: *GATA2, CEBPA, PPARG, FABP4*. Additionally, altered (decreased) expression profiles were documented for proliferation marker genes: *CCND1, MCM2, PCNA*. Changes were observed in both hetero- and homozygous cell lines, clearly indicating the key role of the *CEBPB* gene primarily in the early stages of adipogenesis, but also in regulating the cells' proliferative potential.

Paper 3 focused on the epigenetic regulation aspect for adipogenesis markers, as: *PPARG, GATA2, CEBPA*, and *CEBPB*. The study selected evaluation of histone lysine residue modifications that are hallmark indicators of transcriptional activity and chromatin configuration: modifications that support transcriptional activity and open/loosen chromatin – acetylation at position 9 of histone 3 (H3K9ac) and position 8 of histone 4 (H4K8ac) – as well as modifications that inhibit transcriptional activity and promote heterochromatinization – trimethylation of lysine residues at position 20 of histone 4 (H4K20me3). By analyzing the profiles of the studied histone residue modifications across differentiation stages, dynamically occurring changes in chromatin organization within the promoter region or specific coding sequences of the studied genes were demonstrated. That represents an excellent complement to earlier research by Prof. I. Szczerbal's group, previously focused on changes at the global level. As a result of the research, paper 3 demonstrated for the first time in the context of adipogenesis, the multi-layer of the differentiation process, including simultaneous changes at the transcriptional level with accompanying spatial changes in chromatin conformation specific to particular differentiation stages.

In summary, it should be stated that Mehmet Aksoy, M.Sc., presented in a well-documented and clear manner, the complexity of the molecular interactions, such as the relationships between transcriptional and epigenetic factors closely linked to chromatin organization and gene expression during adipogenesis. The Doctoral Candidate involved a range of molecular biology methods, demonstrating his very good technical preparation. Beyond the scientific data produced, the Doctoral Candidate demonstrated potential for usage of genome editing methods in livestock breeding, which may have practical applications in the future for obtaining desired features of the animals.

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The doctoral dissertation of Mehmet Aksoy, MSc, is based on experimental data published in peer-reviewed journals listed in the JCR database. As such, the papers have already passed through a rigorous peer-review process. The publications were selected logically and thematically in a correct manner. The selection of supplementary literature (125 positions listed in the *Bibliography* chapter) covers the most important literature sources within the scope of the research conducted. The dissertation title is also adequate to the stated aim and content of the dissertation. Thus, from a formal standpoint, the dissertation raises no objections.

Questions:

1. The presented research was based primarily on analysis of transcription levels, i.e., mRNA. As is well known, that the presence of mRNA does not always correspond to the presence or activity of the protein. In the dissertation, no protein-level validation was performed. The lack of validation was highlighted by the Doctoral Candidate in the *'Limitations and Future Perspectives'* chapter. Could the Candidate elaborate further on plans for protein-level validation from a methodological standpoint? Is it known how frequently the transcript-to-protein translation fails to occur; can this be predicted?

2. What potential perspectives for applying knowledge about epigenetic changes in the regulation of the adipogenesis process could be proposed? Please, discuss this issue not only in the context of obtaining desired features in farm animals, but also in the treatment of (for example) human obesity. Do such studies exist?

3. Which molecular regulators are responsible for the global level of DNA methylation and acetylation, and which for changes in specific histone amino acid residues? Are these universal compounds, or are they specific?

III. Evaluation of other scientific and research achievements

The dissertation was also supported by a list of the Candidate's achievements, containing:

- list of publications
- list of conference presentations
- list of scientific projects in which the Doctoral Candidate was involved
- information about a scientific internship
- bibliometric summary.

Mr. Mehmet Aksoy's publication activity includes co-authorship of a total of 12 scientific articles and 1 popular-science article, of which 7 carry affiliation with the Poznań University of Life Sciences, where the Candidate was involved in the Department's research. Six papers carry affiliation with Anadolu University in Turkey, related to the biochemistry of anticancer compounds. The total Impact Factor value equals 38.9 (28.0 excluding the papers included in the doctoral dissertation), and the total ministerial (MNiSW) score is 1050 (670). The total number of citations of all the Doctoral Candidate's works was 139 (according to Google Scholar; as of the date of submission of the doctoral dissertation), confirming the positive reception of the publications within the scientific community. The Hirsch index is 6, which is a high value at this stage of a scientific career.

Mr. Aksoy is co-author of 10 conference presentations, delivered at two domestic and three international scientific conferences. Conference presentations include: 4 first-author posters (2 domestic, 2 international) and 6 co-authored presentations (including one oral presentation). Seven presentations are related to the Doctoral Candidate's activity at the Poznań University of Life Sciences.

The Candidate also demonstrated activity in investigation of grant projects – he was a researcher in a total of five projects, including one funded by the National Science Centre (Principal Investigator: Prof. Izabela Szczerbal, Ph.D., D.Sc.), within which he conducted research for his doctoral dissertation.

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It is worth mentioning that Mr. Aksoy also completed a 5-month internship at the Institute of Human Genetics of the Polish Academy of Sciences under the Erasmus+ program in 2020. Candidate was then supervised by Prof. Jadwiga Jaruzelska, Ph.D., D.Sc.

In summary, it should be stated that the Candidate's achievements are high relatively to such an early stage of a scientific career and are documenting Mr. Aksoy's regular activity within the scientific community.

IV. Final Conclusion

In summary, the contribution of the listed scientific achievements to the development of the scientific discipline pursued by the Doctoral Candidate – including the cycle of papers, that stated for the core of the doctoral dissertation, and scientific activity carried out at more than one institution (publications, conference presentations, projects, and internship) – is high for this stage of career, and I therefore find that Mehmet Onur Aksoy, M.Sc., meets the criteria for doctoral candidates as specified in law regulations in Poland (article 187, Act of July 20th, 2018 on Higher Education and Science; Dz.U. 2020, position 85, as amended).

On this basis, I recommend the Scientific Council of the Biological Sciences discipline at the Faculty of Veterinary Medicine and Animal Science of the Poznań University of Life Sciences to proceed with all necessary procedural steps to confer Mehmet O. Aksoy, M.Sc., the academic degree of Philosophy Doctor in the field and discipline of biological sciences. Due to the high scientific value and future potential of the results, I also recommend for the dissertation to be distinguished with an honor.

Podpisano przez/ Signed by:
Marta Anna
Olszewska
Data/ Date: 30.08.2026 21:39
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