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Review of the Doctoral Thesis entitled "Identification of a novel, transcription-independent role of Nrf2 in lung cells"
by candidate Ms Sara Mikac, MA

Thesis quality, style & illustrations

The thesis entitled "Identification of a novel, transcription-independent role of Nrf2 in lung cells" submitted by candidate Ms Sara Mikac, MA, contains 117 pages and encompasses the formal essential sections: Abstract in English and Polish, Abbreviations, List of Figures, List of Tables, Introduction, Materials and Methods, Results divided into two parts, each with separate background, aims, methodology and discussion, Conclusion, Bibliography, Appendices containing publications, and Scientific accomplishments. The division of the body of the thesis into four separate chapters creates an «easy-to-follow» text which facilitates understanding of the scientific field, experimental procedures and results. The thesis is written in a studious manner with numerous illustrations, schematic representations and tables. The figures are described in detail.

Background, state of the art

The thesis deals with a very interesting and important field of Nrf2 transcription factor, which is a major regulator of the response to cellular xenobiotic and oxidative stress. Nrf2 is mainly regulated by Keap1, which binds Cul-3-E3 ubiquitin ligase and degrades Nrf2 under stress-free condition. Transient activation of Nrf2 is protective, however, when Nrf2 is imbalanced, it becomes constitutively active and promotes carcinogenesis, metastasis and resistance to therapy. Regarding the dual role of Nrf2 as an activator or suppressor of several diseases, several activators and inhibitors are developed with promising therapeutic potential.

Nrf2 has also a role in regulating immunity what is in the focus of this thesis. The thesis aims to elucidate how Nrf2 affects expression of major histocompatibility complex class I

molecules (MHC-I), which present antigenic peptides to the immune cells. Moreover, NRF2 forms direct interaction with MHC-I molecules and affects their stability. In the second part, the thesis deals with the identification and characterization of a novel isoform of Nrf2, ΔN-Nrf2, which lacks first 16 amino acids and prevents binding to Keap1. It is localized in cytoplasm and does not act like a transcription factor.

The scientific papers published in the course of the last several years, some of which are co-signed by the candidate, definitely confirm the significance of the subject, competence of the authors and the importance of the field.

Scientific quality, methodology, experiments, validation

The objectives of the thesis are challenging. The methodology with which the problems are addressed include standard and reliable biochemical and cell biology techniques, accompanied by novel molecular biology techniques. The experimental work was planned in detail with all the necessary controls. The results are discussed thoroughly and with caution in the light of current knowledge on the topic which is supported by an extensive reference list comprising of both seminal and recent publications.

Personal contributions, originality, valorization, prospects

The contribution of the candidate to the scientific research in this field is visible in her co-authorship on four scientific papers and one to be submitted (on 2 of 5 papers the candidate is the first author). The thesis is an original scientific contribution with the impact on two major scientific topics related to Nrf2 transcription factor: a) the role of Nrf2 in the regulation of immunity and b) identification of a novel isoform ΔN-Nrf2, which may be important for resolving critical questions associated to the role of Nrf2.

Conclusions

The thesis represents original scientific research in the field of Nrf2. It is well written with all the essential parts, supported by extensive bibliography. Therefore, I recommend the thesis defense to proceed as scheduled.

The reviewer:

Neda Slade, Ph.D.