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Lausanne, August 4th 2022

Review of the thesis manuscript from Ambroise WU

Dear Prof. Kadej,

The manuscript entitled "Role of ABCA1 transporter in the plasma membrane reorganization in mammalian cells" and written by Ambroise Wu deals with the study of the role of the ABCA1 protein, involved in cholesterol transport within the plasma membrane in two situations, i.e the resistance of mammalian cells to a drug and the impact of ABCA1 function on cancer cells properties. The manuscript is composed of an introduction, two result parts and the associated discussions.

For the introduction, the candidate first described thoroughly the composition of the plasma membrane, which is of central importance for his work. In a second part, the candidate described the functions of the various members of the ABC family. He then focused on ABCA1 and described with details the regulation of ABCA1, its function, and the consequences of its inactivation in several models. He also discussed the role of ABCA1 or its absence in some pathologies such as Tangier disease, atherosclerosis and cancer. This introduction is well balanced, focused, and sufficient to understand the work accomplished during the PhD.

The candidate studied two projects centered around the role of ABCA1 in the plasma membrane of mammalian cells. The first project is focused on the study of the role of ABCA1 in the resistance to amphotericin B, a drug used to treat systemic mycoses. This study is already published in a good journal and the candidate is the first author of this work (Wu et al, 2019 Cell Mol Life Sci). The candidate and his colleagues demonstrated that active ABCA1 expressed by mammalian cells allowed the cells to be more resistant to the drug. The mechanism involved the role of ABCA1 in the transport of cholesterol. Efflux of cholesterol from the membrane led to an inhibition of the amphotericin. Inactivation of ABCA1 led to an increased sensitivity to the drug. Interestingly, the depletion of cholesterol from the membrane led to an increased sensitivity to the drug. This part is clear, well designed and the results are convincing and well interpreted.

For the second part, the candidate studied the role of ABCA1 in cancer cells, more precisely in the capacity of melanoma cells to metastasize. This work has been performed mostly in vitro by inactivating or not ABCA1 in a human melanoma cell line. The candidate nicely showed that ABCA1 and its impact on the fluidity of the plasma membrane influence cancer cells in their migration and

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invasion potential. As in the previous part, this effect is related to the function of ABCA1 in the efflux of cholesterol. In this model, ABCA1 modulates the content in cholesterol of the plasma membrane of the cancer cell, allowing it to better invade and migrate in the extracellular matrix. This section is clear and the results are convincing. This work is not yet published.

Altogether, the manuscript is of excellent quality. The work achieved during this thesis is of high importance in the field of cholesterol transporter and membrane dynamics but goes also beyond. The role of ABCA1 in cancer cells may be important in the context of cancer therapies. As a consequence, I strongly recommend Ambroise WU for the grade of PhD.

Best wishes,

Grégory Verdeil