Posudek na bakalářskou práci

☐ školitelský posudek ☒ oponentský posudek	**Jméno posuzovatele:** RNDr. Karel Drbal, Ph.D.
	Datum: 1.6.2015

Autor:
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Název práce:
Impacts of chemotherapy and genotoxic stress on the immunological properties of tumour cells

☒ Práce je literární rešerší ve smyslu zveřejněných požadavků (pravidel).
☐ Práce obsahuje navíc i vlastní výsledky.

Cíle práce (předmět rešerše, pracovní hypotéza…)
I will comment next to the individual goals whether these have been fulfilled or not.
According to the author: *„The objective of this thesis is to review and summarize information on the impacts of chemotherapy on the immunological properties of tumour cells.“*
I have not learned what the author meant by the term *“immunological properties of tumor cells”* – it has not been defined and even mentioned throughout the 25 pages!
„The main goals are as follows:
(a) Review the information on selected chemotherapeutic agents and their effects on the immune system“ – FULFILLED, however the selection criteria of a few chemotherapeutic (CTX) agents was not justified and the immune system impact was underrepresented.
(b) Summarize current knowledge about senescence induction in general and by chemotherapy – PARTIALLY FULFILLED: the stressors have been described with link to senescence induction, however the senescence itself has not been defined carefully with its markers and varieties of the induction processes.
(c) Describe the properties of senescent cells, focusing on the senescence-associated secretory phenotype and its negative effects – PARTIALLY FULFILLED: the tumor / immune system interaction was simplified with respect to senescent cells as the driving factor of tumorigenesis. This field is in constant development and it is not that simple at all. On the other hand, the prevailing hypothesis is that senescence markers were only found in the early, precancerous lesions, which then needs to be suppressed for the tumor to progress – there are both positive and negative factors, different forms of inflammation, etc. The context must be covered first before giving any details.
(d) Consider the impacts senescent cells have on the immune system and the possibility of chemotherapy being based on elimination of such cells – NOT FULFILLED: the logic of the objective shift has not been fully clarified from the title itself over the main goals to the details. The term *„immunological properties if tumour cells“* evokes the immune function of the tumor cells themselves. Here, the author describes more the impact of stressors on tumor cells and stroma – not only CTX but also intrinsic genotoxic stress in general – and not the final outcome of senescent tumor cells on the immune cells themselves. Elimination of senescent cells by innate or adaptive immune system and the immunotherapy effect on this process has not been described at all, although it has been stressed in the Abstract.

Struktura (členění) práce:
Correct thesis structure with 3 figures and 113 references in correct format (with exceptions below).
The author has described some genotoxic stressors in chapters 2-4 (11 pages) with the focus on senescence in chapters 5-6 (10 pages) and its role in pro-tumorigenic process in chapter 7 (only 1 page). Abstract and Conclusion chapters are present.

Jsou použité literární zdroje dostatečné a jsou v práci správně citovány? Použil(a) autor(ka) v rešerši relevantní údaje z literárních zdrojů?

The covered field is rapidly evolving and it is inappropriate to add only 5 citations from years 2013, 2014 and 2015 each among 113 references in total. This number is superfluous. Synthesis of information is scarce – often a single chapter is based on a single major citation. In the field of immunology, the references are outdated.

No reference out of almost 10 critical references on the very same topic from the collaborating lab of Zdeněk Hodný is present. Moreover, the most important references cited in those publications are exactly the same as the seminal references of this thesis. This is not acceptable!

Some cited publications are missing in the reference list – e.g. p.4 (*Correale, P. et al., 2005*), others are misreferenced – citations, 8, 66, 68, 72, 81, 105.

Important recent reviews/papers on the major topic senescence are missing:

Lasry, A. et al. *Trends Immunol.* **36**: 217 (2015).

Muñoz-Espín, D. et al. *Nat. Rev. Mol. Cell Biol.* **15**: 482 (2014).

Salama, R. et al. *Genes Dev.* **28**: 99 (2014).

Pribluda, A. et al. *Cancer Cell* **24**: 242 (2013).

Pokud práce obsahuje (nadstandardně) i vlastní výsledky, jsou tyto výsledky adekvátním způsobem získány, zhodnoceny a diskutovány?

The thesis contains no primary results.

Formální úroveň práce (obrazová dokumentace, grafika, text, jazyková úroveň):

The thesis was very difficult to read. A typical example of the poor wording, logic and expressions used is the chapter Conclusion. Here, the author used 7 times the non-conclusive words can/could. It simply does not conclude any of the thesis aims, when Introduction and Conclusion chapters are confronted.

Some general information has been often repeated without connection to any detail and substantiation of the statements. Improper referencing with low impact publications for general statements is frequently used.

A chronic misuse of human/mouse gene nomenclature was present here: Dcr2, p63, p73, p53/TP53 has been frequent, which is not valid according to HGNC classification: TNFRSF10D for Dcr2 or TP53 for p53. One can use the generic terms, but only after it has been first correctly introduced with the official gene name. Gene names should not be part of Abbreviation list and must be written in italics, while protein names strictly not.

Some terms are not correct (*tumour necrosis growth factor*), not spelled correctly (*β-galactosiadase activity, apoptopic*) or in other cases even misleading.

Splnění cílů práce a celkové hodnocení:

The author has touched some parts of described complex biological process and has correctly mentioned the senescence-associated secretory phenotype (SASP) as one of many CTX-induced phenomena. The other important immune-related features of tumor cells were covered in an oversimplified manner or not at all: immune-type cell surface markers induced on tumor cells, polarization classes of immune cells, the important switch of tumor inflammatory environment and its regulators.

Very often, the author interchanges the impact of CTX on tumor cells for its effect on immune cells or fibroblasts. It is not clear the whether the role of described intrinsic (oncogenes/tumor suppressor mutations) and extrinsic (CTX) genotoxic stressors is different for the outcome of tumor cell development.

Seriously, the definition of terms has not been given throughout the thesis:
p.3: *Senescence, Immunosuppression, Immunogenic tumour cell death, Immunological phenotype of cancer cells*, p.21: *Immunosenescence*.

The link between SASP, inflammation, immunosuppression and immunogenic cell death has not been elaborated. The role of immune system in anti-tumor immune response has not been introduced and as a result, innate and adaptive responses were frequently interchanged. Lack of conclusive statements at the end of individual chapters or in Conclusion is obvious.

Otázky a připomínky oponenta:

The thesis is focuses on senescence itself. I would like to ask a few questions on this topic (please, select 3 questions for the Thesis defense).

1. What is the functional difference in apoptosis, immune cell death and senescence of tumor cells in respect to the induction of anti-tumor immune reaction?
2. Is chemotherapy inducing one of these types of cell death programs or cell cycle block preferentially?
3. Is senescence pro- or anti-tumorigenic itself?
4. Please, name the current markers of senescence. Is beta-galactosidase activity still the predominant marker? Your references on p.14 are dated mostly prior to year 2003!
5. You have stated on p.16: „Not all senescent cells express identified senescence markers and their phenotypes can exist in several different forms.“ I would like to know what are these forms and which effector programs these show *in vivo*.

Návrh hodnocení školitele nebo oponenta (bude zveřejněn)

☐ výborně ☐ velmi dobře ☒ dobře ☐ nevyhověl(a)

Podpis školitele/oponenta: