Investigation of NLRP3 inflammasome activation in a rat model of 5-fluorouracil and methotrexate chemotherapy induced cognitive impairment

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GRAPHICAL ABSTRACT

1. Is the NLRP3 inflammasome upregulated in CICI?

2. IP injection: MTX, 5-FU or saline → PFC and HIPP dissected

3. Protein analysed for NLRP3, Caspase-1 and IL-1β upregulation using western blot and ELISA

4. No upregulation found for NLRP3, Caspase-1 and IL-1β in the HIPP and PFC

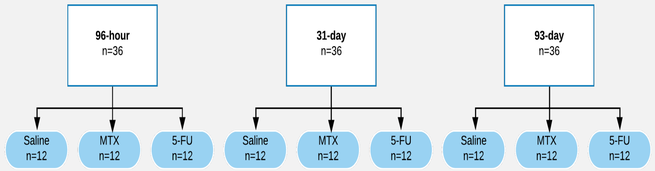
INTRODUCTION

- Chemotherapy-induced cognitive impairment (CICI) affects as many as 75% of cancer patients receiving chemotherapy[1,2].
- Patients report issues with learning, memory and concentration, negatively impacting quality of life[3].
- Neuroinflammation is a proposed mechanism driving CICI[1].
- NLRP3 inflammasome: a key component of inflammation, potentially driving cognitive impairment[4]. NLRP3 upregulation has been demonstrated in Parkinson's and Alzheimer's Disease[4].
- However, it has yet to be investigated in CICI, particularly its role as a therapeutic target.

Aim: Investigate NLRP3 inflammasome upregulation and its related inflammatory markers in a rat model of CICI.

METHODS AND MATERIALS

Female Sprague Dawley Rats (n=108) randomly assigned to 3 treatment groups, across 3 time points.



- IP injection: 5-FU (75mg/kg) or MTX (37.5mg/kg) chemotherapy or saline, once a week for two weeks. Followed by humane euthanasia at assigned time-point.
- Pre-frontal cortex (PFC) and hippocampal (HIPP) tissue assessed for **NLRP3** and **Caspase-1** upregulation via western blot analysis and **IL-1β** assessed using ELISA.

RESULTS

No significant upregulation of NLRP3, Caspase-1 or IL-1β found **in either brain region at any of the three time-points** in chemotherapy treated animals compared to controls ($P > 0.05$).

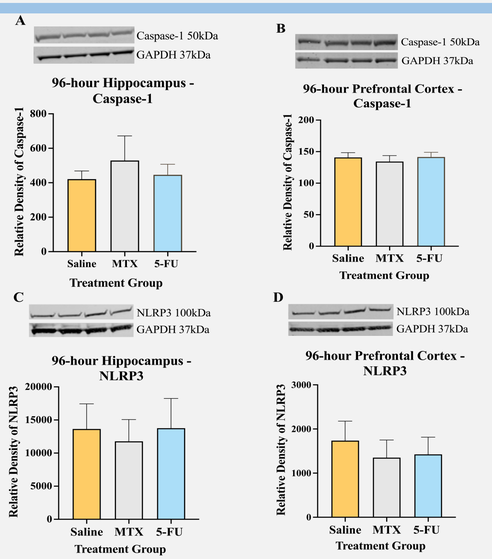


Figure 1. Relative density of Caspase-1 and NLRP3 in the HIPP (A and C) and PFC (B and D) through western blot analysis at 96-hrs ($P > 0.05$).

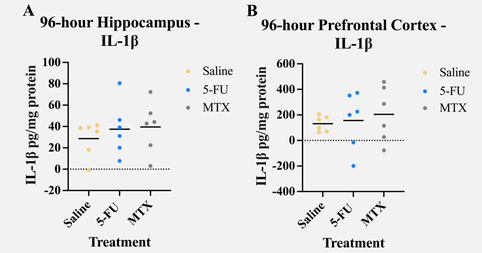


Figure 2. ELISA analysis of IL-1β in the HIPP (A) and PFC (B) at 96-hrs ($P > 0.05$).

DISCUSSION

- No upregulation of the NLRP3 inflammasome and its related inflammatory markers found in this rat model of CICI.
- If this is the case, then perhaps NLRP3 is not a key component driving inflammation in CICI and that maybe there is another key mechanism driving these impairments.
- However, the NLRP3 inflammasome has been shown to be upregulated in Parkinson's and Alzheimer's Disease, which both have strong inflammatory processes, potentially causing cognitive impairment[4].
- CICI models show a more subtle increase in inflammation[5], which could be why no upregulation was found in this study.
- It was surprising that IL-1β, which is commonly upregulated in CICI animal models[6], was not upregulated in this study.
- The issue with animal models of CICI is that there is no gold standard model, making it challenging to draw comparisons and know whether there truly is upregulation of these markers or not.
- Therefore, further research is warranted, such as investigating this upregulation in a cell culture model before taking it into an ideal animal model of CICI.

REFERENCES

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