OPTIMIZING CANCER IMMUNOTHERAPY USING STING AGONIST

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INTRODUCTION

Genetic mutations leading to uncontrolled and sustained cell growth coupled with an Immune system that fails to recognise and eliminate the mutations is what leads to cancers. Cancer is a life-threatening disease and hence is the focus of numerous studies. The proliferation of cells in cancer leads to the formation of tumours, whose microenvironment is Immunosuppressive and hence prevents immune cells from attacking the cancer cells.

Stimulator of Interferon Genes (STING) is a protein encoded in humans that promotes local tissue inflammation and hence attracts immune cells. STING induces Type 1 Interferon (IFN1), which protects both malignant and nearby healthy cells. IFN1 in turn helps to induce IDO (indolamaine-2,3- dioxygenase) which helps to modulate immune function through limiting T-cell function and engaging immune tolerance mechanisms. The function of STING is that it acts as both a Cytosolic DNA sensor and as an adaptor protein. When the STING agonist, cyclic di-AMP (CDA) is injected intra-tumour, it shows therapeutic effects in mouse tumour models but this fails in mice with larger tumours or more chronic conditions.

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that works by being a COX2 inhibitor. In cancer, it helps by affecting genes involved in inflammation and the malignant transformation of tumours but not healthy tissues.

AIMS

The aim of the project was to understand the changes in Inflammatory immune components in the tumour microenvironment (TME) after the STING agonist is injected into the mouse tumour models. The long term goal involved is to improve to therapeutic efficiency of the STING agonists.

METHODOLOGY

Part 1: Mouse model

Mouse lung cancer cells were implanted into genetically matching mice as lung cancer models to test for novel cancer treatment

Part 2: Treatment

Once the tumours were fully developed, the models were given Celecoxib and CDA. The Celecoxib was administered through oral feeding via a Gavage. The CDA was given intra-tumour.

RESULTS

Figure 1

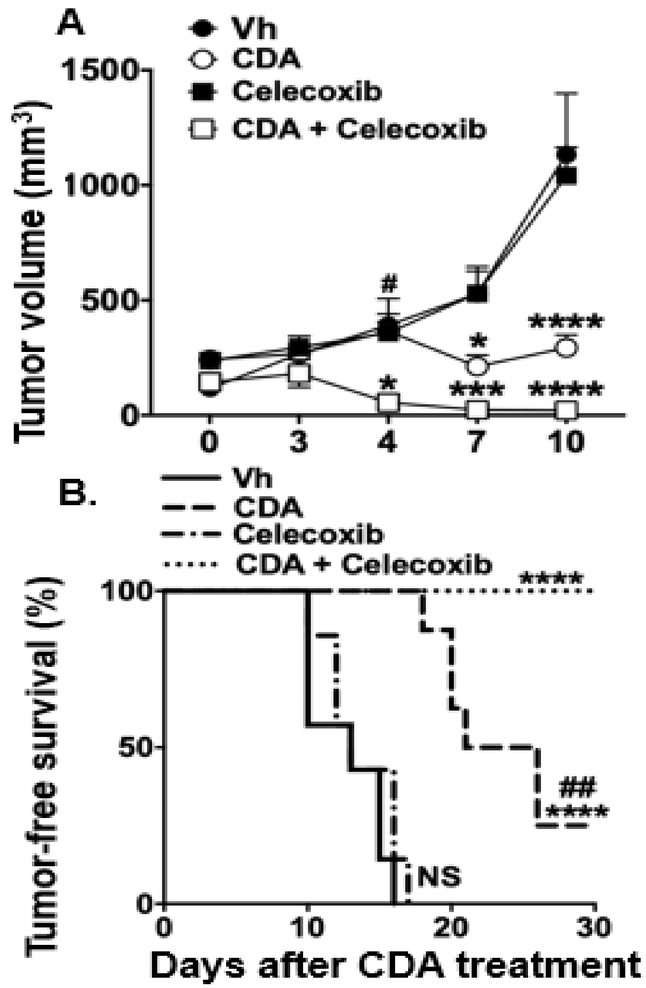

Figure 1: CDA treatments induce COX2 expression in the TME that attenuates anti-tumor responses.
A: B6 mice bearing LLC tumors (170-350mm^3) were treated with CDA with or without Celecoxib (via a gavage for celecoxib and intra-tumor injection for CDA) and tumor volumes.
B: Survival of B6 mice bearing LLC tumors (170-350mm^3) were treated with CDA with or without celecoxib

DISCUSSION AND CONCLUSION

From the data presented in figure 1.A, the following is evident:

- When just the STING agonist is administered intra-tumor the tumor size is not affected as the tumor keeps increasing. This means that STING agonist is not sufficient for the eradication of the tumors.
- When CDA is added along with the STING agonist intra-tumor, the tumor growth and proliferation slow down but does not completely stop. In the future the tumor comes back and is hence not eradicated.
- When Celecoxib is added via a gavage alongside the STING agonist which is administered intra-tumor, the tumor keeps increasing. This shows that just celecoxib with the STING agonist is not sufficient for tumor eradication.
- However, when CDA, Celecoxib and the STING agonist are all administered, the tumor size starts to reduce and is eventually completely eradicated. This shows great evidence that in combination, these 3 factors can help to eliminate tumors.

From the data presented in figure 1.B, it is shown that the survival rate of mice with tumors was 100% only in treatment with celecoxib and CDA along with the STING agonist. On the other hand, the STING agonist alone as well as Celecoxib alongside the STING agonist shows that the mice are tumor-free and survive for only a short amount of time upon treatment, and then the tumors start to grow back.

In conclusion, the only therapy that works effectively is that of CDA and celecoxib in combination with the STING agonist as it completely eradicates the tumor. This treatment can be of great help to people with Cancers once it successfully passes through clinical trials.

ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr Henrique Lemos and Dr Lei Huang for their constant support and guidance throughout this project.

I would also like to extend a thanks to Newcastle University for helping me undertake this project through awarding me the Vacation Scholarship.

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