Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

THE DEVELOPMENT OF CHEMOKINES AS NOVEL, CLINICAL GRADE SORTING TOOLS

Researchers
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Aims

1. To initiate translation of our sorting technology into the human clinical context by producing and testing, novel chemokine-based structures designed to improve the efficiency and translatability of the cell sorting process;
2. To develop protocols for clinical grade chemokine-based sorting of human dendritic cells;
3. To use an *in vivo* model of dendritic-cell-driven immune responses to validate the effectiveness of the sorting protocols.

Project Outline/Methodology

This was a continuation of a previous CSO grant to develop our method of sorting cells with specific therapeutic homing potential in the University of Glasgow. Blood samples for human dendritic cell and T cell generation were obtained from the Scottish National Blood Transfusion Service. Human monocyte-derived and mouse bone-marrow-derived dendritic cells were cultured to generate mixed immature and mature populations, and sorted based on the expression of the lymph node homing chemokine receptor CCR7, using the receptor ligand, CCL19. Once sort methodology was optimised, the sorted cells were compared to their unsorted counterparts in ability to generate an antigen-specific T cell response *in vitro*.

Key Results

Using a chemically synthesised, modified version of CCL19 we were able to optimise protocols to successfully sort therapeutically relevant murine and human CCR7+ mature dendritic cells (DCs). Our murine experiments showed that our mature, sorted DCs were just as capable as the unsorted (mixed immature and mature) DCs at initiating a T cell response, generating both effector and memory T cell phenotypes. This result suggested that the mechanical sort process was not negatively affecting the normal function of antigen presentation to T cells. Our results with human DCs showed that not only are we able to sort mature DCs to high purity, but the sorted DCs were superior to unsorted DCs (which are currently used in therapeutic regimens) at successfully presenting antigen and initiating a robust effector and memory T cell response to viral antigen *in vitro*.

Conclusions

Our sorting methodology can potentially be used to sort for a "fitter" cell population for DC therapy.

What does this study add to the field?

Current cell therapy regimens are frequently compromised by the inability of the cells to migrate to the required therapeutic niche. Here, for the first time, we have shown that with a minor, GMP-compliant modification to existing cell therapy protocols it is possible to select for a "fitter" cell population for therapy.

Implications for Practice or Policy

Our sorting protocol has been developed with a view to be easily adapted into current clinical treatment regimes. This study is therefore crucial for the development of a novel cell sorting protocol which we believe will be invaluable in a wide range of cell therapies.

Where to next?

Further development of the protocol using a new, GMP, fluorescence-based cell sorter to reduce sorting time and minimise mechanical stress to the DCs during the sort process. Our sorted DCs also need to be further tested in both *in vitro* and *in vivo* systems to further investigate their potential immune modulatory functions and also the optimal treatment parameters, such as cell dose and injection site.

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