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Investigating a potential role of Got1 in T cell exhaustion.

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Purpose/Objectives: During cancer and chronic infections, T cells can become exhausted and gradually lose their effector functions. Although clinical studies targeting immune checkpoint molecules (e.g. PD-1) lead to promising results, not all patients can benefit from that kind of treatment, indicating the mechanism of T cell exhaustion is much more complex and has to be understood in more detail in order to develop better therapies. Regulation of T cell exhaustion is not only mediated by immunosuppressive receptors, but also by cell intrinsic metabolic changes. The cytoplasmatic enzyme Glutamic-oxaloacetic transaminase 1 (Got1) plays an important role during amino acid metabolism and energy production in the cell. Since Got1 has been found to be upregulated during T cell exhaustion, our research aims to investigate a possible role of Got1 in this process.

Materials/Methods: To study the T cell-intrinsic role of Got1, we use transgenic mouse lines with Cre-loxP recombination. We are using CD4-Cre*Got1flox/flox mice to study Got1 deficiency in CD4+ and CD8+ T cells. Additionally, we use P14*CD4-Cre*Got1flox/flox mice, which bear a transgenic TCR and allow us to perform adoptive transfer experiments to investigate the CD8+ T cell-intrinsic function of Got1. The mice are challenged with Lymphocytic choriomeningitis virus strains Armstrong or cl-13 to induce acute or chronic viral infections, respectively.

Results: Got1-deficient T cells develop and proliferate normal in naïve mice. First preliminary results indicate that, after chronic viral infection, Got1-deficiency resulted in a reduction of EOMES/TCF7 high “stem cell-like” T cells. This population has previously been demonstrated to be needed for a sustained long-term chronic immune response [1, 2]

Conclusion: Our preliminary studies of Got1 during T cell exhaustion indicate an importance for this enzyme during the long term chronic immune response. By maintaining the pool of “stem cell-like” T cells that give rise to effector T cells, maintaining the long term chronic immune response, Got1 might positively influence T cell function during chronic stimulus. It will be interesting to see in the future, whether the deficiency of Got1 will also impair T cell function during cancer development.

References

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