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Effects of lenalidomide and pomalidomide on antigen-specific T cells

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Multiple myeloma (MM) is a potentially lethal plasma cell malignancy, and can be cured only by allogeneic stem cell transplantation in a part of the patients.
The immunomodulatory drug (IMiD®) lenalidomide exhibits good efficacy on MM therapy, and the immunomodulating effects of lenalidomide has been well described, including the enhancement on the activity of myeloma specific T cells *in vitro*. However, it is often observed that agents show different efficacy *in vitro* and *in vivo*, which might result from the different tumor microenvironment *in vivo* with various immunosuppressors such as regulatory T cells (Tregs). One subset of Tregs: $CD8^+CD28^-$ Tregs was shown to be increased in MM, which might play an important role in the progression of the malignant plasma cell clone.

Thus the first part of this study aimed to investigate whether lenalidomide would overcome the immunosuppressive effects of $CD8^+CD28^-$ Tregs and enhance the activation of myeloma specific T cells *in vitro*. Furthermore, this study explored the role of the immunosuppressive cytokine interleukin (IL)-6 in lenalidomide-induced activation of myeloma specific T cells.
The study analyzed the *in vitro* myeloma specific T cell responses of seven healthy donors with or without lenalidomide administration in the presence of $CD8^+CD28^-$ Tregs. Lenalidomide was able to overcome the immunosuppressive effects of $CD8^+CD28^-$ Tregs, achieving the enhancement on generation of myeloma specific T cells (analyzed by interferon gamma Enzyme-linked immunospot assay, IFN-γ ELISpot) as well as the secretion of cytotoxic agent granzyme B (analyzed by Enzyme-linked immunosorbent assay, ELISA). Furthermore, lenalidomide blocked IL-6 secretion in the presence of $CD8^+CD28^-$ Tregs in ELISA tests. Addition of IL-6 might inhibit the effect of lenalidomide on the activation of myeloma specific T cells. Moreover, by analyzing the immunophenotype regarding the expression of T cell maturation marker CD45RA, lenalidomide promoted the maturation of T cells in the presence of $CD8^+CD28^-$ Tregs while IL-6 diminished the lenalidomide-induced maturation of these T cells. In conclusion, lenalidomide enhances the generation of myeloma specific T cells in the presence of immunosuppressive $CD8^+CD28^-$ Tregs while IL-6 prevents this effect.

Pomalidomide as the most recent commercially available IMiD® is expected to be the most potent IMiD®. Thus the second part of the study aimed to investigate the *in vitro* effects of

pomalidomide on the activation of myeloma specific T cells.
This study for the first time showed that pomalidomide was able to enhance significantly the generation of myeloma specific T cells in 8 of 16 healthy donors and in 6 of 14 MM patients (as analyzed by IFN-γ ELISpot assay). In addition, a longer duration of the IMiD® exposure on the T cells induced a higher frequency of the specific T cells. It was observed that the secretion of the cytotoxic agent granzyme B of the specific T cells was increased by pomalidomide in 7 of 15 healthy donors and in 4 of 12 patients (as analyzed by ELISA). Furthermore pomalidomide could enhance the secretion of the immunomodulating cytokine IL-6 from myeloma specific T cells in 7 of 16 healthy donors and in 4 of 14 patients, which is different from its parental IMiD®-compound lenalidomide that shows blockade of IL-6 release.

This study adds more information on mechanisms of lenalidomide and pomalidomide involved in immunomodulation in MM. Therefore, it is promising to apply lenalidomide and pomalidomide in immunotherapy strategies for an improvement of the clinical outcome for MM patients. In addition, it is promising to further investigate the role of pomalidomide on $CD8^+CD28^-$ Tregs in the future.