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Abstract

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Recognition of PAMPs via pattern recognition receptors is central to the immune recognition and to the generation of a coordinated innate and adaptive immune response. Cancer cells lack PAMPs and are poorly immunogenic. Consequently, the immune system fails to mount an effective, coordinated anti-cancer immune attack. Multiple immunotherapies (e.g. checkpoint inhibitors) are effective in some cancer patients, the majority of patients fail to achieve substantial therapeutic benefit. To fully realize the potential of immune checkpoint inhibitors, there is substantial interest in developing therapeutically-useful PAMPs capable of enabling the maturation and function of professional antigen presenting cells (e.g. dendritic cells, DCs). Bacterial and viral PAMPs (i.e. TLR and STING agonists) can elicit DC maturation but are poorly tolerated systemically and are thereby limited to intra-tumoral delivery. The soluble yeast β-1,3/1,6-glucan, Imprime PGG (Imprime), is a PAMP that has been successfully administered and systemically tolerated and shows promising efficacy in a series of clinical trials with > 400 subjects. We sought to determine whether Imprime could drive maturation and enhanced function of antigen-presenting cells in vivo. We now show that Imprime binds to various dendritic cell (DC) subsets in both human and mouse. In mice dosed IV, Imprime also elicited DC maturation as indicated by CD86 upregulation and successfully induced a type I interferon transcriptional profile. In C57Bl/6 mice immunized with the OVA peptide for 10 days, Imprime treatment elicited the specific expression of adaptively transferred OT-I CD8 T cells (transgenic T cells engineered to recognize a non-mutated, OVA-derived peptide) and CD8 T cells, showing enhanced degranulation and increased capacity to produce IFN-γ. Imprime also protected OT-I cells from an OVA-challenged with OVA peptide alone. In an in vivo human whole blood, Imprime also induced DC maturation (enhanced expression of CD80, CD86, MHC II, and PDL-1) cell expansion and production of the potent anti-tumor cytokines IFN-γ. Importantly, we now show preliminary data that peripheral blood monocytes and DC subsets from Imprime-treated cancer patients show elevated CD86 expression. Collectively, these data show that Imprime, a systemically-administered, well-tolerated PAMP, can effectively drive the maturation and function of antigen-presenting cells in vivo and may thereby enhance T cell priming and anti-tumor immune response elicited by checkpoint inhibitors.

Background

A general structure of yeast-derived Imprime PGG.

- Imprime is a soluble, yeast-derived β-1,3/1,6-glucan immunomodulator being developed for cancer treatment in combination with anti-tumor antibodies.
- Imprime is administered intravenously and is well-tolerated (> 400 patients treated).
- In 1st stage IV NSCLC patients, Imprime, when combined with bevacizumab/cetuximab increased ORR (60% vs 44% in control) and yielded a 6 month OS benefit (control = 11.6 months).
- Imprime binds to various leukocytes including monocytes, neutrophils, B and T cells via a combination of a β-glucan, Fc, and complement receptors.
- CD8 T cell differentiation and acquisition of effector functions is shaped by co-stimulation provided by professional antigen-presenting cells and cytokines (e.g. IL-12 or type I IFNs).
- Here we evaluate the hypothesis that Imprime matures monocytes/DCs and enhances T cell priming.

Human dendritic cell bind Imprime in vivo

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