Abstract

Imprime PGG is a soluble yeast-derived 6-131,6 glucan immune cell modulator that is in phase 3 and multiple phase 2 clinical trials in combination with complement activating monoclonal antibodies (e.g., bevacizumab, cetuximab). We have previously shown that Imprime PGG can target complement receptors and modulates the function of a variety of immune cells, including monocytes, neutrophils, and CD8+ T cells. We have also demonstrated that Imprime PGG binds to various subsets of dendritic cells (DCs) and can cause intermediate upregulation of MHC class II and the co-stimulatory molecules CD80/86 critical for antigen presentation and T cell activation. Based on these findings, we hypothesized that Imprime PGG conjugated to a protein would efficiently deliver antigen to DCs and prime a cytotoxic CD8+ T cell response. To test this hypothesis, we employed the model described recently in mice with Imprime-OVA intravenously and examined the expansion and functional generation of OVA-specific CD8+ T cell responses. We continued OVA to Imprime PGG to generate a OVA-conjugation (Imprime-OVA). Using T cell receptor transgenic OT-1 CD8+ T cell to track responses to OVA, we found mice with Imprime-OVA intravenously and examined the expansion and functional quality of the T cell response 7 days later at the peak of expansion. Following Imprime-OVA treatment, OVA-specific CD8+ T cells underwent significant expansion, upregulated the transcription factor T-bet, that is central to developing effector functions, and gained the ability to produce the cytokines IFN-γ, TNF-α and IL-2. By comparison, OVA alone did not generate a functional CD8+ T cell response and instead induced autoimmunity. In contrast, when cross-presenting DCs are required for CD8+ T cell activation, we used mice deficient in the transcription factor Batf3, which selectively removes CD8+ T cell cross-presenting DCs. Following treatment with Imprime-OVA and OVA alone, OT-I CD8+ T cells were analyzed for (A) spontaneous binding, (B) CD69 expression, and (C) T-bet transcription factor. Spontaneous binding and activation profiles were similar in wild-type and Batf3-deficient mice. Further, these data failed to establish effector functions. Inhibiting that CD8+ T cell cross-presenting DCs are crucial for this response. Together, these data show that Imprime PGG-protein conjugates can efficiently elicit the expansion and functional activation of cytotoxic T cells and may have utility as a potential cancer vaccine.

References

2. Segal NH, et al., European Society of Medical Oncology, World Congress on Gastrointestinal Cancer. Annals of Oncology, June 2014. 
4. No cytokine 
5. Double producer 
6. Single producer 

Figure 1. A general structure of yeast-derived Imprime PGG

Figure 2. Imprime PGG binds to and activates dendritic cells.

Figure 3. Synthesis of Imprime PGG-OVA protein conjugate.

Figure 4. Imprime PGG-OVA protein conjugate generates a multi-functional effector CD8+ T cell response.

Figure 5. Imprime PGG-OVA vaccination generates an OVA-specific CD4 T cell response.

Figure 6. Imprime PGG-OVA vaccination utilizes classical CD8+ cross-presenting DCs to generate CD8+, but not CD4+ T cell responses.

Figure 7. Co-administration of free Imprime PGG

Figure 8. Working model of T cell priming following Imprime-OVA immunization.

Summary

1. Imprime PGG binds to dendritic cells and provides a “danger” signal, causing increased expression of the co-stimulatory molecules CD80 and MHC class II.

2. Protein conjugated to Imprime PGG drives robust expansion of effector CD4+ and CD8+ T cells without the addition of traditional high-inflammatory TLR agonists.

3. Imprime-OVA vaccination generates T-bet+ multi-functional effector CD8+ T cells capable of co-producing IFN-γ, TNF-α, and IL-2.

4. Direct conjugation of OVA to Imprime is required for T cell priming, suggesting that Imprime PGG may enable OVA to an antigen-presenting cell.

5. Dendritic cell cross-presentation of OVA antigen to CD8+ T cells requires classical CD8+ DCs.

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