A novel microbiome-derived peptide, SG-3-00802 reverses resistance to anti-programmed cell death protein-1 (PD-1) therapy by modulating chemokine receptor signaling

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ABSTRACT

Despite the clinical success of immune checkpoint inhibitors (IC) in many cancers, large unmet needs remain, as many patients respond inadequately. Fecal microbiome transplant from anti-PD-1 responders into non-responders improves responses to IC, providing a strong rationale that the gut microbiome influences response to IC.

Methods

Using Second Genome’s proprietary algorithm, we derived an IC responder-specific microbial signature and explored the biologically active molecules derived from IC responder microbiome. Here, we report the anti-tumor activity and immunomodulatory function of a novel microbiome peptide SG-3-00802.

Results

In vitro, SG-3-00802 treatment of human dendritic cells resulted in the interferon-gamma (IFN-γ) - responsive CXCL10 induction. In vivo treatment of mice increased CXCL10 and COX levels in tumors. Furthermore, SG-3-00802 improved anti-tumor responses in combination with anti-PD-1 in the anti-PD-1 monochemo-resistant RENCA mouse model or control peptide or anti-PD-1 antibody alone. Treatment with SG-3-00802 or anti-PD-1 significantly improved overall survival with many mice showing complete tumor regression. Surprisingly, mice with fully regressed tumors (IRB) rejected newly implanted tumors when challenged with RENCA cells, showing that the SG-3-00802 + anti-PD-1 combination yields long-lasting anti-tumor memory responses.

To identify the mechanism of action by which SG-3-00802 was exerting its anti-tumor effects, we sought to identify its cellular target on immune cells. Using mass spectrometry-based binding assays, we identified the chemokine receptor CXCR3 as an interaction partner of SG-3-00802. Receptor activation and immune cell recruitment assays demonstrated that SG-3-00802 enhanced the activity of CXCR3 in the presence of its endogenous ligands CXCL11/12/13 in human and mouse immune cells. CXCR3 expression increased in lymphocyte migration, validating CXCR3 as the functional target. These observations were confirmed in vivo, as CXCR3 inhibition decreased anti-tumor activity of SG-3-00802 alone and in combination with anti-PD-1.

Conclusions

In summary, we demonstrated that the microbiome encodes for molecules that directly interact with the human immune system resulting in enhanced immunity that also impacts anti-tumor activities. SG-3-00802 has the potential to improve responses in IC-resistant patients via mechanisms related to effecting immune cell migration to lymphatic tissues and the tumor microenvironment to drive robust immune responses.

FIGURE 2. SG-3-00802 and Drug Development candidate SG-3-00802™ are positive allosteric modulators of CXCR3

FIGURE 3. SG-3-00802 induces tumor regression, improves survival, and inhibits tumor growth in an anti-PD-1 resistant model

FIGURE 4. SG-3-00802 increases CXCL10 levels and lymphocyte infiltrates in the tumor microenvironment

FIGURE 5. SG-3-00802™ simplifies T cell migration to natural ligands of CXCR3

CONCLUSIONS

- The CXCR3 chemokine pathway is a key pathway that regulates immune cell migration, differentiation, and activation and recruits cytolytic T cells, NK cells, NK T cells, and macrophages to the tumor site. Its activation enhances anti-tumor CD8+ T cell responses and promotes tumor effector function models treated with anti-PD1 in chemokine receptor antagonists in preclinical models.
- Our proprietary drug discovery platform identified a potent peptide, SG-3-00802 expressed in and anti-PD-1 resistant IC, that modulates CXCR3.
- Engaged SG-3-00802™ simplifies the activity of endogenous ligands CXCL11/12/13 resulting in increased receptor signaling and cell migration.
- With its highly retentive binding IC, SG-3-00802™ is a potential lead in class 1/2/3 IC immune activator that can result in tumor growth inhibition.