ABSTRACT

Gut microbiota play a major role in the development, maturation, and modulation of the immune system throughout our life. Therefore, discovery of microbe-driven bioactive drug holds great promise as therapies for immune-related diseases such as inflammatory bowel disease (IBD). However, identification of disease-associated microbiome-host interactions is challenging, owing largely to the complexity of a diverse community and the myriad of direct and indirect interactions through which the microbiome can influence its host.

We developed a discovery pipeline to enrich for therapeutic candidates by combining a systematic computational workflow with in vitro assays to identify biologically active compounds that interacted with specific immune cells and had functional activity. To establish concordant changes in 5,860 cohorts with 21 datasets, we used a novel multi-technology meta-analysis (PTMA) procedure and a curated reference database (SimiSelect). From the genomes of these strains, and from metagenomic assemblies, a peptide library was generated and assessed in a large-scale screening using phase phaging against primary human cells to identify binding to immune cells of interest, such as T cells. Positively selected peptides were then screened in functional assays to identify activity capable of modulating cytokine production. Bioactive peptide were further tested in mouse models of colitis to evaluate therapeutic efficacy. Our ability to discover bioactive peptides in this manner demonstrates a novel workflow in which a computational pipeline is employed to identify microbe-derived peptides that are consistently decreased in IBD patients; ii) peptides are screened by their ability to bind to specific cells of interest, and iii) peptides are identified for their functional activity and therapeutic potential.

SUMMARY AND CONCLUSION

Summary

- Microbiome-derived peptides that are enriched in "health-associated" samples and interact (by binding) with our cells of interest induced IL-10 levels and/or reduced IFN-γ levels in CD4+ T cells.
- Peptide 1 increased levels of IL-10 in a dose-dependent manner.
- Peptide 1 increased frequency of Th3 cells and IL-10 expression.
- Peptide 1 improved DNB6 and DSS-induced colitis in acute models.

Conclusion

Through our differential analysis of the microbiome between populations, such as healthy and diseased individuals, we have identified novel immunomodulatory peptides that have effects in vitro and in vivo.

The ability of our proprietary technology-enabled platform to obtain microbial strain level genetic insights, combined with our function-forward workflow to "mine" and discover novel bioactive molecules with potential therapeutic benefit represents a unique and differentiated microbiome-based drug discovery and development approach.

Disclosure

All authors are or were employees of Second Genome. This project was supported internally and externally.

Acknowledgments

Snap Line Studio for design of the poster.