Roles of common gamma chain on intestinal lymphoid organogenesis using an animal model and patients' samples of X-SCID

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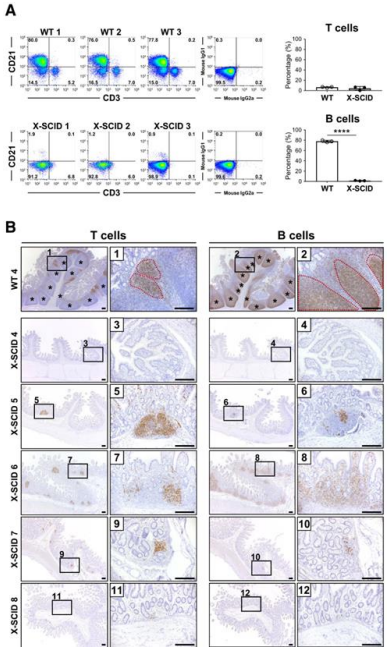
Background: Organ-level research for intestinal lymphoid organogenesis regulated by IL2RG, the gene responsible for X-linked severe combined immunodeficiency (X-SCID), is clinically unavailable in humans. The establishment of *in vivo* animal model lacking Il2rg could be a powerful tool for gaining deeper insights into the roles of common gamma chain on intestinal immunity in patients with X-SCID.

Methods: We established an X-SCID animal model, which was first reported by our group, by deleting the Il2rg in pigs, to understand the clinical significance of IL2RG in intestinal lymphoid organogenesis and microenvironment 1). Pigs with X-SCID underwent bone marrow transplantation (BMT) to mimic the current therapeutic treatment for patients with X-SCID. We investigated the effect of BMT on organ-level immune reconstitution. Moreover, the results were confirmed using serum and fecal samples collected from patients with X-SCID treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) 2).

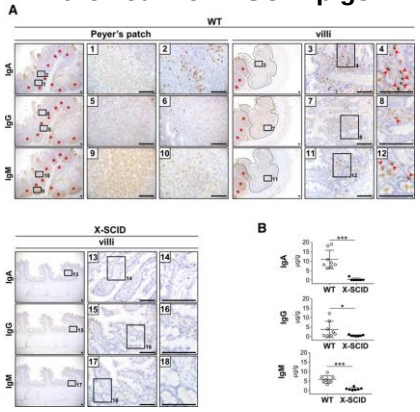
Results: We demonstrated that pigs with X-SCID completely lacked Peyer's patches (PPs) and IgA production in the small intestine but possessed some dysfunctional intestinal T and B cells. Moreover, pigs with X-SCID developed a heterogeneous intestinal microflora, indicating that X-SCID could be an immune disorder that affects normal intestinal lymphoid organogenesis and microenvironment. Importantly, PP organogenesis in pigs with X-SCID was not completely reconstituted by BMT. Although a few isolated lymphoid follicles developed in the small intestines of BMT-treated pigs with X-SCID, there was no evidence that they contributed to IgA production and normal microflora formation. Consistently, most patients with X-SCID who underwent allo-HSCT showed insufficient IgA production and dysbiosis, especially those with incomplete immune reconstitution and low serum IgG levels after allo-HSCT.

Conclusion: Our results indicate that common gamma chain has indispensable roles in intestinal lymphoid organogenesis and microenvironment, suggesting that loss of function of IL2RG product is associated with an increased risk of intestinal infections, malnutrition, and dysbiosis in untreated patients with X-SCID. Our animal model indicated that current allo-HSCT for patients with X-SCID may be insufficient to induce complete reconstitution of intestinal lymphoid organogenesis *in vivo*.

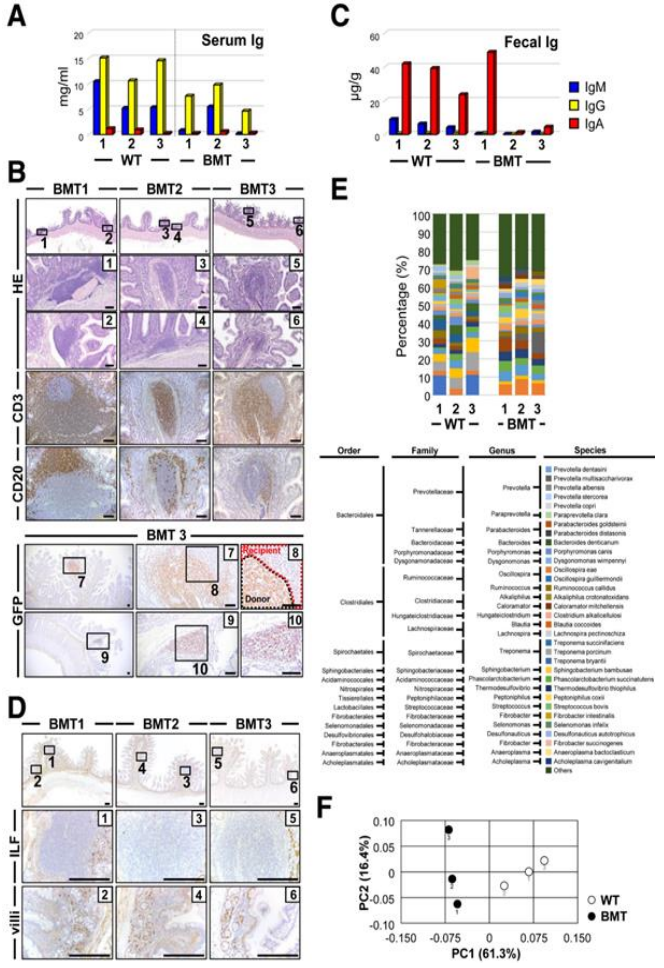
Analyses of immune cells in the ileum of X-SCID pigs.



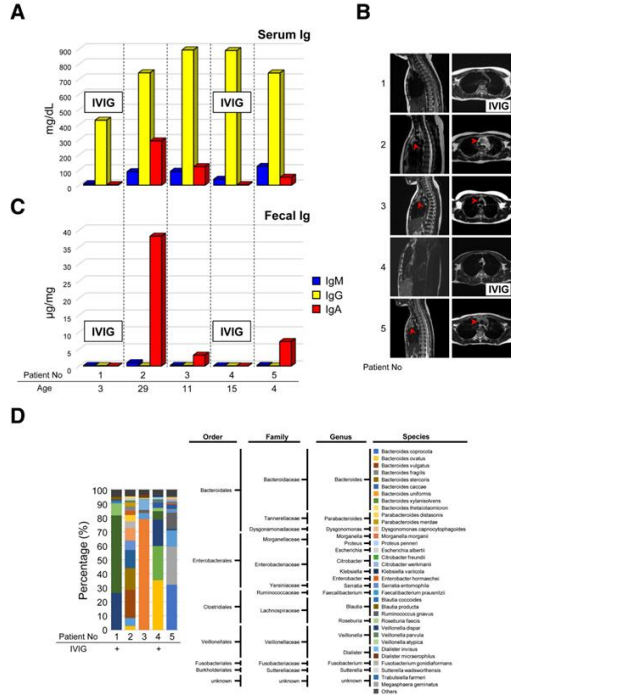
Lack of antibody production in the ileum of X-SCID pigs.



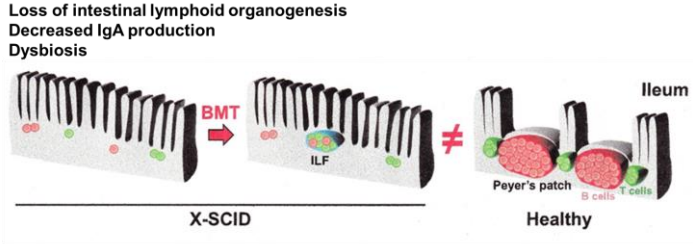
The effect of HSCT for X-SCID pigs on the development of the lymphoid tissue structure and intestinal immune and microbial environments.



The effect of HSCT for patients with X-SCID on the development of the lymphoid tissue structure and intestinal immune and microbial environments.



Graphical Summary



(modified from Cell Mol Gastroenterol Hepatol,10:83-100,2020)

References

1) Suzuki S, et al. Cell stem cell 10: 753-758, 2012.

2) Nochi T, Sasahara Y, et al. Cell Mol Gastroenterol Hpatol 10: 83-100, 2020.