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COMMENT

Truncation of TGF-β docking receptor GARP is linked to human disease

Zihai Li[1]

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Transforming growth factor-β (TGF-β) is a pleotropic cytokine that plays important roles in development, immune tolerance, cancer and a myriad of other processes. It is made as a latent form which requires subsequent binding to TGF-β milieu molecules for activation in a highly tempo-spatially regulated fashion to carry out its function [1].

Two cell surface TGF-β milieu molecules have been described, including Leucine Rich Repeat Containing Protein 32 (LRRC32) [2] and LRRC33 [1]. Glycoprotein-A Repetitions Predominant (GARP), encoded by *LRRC32*, is a type I transmembrane protein with a large extracellular domain for cell surface docking and activation of all three isoforms of latent TGF-β: TGF-β1, TGF-β2 and TGF-β3. GARP has gained increasing attention due to its important roles in immune tolerance [3] and palatogenesis [4] from mouse genetic studies. Genome-wide association study and targeted next-generation sequencing of 11q13.5 in humans has previously linked missense mutation of GARP to atopic dermatitis [5]. In this issue of *EJHG*, Harel et al. [6] reported three human cases of developmental delay, cleft palate and proliferative retinopathy with homozygous point mutation of *LRRC32*. The mutation leads to premature termination of GARP translation ($GARP^{Arg544Ter}$) and presumably a production of soluble GARP without the transmembrane domain. The biochemical confirmation of soluble $GARP^{Arg544Ter}$ was not provided.

To what extent does $GARP^{Arg544Ter}$ contribute to the pathogenesis of the disease is unclear, because there is still a remote possibility of other disease-causing genetic mutations in these three patients. It is also unclear if $GARP^{Arg544Ter}$ is produced at a sufficient level, nor is it known if the truncated protein completely loses its ability to bind and activate latent TGF-β. However, this work is significant because it describes, for the first time, a human genetic condition associated strongly with the possibility of a loss-of-function GARP mutation. The shared phenotype described in all of these patients is consistent with the impairment of some aspects of TGF-β function, arguing strongly the causative role of GARP mutation in the pathogenesis. Although more work is desired including thorough characterization of the immune function and the long-term follow-up of these patients, this study does raise a number of potentially intriguing and important questions regarding the biology and function of GARP.

First, mouse studies have uncovered roles of GARP only in palatogenesis, immune tolerance and cancer immune evasion (Fig. 1), but these three cases suggest that GARP may play other roles including in development of the central nervous system and the retina. Thus the function of GARP may be more than what have been appreciated. Second, if truncation of GARP leads to loss of function, then will GARP cleavage be a mechanism for its down-regulation? This question deserves experimental scrutiny, particularly in pathological conditions such as autoimmune diseases, allergy and cancer. Third, no obvious autoimmune diseases were reported in these three patients, arguing either GARP does not play key roles in immune tolerance in the steady state or $GARP^{Arg544Ter}$ still retains some function in activating latent TGF-β. Alternatively but not mutually exclusively, there might be other redundant or compensatory mechanisms such as increasing expression of LRRC33 in these patients to mask some of the phenotype. Fourth, the current study also suggests that loss of GARP function does not cause acute lethality. This revelation is actually a piece of good news for drug development given the increasing interests in the field to target GARP for immunotherapy of human diseases. This study also enforces the notion that local targeting of GARP is preferred over systemic silencing of the molecule to avoid the potential systemic adverse effect.

✉ Zihai Li
Zihai.li@osumc.edu

[1] Institute for Immuno-Oncology, The Ohio State University, Columbus, OH, USA

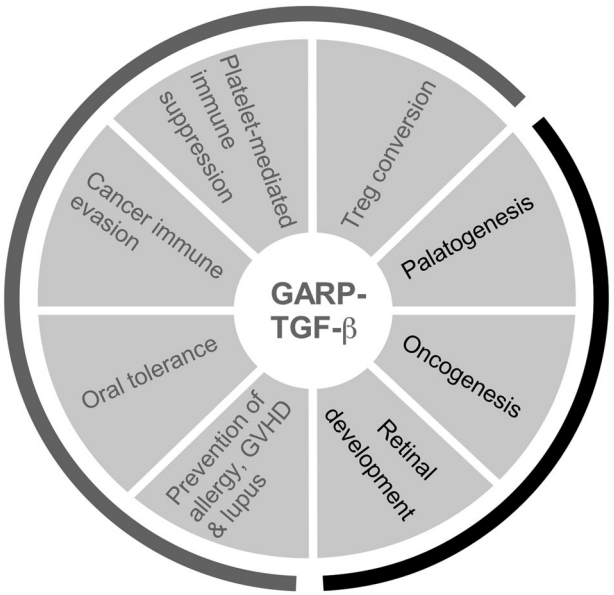

Fig. 1 GARP-GF-β axis plays important roles in development (black) and immune tolerance (green). Treg: regulatory T cells; GVHD: graft versus host disease

With the current genomics revolution, future studies in patients is promised to accelerate the functional definition of genes. Without a doubt, the biology and human disease relevance of the GARP-TGF-β pathway will continue to unravel thanks to the study by Harel et al. [6] and others. Hopefully, GARP-based therapeutics will eventually enter the clinic including GARP gene replacement therapy for patients with loss of function mutations like the current patients.

Compliance with ethical standards

Conflict of interest ZL's work has been funded by the NIH, and has a sponsored research agreement with Bristol-Myers Squibb to develop GARP-targeted immunotherapeutics against cancer.

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