See Article page 85.

Commentary: From Old World monkeys to New World humans—Evolved protection from tick bites and bioprosthetic material

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CENTRAL MESSAGE

Next-generation bioprosthetic valves for transcatheter and surgical implantation should have optimal tissue biocompatibility to minimize inflammatory immune response.

In a fascinating twist of evolution, Old World monkeys, apes, and humans developed a remarkable inactivation of the alpha-1,3-galactosyltransferase gene, which, in turn resulted in a unique recognition of alpha-gal epitope so that high titers of antibodies against this antigen are produced. Although in nature this evolutionary advantage protected us against tick bites and other arthropod vector-borne diseases, in clinical practice, it may cause a spectrum of immune response from immediate anaphylaxis to xenotransplantation to delayed calcifications of bioprosthetic material. This phenomenon, including delayed anaphylaxis to red meat consumption, is known as alpha-gal syndrome.[1,2] In the last decade, an increasing variety of patients have benefitted from transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement.[3,4] In this issue of the *Journal*, Veraar and colleagues[5] challenge us to improve the biocompatibility of bioprosthetic heart valves used for TAVI, as it might be a limiting factor for durability. The study demonstrates significantly increased serum concentrations of alpha-gal–specific antibodies, augmented complement activity, and nonspecific inflammation in 27 patients 3 months after TAVI compared with patients undergoing a MitraClip procedure, who served as controls. Similar xenograft-specific immune response has been observed after surgical bioprosthetic valve replacement.[6,7] Alpha-gal epitopes were also identified in decellularized bioprosthetic material when complete decellularization was not achieved.[8] The resulting humoral response leads to activation of the complement system, triggering endothelial cell dysfunction, platelet aggregation, and promotes calcification.[2,9-11]

Although the presented study of Veraar and colleagues[5] did not explore any relationship between the degree of immunogenic response and valve durability, other groups were able to show an association of anti–alpha-gal antibodies and premature bioprosthetic valve degeneration.[12] Furthermore, several experimental studies demonstrated a connection between anti–alpha-gal antibodies and the calcification process in valvular bioprosthesis.[10,11] Less immunogenic materials and improved processing methods have already been described to increase biocompatibility and to prevent an immunologic response to the xenogenic valve tissue.[9,11] It appears that a proper understanding of alpha-gal syndrome is important to improve the longevity of bioprosthetic material[13-17] in patients with a wide range of congenital and acquired heart disease.

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References

1. Hilger C, Fischer J, Wölbing F, Biedermann T. Role and mechanism of galactose-alpha-1,3-galactose in the elicitation of delayed anaphylactic reactions to red meat. *Curr Allergy Asthma Rep*. 2019;19:3.

2. Naso F, Gandaglia A, Iop L, Spina M, Gerosa G. Alpha-Gal detectors in xenotransplantation research: a word of caution. *Xenotransplantation*. 2012;19:215-20.
3. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;77:450-500.
4. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40:3143-53.
5. Veraar C, Koschutnik M, Nitsche C, Laggner M, Polak D, Bohle B, et al. Inflammatory immune response in recipients of transcatheter aortic valves. *J Thorac Cardiovasc Surg Open*. 2021;6:85-96.
6. Konakci KZ, Bohle B, Blumer R, Hoetzenecker W, Roth G, Moser B, et al. Alpha-Gal on bioprostheses: xenograft immune response in cardiac surgery. *Eur J Clin Invest*. 2005;35:17-23.
7. Mangold A, Szerafin T, Hoetzenecker K, Hacker S, Lichtenauer M, Niederpold T, et al. Alpha-Gal specific IgG immune response after implantation of bioprostheses. *Thorac Cardiovasc Surg*. 2009;57:191-5.
8. Kasimir MT, Rieder E, Seebacher G, Wolner E, Weigel G, Simon P. Presence and elimination of the xenoantigen Gal (α1, 3) Gal in tissue-engineered heart valves. *Tissue Eng*. 2005;11:1274-80.
9. Naso F, Stefanelli U, Buratto E, Lazzari G, Perota A, Galli C, et al. Alpha-Gal inactivated heart valve bioprostheses exhibit an anti-calcification propensity similar to knockout tissues. *Tissue Eng A*. 2017;23:1181-95.
10. McGregor CGA, Carpentier A, Lila N, Logan JS, Byrne GW. Cardiac xenotransplantation technology provides materials for improved bioprosthetic heart valves. *J Thorac Cardiovasc Surg*. 2011;141:269-75.
11. Lila N, McGregor CGA, Carpentier S, Rancic J, Byrne GW, Carpentier A. Gal knockout pig pericardium: new source of material for heart valve bioprostheses. *J Hear Lung Transpl*. 2010;29:538-43.
12. Hawkins RB, Frischtak HL, Kron IL, Ghanta RK. Premature bioprosthetic aortic valve degeneration associated with allergy to galactose-alpha-1,3-galactose. *J Card Surg*. 2016;31:446-8.
13. Buratto E, Konstantinov IE. Commentary: immune cell infiltration in aortic stenosis: cause or consequence. *J Thorac Cardiovasc Surg Open*. 2021;5:15-6.
14. Erkhem-Ochir B, Tatsushi W, Yokobori T, Ohno T, Hatori K, Handa T, et al. Inflammatory and immune checkpoint markers are associated with the severity of aortic stenosis. *J Thorac Cardiovasc Surg Open*. 2021;5:1-12.
15. Konstantinov IE, Ivanov YY. Commentary: aortic valve calcifications: a new story with a twist? *J Thorac Cardiovasc Surg*. 2021;161:e188-9.
16. Buratto E, Konstantinov IE. Aortic valve surgery in children. *J Thorac Cardiovasc Surg*. 2021;161:P244-50.
17. Konstantinov IE, Fricke TA, Ivanov Y, Porello E. Commentary: from bioprosthetic tissue degeneration to regeneration: a new surgical horizon in the era of regenerative medicine. *J Thorac Cardiovasc Surg*. 2019;158:742-3.