A major weapon used by the immune system to combat infection is the secretion of antibody molecules into bodily fluids. Antibodies, which bind to and eliminate foreign antigens, represent soluble versions of the cell surface Ig proteins that act as the B cell receptor for antigen (BCR). More than 70 yr ago, antibodies were found to alter their antigen-binding properties over the course of an immune response (1). The term “maturation of the immune response” was subsequently coined to describe the increase in antibody affinity that is now recognized to be a defining characteristic of T cell–dependent (TD) humoral immune responses (2).

To secrete antibody, antigen-activated B cells must first differentiate into plasma cells. During TD immune responses, plasma cells are initially produced in transient extrafollicular proliferative foci (3) but are subsequently derived from B cells participating in the follicular germinal center (GC) reaction (4, 5). Evidence that GCs might be connected with maturation of the serum antibody response was provided by the discovery that somatic hypermutation (SHM) of Ig genes occurs in GCs (6) and that rare mutant clones expressing BCRs with increased affinity for the immunizing antigen preferentially survive there (4, 7). Nevertheless, the precise factors that cause GC B cells to differentiate into plasma cells and, thus, drive affinity maturation of the antibody response remain unclear (8). In vitro experiments have suggested that stochastic or nonselective mechanisms are of primary importance in the regulation of plasma cell differentiation (9). On the other hand, indirect evidence suggests that plasma cell differentiation of GC B cells may be more selective, with only those cells that exceed a threshold antigen affinity contributing to the antibody response (10, 11). Distinguishing between these two possibilities has proven difficult because current experimental models do not allow affinity-based selection and plasma cell differentiation of GC B cells to be comprehensively tracked in vivo.

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The SWHEL-Ig knock-in mouse model was developed to analyze TD B cell responses to the protein antigen hen egg lysozyme (HEL) conjugated to the sheep RBC (SRBC) carrier (12). SWHEL B cells express the anti-HEL BCR encoded by the high affinity mAb HyHEL10 and can undergo both class switch recombination and SHM (13). Adoptive transfer of small numbers of SWHEL B cells into CD45.1 congenic recipients and challenge with HEL-SRBC results in a typical TD immune response dominated by secretion of IgG1 antibodies derived from donor SWHEL B cells (12). Responding SWHEL B cells can be tracked with precision by virtue of their expression of the anti-HEL BCR and the CD45.2 allotypic marker. The recombinant mutant HEL protein (HEL3X) binds HyHEL10 with >10,000-fold lower affinity than wild-type HEL (HELWT) (14). HEL3X-SRBC triggers migration of responding SWHEL B cells into GCs but is ineffective at eliciting an extrafollicular plasma cell response (14). In this report we exploit the low affinity of HEL3X to develop a system in which the affinity-based selection of GC B cells and their differentiation into plasma cells can be followed. This approach revealed that affinity maturation of TD antibody responses is driven by a mechanism that permits only GC B cells that have acquired high affinity for antigen to differentiate into plasma cells.

**RESULTS AND DISCUSSION**

When SWHEL B cells are challenged with either high affinity (HELWT-SRBC) or low affinity (HEL3X-SRBC) antigen in CD45.1 congenic recipient mice, similar frequencies of donor-derived (CD45.2+) GC B cells are produced at over the first 15 d of the response (14), and these cells undergo equivalent rates of class switch recombination to IgG1 (Fig. 1 A). The extent of SHM measured during the early stages of

![Figure 1. GC and antibody responses to low and high affinity antigens.](image)

SWHEL B cells were adoptively transferred into CD45.1 congenic mice and challenged with HELWT-SRBC, HEL3X-SRBC, or mock antigen. (A) Splenocytes from recipient mice were analyzed by flow cytometry for expression of CD45.2, IgG1, and the ability to bind HELWT. The percentage of donor-derived HELWT-binding GC B cells that had switched to IgG1 was determined and plotted over the course of the response. Data points represent individual recipients, and lines connect the means. (B) Splenocytes from recipient mice (n = 3) were pooled and stained with CD45.2+, syndecan-1, and HELWT. Single CD45.2+ HELWT-binding, GC (syndecan-1−) B cells were sorted, and the targeted Ig heavy chain variable gene was PCR amplified and sequenced. Points represent the frequency of somatic mutations in individual clones (integers). A statistically significant difference in mean mutation frequency per clone (bars) was detected at day 15 and appeared close to significant at day 10 but was not significant at day 5. (C) Sera were collected from recipient mice, and the concentration of anti-HELWT IgG1 antibodies was measured by ELISA. Data points represent individual recipients, and lines connect the means. (D) Affinity maturation of the IgG1 antibody response to HEL3X-SRBC. IgG1 antibodies in pooled sera from recipient mice (n = 5) on day 15 of the responses to HELWT-SRBC and HEL3X-SRBC were analyzed for their ability to bind HELWT and HEL3X in parallel ELISAs.
the GC response (day 5) also does not differ (Fig. 1 B). However, as the responses progress, GC B cells responding to the lower affinity HEL<sup>3X</sup>-SRBC accumulate somatic mutations faster and by day 15 contain significantly more mutations per Ig heavy chain variable region gene than GC B cells responding to HEL<sup>WT</sup>-SRBC (Fig. 1 B). These observations confirm previous analyses of TD antihapten responses showing similar rates of SHM when initial antigen affinity is high or low but enhanced selection for mutated variable regions in B cells with low initial antigen affinity (15).

SW<sub>HEL</sub> B cells challenged with HEL<sup>3X</sup>-SRBC do not produce the burst of extrafollicular plasma cells that typically peaks around day 5 of responses to higher affinity antigens such as HEL<sup>WT</sup>-SRBC (14). As a result, the levels of both total anti-HEL antibody (14) and anti-HEL IgG1 (Fig. 1 C) present at day 5 are ~100-fold lower when SW<sub>HEL</sub> B cells are challenged with HEL<sup>3X</sup>-SRBC compared with HEL<sup>WT</sup>-SRBC. Nevertheless, the concentration of anti-HEL IgG1 in recipient serum increases progressively from days 5 to 20 of the response to HEL<sup>3X</sup>-SRBC (Fig. 1 C). This antibody is derived from SW<sub>HEL</sub> donor B cells, because it is not detected in recipients receiving HEL<sup>3X</sup>-SRBC alone (unpublished data). To examine whether the antibodies elicited in response to HEL<sup>3X</sup> undergo affinity maturation, serum anti-HEL IgG1 present at day 15 of the two responses was tested by ELISA for binding to HEL<sup>WT</sup> and HEL<sup>3X</sup>. As expected, the IgG1 produced in response to HEL<sup>WT</sup>-SRBC bound efficiently to HEL<sup>WT</sup> but showed negligible binding to HEL<sup>3X</sup> (Fig. 1 D). In contrast, the serum anti-HEL IgG1 from recipients challenged with HEL<sup>3X</sup>-SRBC showed almost equivalent binding to HEL<sup>WT</sup> and HEL<sup>3X</sup> (Fig. 1 D), indicating that affinity maturation to HEL<sup>3X</sup> had indeed occurred.

To track the appearance and ultimate fate of GC B cells acquiring increased affinity for HEL<sup>3X</sup>, single donor-derived GC B cells were sorted from immunized mice, and their Ig heavy chain variable region genes were sequenced. By day 15 of the response to HEL<sup>3X</sup>-SRBC, 82% (23 out of 28) of the clones analyzed carried a specific point mutation in the tyrosine 53 codon encoding its substitution with aspartate (Y53D<sub>HyHEL10</sub>; Fig. 3 A). No selection of any heavy chain mutation was evident in day 15 GC B cells produced in response to HEL<sup>WT</sup>-SRBC (Fig. 3 A), which was consistent with the proposition that the affinity of the HEL<sup>WT</sup>-HyHEL10 interaction is too high to permit further affinity maturation (16). None of the 24 clones analyzed from the day 15 HEL<sup>WT</sup>-SRBC GC response contained a mutation in the Y53<sub>HyHEL10</sub> codon, indicating that the Y53D<sub>HyHEL10</sub> mutation is selected specifically in response to HEL<sup>3X</sup>-SRBC and is therefore likely to increase the affinity of HyHEL10 for HEL<sup>3X</sup>. This was confirmed by sorting high affinity anti-HEL<sup>3X</sup> IgG1<sup>+</sup> donor B cells (see gate in Fig. 2), as subsequent sequence analysis revealed that 96% (23 out of 24) of these clones carried the Y53D<sub>HyHEL10</sub> mutation (unpublished data).

**Figure 2. Tracking affinity-based selection in vivo.** Splenocytes from the response shown in Fig. 1 were analyzed by flow cytometry for their expression of CD45.2, IgG1, and the ability to bind the mutant antigen HEL<sup>3X</sup>, and the analogue data are presented on logarithmic axes. The frequency of donor-derived (CD45.2<sup>+</sup>) cells as a proportion of total splenocytes and the mean fluorescence intensity (mfi) of HEL<sup>3X</sup> binding are shown. CD45.2<sup>+</sup> cells were also analyzed for HEL<sup>3X</sup> binding counterstained against IgG1 (to correct for surface Ig expression level) to show a population of high affinity HEL<sup>3X</sup>–binding IgG1<sup>+</sup> cells that emerges on day 10 and dominates the response to HEL<sup>3X</sup>-SRBC by day 15 (oval gate). The frequency of these high affinity cells as a proportion of donor-derived cells is shown. Concatenated data are representative of five mice in each group.
Analysis of the binding of HEL3X to recombinant wild-type and Y53D-mutated HyHEL10 IgG1 antibodies showed that the Y53D mutation increases the affinity of HyHEL10 for HEL3X by ~85-fold (Fig. 3 B). This affinity increase was also evident from the ability of the mutated form of HyHEL10 to recognize plate-bound HEL3X efficiently in ELISA under conditions in which binding of wild-type HyHEL10 to HEL3X was virtually undetectable (Fig. 3 C). Computer modeling revealed that the arginine side chain introduced at position 101 of HEL (D101RHEL) to produce HEL3X (14) is likely to cause a major steric conflict with the phenol group of Y53H and that this conflict is resolved by the Y53D substitution (Fig. S1, available at http://www.jem.org/cgi/content/full/jem.20061254/DC1).

To examine the selection of the Y53D mutation over the course of the response to HEL3X-SRBC, Ig heavy chain gene sequence analysis of single GC B cells and plasma cells was performed on days 5, 10, and 15. On day 5, the Y53D mutation was not detectable in either the GC or the small plasma cell compartment (Fig. 4 A), which was consistent with the absence of high affinity anti-HEL3X B cells at this time point (Fig. 2). By day 10, however, this mutation was detectable in some GC B cells (22% of sequences) but was already present in the great majority of splenic plasma cells (86% of sequences). Similar domination of the GC B cell population by this mutation was not evident until day 15 (Fig. 4 A). Because hypermutated plasma cells must have derived from GC B cell precursors, this result shows that GC B cells generated in response to HEL3X-SRBC do not undergo stochastic differentiation into plasma cells but instead differentiate upon acquisition of the high-affinity Y53D mutation. Accordingly, Y53D-mutated clones that had left the GC and differentiated into plasma cells by day 10 of the response had a significantly lower overall rate of SHM than the Y53D-mutated clones that remained within the GC compartment (2.2 vs. 4.6 mutations/clone, respectively; P = 0.02).

To monitor affinity-based regulation of post-GC plasma cell differentiation more directly, we next challenged donor B cells from SW HEL × Blimp6−/− mice with HEL3X-SRBC. Plasma cells generated in Blimp6−/− mice express GFP under the control of the Blimp-1 promoter and, thus, can be detected via intrinsic green fluorescence (17). By using SWHEL × Blimp6−/− donor B cells in conjunction with our method for identifying somatically mutated B cells with high affinity for HEL3X (Fig. 2), we directly assessed the antigen affinity of post-GC IgG1+ plasma cells in the spleen. Analysis of GFP expression by low and high affinity donor-derived IgG1+ B cells on day 10 of the response to HEL3X-SRBC clearly demonstrated that GFP-expressing plasma cells originated almost exclusively from GC precursors that had acquired a high affinity anti-HEL3X BCR (2.54% of high affinity compared with 0.27% of low affinity cells; Fig. 4 B). These GFP+ cells also had low but detectable levels of surface CD45.2 and IgG1 (Fig. 4 B and not depicted), as is typical of plasma cells (14). Because >95% of high affinity clones detected by HEL3X binding have the Y53D mutation, most of these GFP+ plasma cells are likely to secrete antibodies carrying this amino acid change. Indeed, the serum IgG1 found in mice challenged with HEL3X-SRBC shows almost identical antigen-binding characteristics to Y53D-mutated HyHEL10 (Fig. 1 D and Fig. 3 C).

The model system described in this report provides a unique window into the GC reaction by allowing the appearance, selection, and differentiation of high affinity somatically mutated B cells to be followed throughout the response. We have used this system to demonstrate that high affinity B cell specificities generated within the GC are harnessed to drive affinity maturation of the antibody response.
by a mechanism that ensures their rapid and selective differentiation into plasma cells.

Because low affinity B cells survive within GCs without undergoing plasma cell differentiation (Fig. 4 B), it is apparent that the affinity-dependent mechanism that regulates plasma cell differentiation from GC B cell precursors operates independently of the processes that govern GC B cell survival. The existence of this mechanism was not predicted from in vitro experiments, because these show that B cells can undergo stochastic plasma cell differentiation without requiring a BCR signal (9). This would suggest that specific controls exist within the GC microenvironment that suppress plasma cell differentiation in the absence of signals from high affinity antigen.

The requirement for antigen-dependent signals to drive plasma cell differentiation from GC B cells presents an interesting parallel with the regulation of the extrafollicular plasma cell response. These early plasma cells arise independently of the GC reaction (3) but are similarly biased toward high affinity specificities or epitopes present at high density (14). Therefore, the BCR–antigen interaction appears to play a key role in regulating TD plasma cell differentiation both before and after GC formation. It is possible that BCR signaling could facilitate plasma cell differentiation via the induction of Bcl-6 degradation (18) and subsequent lifting of Blimp-1 repression (19). Alternatively, responding B cells may stochastically commence plasma cell differentiation but require BCR signals to survive beyond the very earliest stages of this process. Whatever the precise mechanism, it is apparent that the immune system places a high priority on ensuring that it devotes resources primarily to the production of relatively high affinity antibodies that are most likely to be biologically effective. The importance of this stringent regulation of plasma cell differentiation is perhaps underscored by the relatively permissive affinity requirements for GC B cells to enter the memory B cell compartment (10, 20). The emphasis on quality control of in vivo plasma cell differentiation may have been a critical development during the evolution of the immune system. Because the body is known to have only a relatively limited capacity within the specialized microenvironments that sustain plasma cells (21, 22), it can be seen that tight control over the specificities that enter the plasma cell compartment would be essential for ensuring that the antibodies that are produced provide effective immune protection.

MATERIALS AND METHODS

Mice and procedures. SW HEL mice (13), Blimp<sup>−/−</sup> mice (17), mutant HEL proteins (14), conjugation of HEL to SRBC, and the adoptive transfer system (12) have been previously described. SW HEL spleen cells were not purified before transfer. Mice were housed in a specific pathogen-free environment at Centenary Institute, and experiments were approved by the University of Sydney Animal Ethics Committee.

ELISA. Serum anti-HEL antibody levels were analyzed by ELISA as previously described (13). The specificity of serum IgG1 antibodies for HEL<sup>WT</sup> concatenated data with equal contributions from five individual recipient mice. Similar results were obtained in two independent experiments.

Figure 4. Affinity threshold for post-GC plasma cell differentiation. (A) SW<sub>HEL</sub> B cells were adoptively transferred and challenged with HEL<sup>2X</sup>-SRBC, and individual donor-derived GC B cells and plasma cells were sorted for SHM analysis, as described in Materials and methods. The proportion of donor-derived GC B cells and plasma cells with the Y53D<sub>HEL</sub> mutation on days 5, 10, and 15 of the response are shown. From left to right, SHM frequencies were 28, 1, 98, 61, 137, and 157 mutations per 10<sup>4</sup> bp. (B) SW<sub>HEL</sub> B cells with (SW<sub>HEL</sub> × Blimp<sup>gfp/+</sup>) and without the Blimp<sup>−</sup>-GFP reporter gene were adoptively transferred and challenged with HEL<sup>2X</sup>-SRBC as in Fig. 1. Splenocytes harvested on day 10 were analyzed by flow cytometry for expression of GFP, CD45.2, IgG1, and HEL<sup>3X</sup> binding, and digital data are presented using biexponential axes. (left) Plots show HEL<sup>3X</sup> binding versus IgG1 gated on CD45.2<sup>+</sup> donor-derived cells. (right) GFP expression by high (top oval gate) and low (bottom oval gate) affinity cells are shown. A distinct population of Blimp<sup>−</sup>-GFP-expressing plasma cells is only evident in high affinity cells in mice that received SW<sub>HEL</sub> × Blimp<sup>gfp/+</sup> B cells. Profiles represent
and HEL3X was determined by coating the ELISA plates with the respective antigens. The relative affinities of HyHEL10WT and HyHEL10Y53D for HEL3X were determined by capture ELISA. 5 μg/ml each of soluble HEL, HEL10WT and HEL10Y53D IgG1 antibodies was captured by plate-bound anti-mouse IgG1. Subsequent binding of HEL3X and HyHEL10Y53D for HEL3X.

Flow cytometry and single cell sorting. Splenocytes were prepared, stained for surface molecules with monoclonal antibodies, and analyzed on a FACSCalibur (BD Biosciences) as previously described (14). To track affinity maturation, cells were stained with recombinant HEL3X conjugated to Alexa Fluor 647 (Invitrogen). For analysis of Blimp-GFP expression, CD45.2 was conjugated to Pacific blue (Invitrogen) to allow identification of donor-derived cells and data acquired on a flow cytometer (LSRII; BD Biosciences). Single cells were sorted on a FACSaria (BD Biosciences) as previously described (14). The gates used for single cell sorting of GC B cells (CD45.2+, syndecan-1+) and plasma cells (CD45.2+, syndecan-1−) were the same as those previously described (14). These gates have been verified through localization of antibody secreting activity (12) and high levels of intracellular Ig staining (14) to cells in the plasma cell gate and demonstration of high levels of GL7, PNA, and Fas on cells in the GC gate (12, 14).

SHM analysis. The HyHEL10 Ig heavy chain variable region gene was amplified from single-responding SWjhel donor B cells and sequenced as previously described (14). Translated sequences were aligned with the original HyHEL10 protein sequence to determine the position and significance of the mutations, as previously described (12). An unpaired t-test was used to calculate the probability (p-value) when comparing SHM frequency per clone in different responding populations.

Expression of wild-type and Y53D-mutated HyHEL10 IgG1 antibodies. The canonical T to G mutation encoding the Y53D helix substitution was introduced by PCR mutagenesis into a pcDNA3 vector (Invitrogen) encoding the HyHEL10 Y1-secreted Ig heavy chain. Wild-type and mutant heavy chain constructs were transiently expressed in Chinese hamster ovary cells along with wild-type HyHEL10 k light chain construct, and culture supernatants were collected and concentrated.

Online supplemental material. Fig. S1 shows Rannot wire frame representations based on the HEL–HyHEL10 complex that model the effects of the D101Rjhel and Y53Djhel substitutions on the interaction. Online supplemental material is available at http://www.jem.org/cgi/content/full/jem.20061254/DC1.

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REFERENCES

1. Heidelberger, M., and F.E. Kendall. 1935. A quantitative theory of the precipitin reaction. III. The reaction between crystalline egg albumin and its homologous antibody. J. Exp. Med. 62:697–720.

2. Siskind, G.W., and B. Benacerraf. 1969. Cell selection by antigen in the immune response. Adv. Immunol. 10:1–50.

3. MacLennan, I.C., K.M. Toellner, A.F. Cunningham, K. Serre, D.M. Sze, E. Zumga, M.C. Cook, and C.G. Vinuesa. 2003. Extracellular antibody responses. ImmunoL Rev. 194:8–18.

4. Jacob, J., R. Kasir, and G. Kelsoe. 1991. In situ studies of the primary immune response to (4-hydroxy-3-nitrophenoxy)acetyl. I. The architecture and dynamics of responding cell populations. J. Exp. Med. 167:1163–1175.

5. Liu, Y.J., J. Zhang, P.J. Lane, E.Y. Chan, and I.C. MacLennan. 1991. Sites of specific B cell activation in primary and secondary responses to T cell-dependent and T cell-independent antigens. Eur. J. Immunol. 21:2951–2962.

6. Jacob, J., G. Kelsoe, K. Rajewsky, and U. Weiss. 1991. Intraclonal generation of antibody mutants in germinal centres. Nature. 354:389–392.

7. Berek, C., A. Berger, and M. Apel. 1991. Maturation of the immune response in germinal centres. Cell. 67:1121–1129.

8. Calame, K.L., K.I. Lin, and C. Tunyaplin. 2003. Regulatory mechanisms that determine the development and function of plasma cells. Annu. Rev. Immunol. 21:205–230.

9. Hassold, J., L.M. Corcoran, D.M. Tarlinton, S.G. Tangye, and P.D. Hodgkin. 2004. Evidence from the generation of immunoglobulin G-secreting cells that stochastic mechanisms regulate lymphocyte differentiation. Nat. Immunol. 5:53–63.

10. Smith, K.G., A. Light, G.J. Nossal, and D.M. Tarlinton. 1997. The extent of affinity maturation differs between the memory and antibody-forming cell compartments in the primary immune response. EMBO J. 16:2996–3006.

11. Smith, K.G., A. Light, L.A. O’Reilly, S.M. Ang, A. Strasser, and D. Tarlinton. 2000. bcI-2 transgene expression inhibits apoptosis in the germinal center and reveals differences in the selection of memory B cells and bone marrow antibody-forming cells. J. Exp. Med. 191:475–484.

12. Phan, T.G., S. Gardam, A. Basten, and R. Brink. 2005. Altered migration, recruitment, and somatic hypermutation in the early response of marginal zone B cells to T cell-dependent antigen. J. Immunol. 174:4567–4578.

13. Phan, T.G., M. Amesbury, S. Gardam, J. Crosbie, J. Hasbold, P.D. Hodgkin, A. Basten, and R. Brink. 2003. B cell receptor-independent stimuli trigger immunoglobulin (Ig) class switch recombination and production of IgG autoantibodies by marget self-reactive B cells. J. Exp. Med. 197:845–860.

14. Paus, D., T.G. Phan, T.D. Chan, S. Gardam, A. Basten, and R. Brink. 2006. Antigen recognition strength regulates the choice between extrafollicular plasma cell and germinal center B cell differentiation. J. Exp. Med. 203:1081–1091.

15. Shih, T.A., E. Meffre, M. Roederer, and M.C. Nussenzweig. 2002. Role of BCR affinity in T cell dependent antibody responses in vivo. Nat. Immunol. 3:570–575.

16. Batista, F.D., and M.S. Neuberger. 1998. Affinity dependence of the B cell response to antigen: a threshold, a ceiling, and the importance of off-rate. Immunity. 8:751–759.

17. Kallies, A.A., J. Hasbold, D.M. Tarlinton, W. Dietrich, L.M. Corcoran, P.D. Hodgkin, and S.L. Nutt. 2004. Plasma cell ontogeny defined by quantitative changes in blimp-1 expression. J. Exp. Med. 200:967–977.

18. Niu, H., B.H. Ye, and R. Dalla-Favera. 1998. Antibiotic receptor signaling induces MAP kinase-mediated phosphorylation and degradation of the BCL-6 transcription factor. Genes Dev. 12:1953–1961.

19. Shafer, A.L., K.I. Lin, T.C. Kuo, X. Yu, E.M. Hurt, A. Rosenwald, J.M. Gilmnate, L. Yang, H. Zhao, K. Calame, and L.M. Staudt. 2002. Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. Immunity. 17:51–62.

20. Takahashi, Y., H. Ohta, and T. Takemori. 2001. Fas is required for extrinsic limits of plasma cell survival. Immunity. 14:181–192.

21. Sze, D.M., K.M. Toellner, C. Garcia de Vinuesa, D.R. Taylor, and I.C. MacLennan. 2000. Intrinsnic constraint on plasmablast growth and extrinsic limits of plasma cell survival. J. Exp. Med. 192:813–821.

22. Odendahl, M., H. Mei, B.F. Hoyer, A.M. Jacob, A. Hamen, G. Muehlenhans, C. Berk, F. Hiepe, R. Manz, A. Radbruch, and T. Dormer. 2005. Generation of migratory antigen-specific plasma blasts and mobilization of resident plasma cells in a secondary immune response. Blood. 105:1614–1621.
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