

# BÖLÜM 4

## HÜMORAL İMMÜNİTE

Yahya GÜL<sup>1</sup>

### B LENFOSİT GELİŞİMİ

#### GİRİŞ

İnsanlarda B hücresi fetal yaşamda karaciğerde ve daha sonra kemik iliğinde olgunlaşır. B hücreleri üretiminde yaşla birlikte azalma olmakla birlikte yaşam boyunca kemik iliğinde üretilmeye devam eder. Erken B hücresinin hayatı kalabilmesi ve işlevi için kemik iliğinde yüzey immünoglobulin ekspresyonunun olması gereklidir. Bu olaylar, lenf düğümleri, dalak ve bağırsaktaki peyer plakları gibi sekonder lenfoid dokulara göç eden olgun B hücrelerinin üretimi ile sonuçlanır. (1) En erken tanınamaz aşama, B progenitör hücresi olarak adlandırılır. Sonraki aşamalar pro-B hücresi, pre-B hücresi, naif veya olgun B hücresi, birkaç farklı tipte antijenle aktive olan B hücresi, plazma hücresi ve bellek B hücresidir.(2)

Kemik iliğinde prekürsör B hücreleri, antijeninden bağımsız olarak gelişir ve immünoglobulin (Ig)

geninin yeniden düzenlenmesi sürecinden geçer. Progenitör B hücreleri, u ağır zincirleri eksprese eden öncü B (Pre B) hücrelerine farklılaşmak için Ig ağır zincir genlerini yeniden düzenler. Pre-B hücreler daha sonra IgM+ immatür B hücrelerine farklılaşmak için Ig hafif zincir genlerini yeniden düzenler ve daha sonra IgM+IgD+ olgun B hücreleri haline gelir. B hücresi gelişimi ve olgunlaşma yolunun her aşamasındaki kusurlar, primer immün yetmezliklere, otoimmün hastalıklara ve hatta B hücresi malignitelerine yol açabilir (3).

Gelişmekte olan B hücresinin membrana bağlı Ig, Igα ve Igβ (CD79a ve CD79b) koreseptörleri ve yardımcı sinyal iletim bileşenlerinden oluşan sağlam ve işlevsel bir B hücresi reseptör (BHR) kompleksi mevcut olmalıdır. Fonksiyonel bir BHR'nin ekspresyonu, B hücresi gelişimi, olgunlaşması ve kemik iliğinden salınması için esastır. BHR ayrıca sekonder lenfoid dokularda olgun B hücrelerinin antijen kaynaklı aktivasyonu sırasında kritik bir rol oynar.(4)

<sup>1</sup> Uzm. Dr. Sağlık Bilimleri Üniversitesi Erzurum Bölge Eğitim ve Araştırma Hastanesi Çocuk İmmünloloji ve Alerji Kliniği, yahya.palu@hotmail.com



dan aktive edebilir. Protein antijenlerine verilen birincil ve ikincil antikor tepkileri farklıdır. İkincil yanıt, birincil yanıtın göre daha hızlı gelişir ve daha büyük miktarlarda antikor üretilir.

## KAYNAKLAR

1. LeBien TW, Tedder TF. B lymphocytes: how they develop and function. *Blood* 2008; 112:1570.
2. Björck P, Kincade PW. CD19+ pro-B cells can give rise to dendritic cells in vitro. *J Immunol* 1998; 161:5795.
3. Wang Y, Liu J, Burrows PD, et all. B Cell Development and Maturation. *Adv Exp Med Biol*. 2020;1254:1-22. doi: 10.1007/978-981-15-3532-1\_1.
4. Kurosaki T, Shinohara H, Baba Y. B cell signaling and fate decision. *Annu Rev Immunol* 2010;28:21–55
5. Matsuda F, Ishii K, Bourvagnet P, et al. İnsan immünoglobulin ağır zincir değişken bölge lokusunun tam nükleotid dizisi. *J Exp Med* 1998; 188:2151.
6. Abbas AK, Lichtman AH, Pillai S. (2018) Cellular and Molecular Immunology. (Ninth edition) Copyright: by Elsevier, Inc
7. Van Gent DC, Hiom K, Paull TT, Gellert M (1997) Stimulation of V(D)J cleavage by high mobility group proteins. *EMBO J* 16(10):2665–2670. <https://doi.org/10.1093/emboj/16.10.2665>
8. Lieber MR. (2010) The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. *Annu Rev Biochem* 79:181–211. <https://doi.org/10.1146/annurev.biochem.052308.093131>
9. Chang HHY, Pannunzio NR, Adachi N, Lieber MR. (2017) Non-homologous DNA end joining and alternative pathways to double-strand break repair. *Nat Rev Mol Cell Biol*. 18(8):495–506. <https://doi.org/10.1038/nrm.2017.48>
10. Ramsden DA, Baetz K, Wu GE. (1994) Conservation of sequence in recombination signal sequence spacers. *Nucleic Acids Res*. 22(10):1785–1796. <https://doi.org/10.1093/nar/22.10.1785>
11. Ciubotaru M, Surleac MD, Metskas LA, et al. (2015) The architecture of the 12RSS in V(D)J recombination signal and synaptic complexes. *Nucleic Acids Res*. 2015;43(2):917–931. <https://doi.org/10.1093/nar/gku1348>
12. Ma YM, Pannicke U, Schwarz K, et all. Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. *Cell*. 2002;108:781–94
13. Lieber MR. (2008) The mechanism of human nonhomologous DNA end joining. *J. Biol. Chem.* 283:1–5
14. Yamtich J, Sweasy JB. (2010) DNA polymerase family X: function, structure, and cellular roles. *Biochim. Biophys. Acta*. 1804:1136–50
15. Melchers F, Karasuyama H, Haasner D, et al. The surrogate light chain in B-cell development. *Immunol Today* 1993; 14:60.
16. Schuh W, Meister S, Roth E, Jäck HM. Cutting edge: signaling and cell surface expression of a mu H chain in the absence of lambda 5: a paradigm revisited. *J Immunol* 2003; 171:3343.
17. Van Zelm MC, van der Burg M, Langerak AW, et all. PID comes full circle: applications of V(D)J recombination excision circles in research, diagnostics and newborn screening of primary immunodeficiency disorders. *Front Immunol* 2011; 2:12.
18. Pillai S, Cariappa A (2009) The follicular versus marginal zone B lymphocyte cell fate decision. *Nat Rev Immunol* 9(11):767–777. <https://doi.org/10.1038/nri2656>
19. Cerutti A, Cols M, Puga I (2013) Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. *Nat Rev Immunol* 13(2):118–132. <https://doi.org/10.1038/nri3383>
20. Witt CM, Won W-J, Hurez V, Klug CA (2003) Notch2 haploinsufficiency results in diminished B1 B cells 1 B Cell Development and Maturation 21 and a severe reduction in marginal zone B cells. *J Immunol* (Baltimore, MD: 1950) 171(6):2783–2788. <https://doi.org/10.4049/jimmunol.171.6.2783>
21. Berland R, Wortis HH (2002) Origins and functions of B1 cells with notes on the role of CD5. *Annu Rev Immunol* 20:253–300. <https://doi.org/10.1146/annurev.immunol.20.100301.064833>
22. Hardy RR, Hayakawa K, Parks DR, et all. (1984) Murine B cell differentiation lineages. *J Exp Med* 159(4):1169–1188. <https://doi.org/10.1084/jem.159.4.1169>
23. Coutinho A, Kazatchkine MD, Avrameas S (1995) Natural autoantibodies. *Curr Opin Immunol* 7 (6):812–818. [https://doi.org/10.1016/0952-7915\(95\)80053-0](https://doi.org/10.1016/0952-7915(95)80053-0)
24. Chen ZJ, Wheeler J, Notkins AL. Antigen-binding B cells and polyreactive antibodies. *Eur J Immunol* 1995; 25:579.
25. Ehrenstein MR, Notley CA. The importance of natural IgM: scavenger, protector and regulator. *Nat Rev Immunol* 2010; 10:778.
26. Allman D, Pillai S (2008) Peripheral B cell subsets. *Curr Opin Immunol* 20(2):149–157. <https://doi.org/10.1016/j.coim.2008.03.014>
27. Hoffmann A, Kerr S, Jellusova J, et al (2007) Sialic acid is a B1 cell inhibitory receptor that controls expansion and calcium signaling of the B1 cell population. *Nat Immunol* 8(7):695–704. <https://doi.org/10.1038/ni1480>
28. Chaudhuri J, Tian M, Khuong C, et all. (2003). Transcription-targeted DNA deamination by the AID antibody diversification enzyme. *Nature* 422, 726–730
29. Yang J, Reth M. Receptor Dissociation and B-Cell Activation. *Curr Top Microbiol Immunol*. 2016;393:27-43. doi: 10.1007/82\_2015\_482
30. Kurosaki T, Kometani K, Ise W (2015) Memory B cells. *Nat Rev Immunol* 15:149–159
31. Tanaka S, Baba Y. (2020) B Cell Receptor Signaling J.-Y. Wang (ed.), B Cells in Immunity and Tolerance, Advances

- in Experimental Medicine and Biology (pp 23-36) Springer Nature Singapore Pte Ltd. [https://doi.org/10.1007/978-981-15-3532-1\\_2](https://doi.org/10.1007/978-981-15-3532-1_2)
32. Gazumyan A, Reichlin A, Nussenzweig MC (2006) Ig beta tyrosine residues contribute to the control of B cell receptor signaling by regulating receptor internalization. *J Exp Med* 203:1785–1794
  33. Hou P, Araujo E, Zhao T, et all. (2006) B cell antigen receptor signaling and internalization are mutually exclusive events. *PLoS Biol* 4:e200
  34. Saijo K, Schmedt C, Su IH, et all. (2003) Essential role of Src-family protein tyrosine kinases in NF-kappaB activation during B cell development. *Nat Immunol* 4:274–279
  35. Harwood NE, Batista FD. Early events in B cell activation. *Annu Rev Immunol* 2010; 28:185.
  36. Peng SL. Signaling in B cells via Toll-like receptors. *Curr Opin Immunol* 2005; 17:230.
  37. Cyster JG, Ansel KM, Reif K, et al. Follicular stromal cells and lymphocyte homing to follicles. *Immunol Rev* 2000; 176:181.
  38. Lanzavecchia A. Antigen-specific interaction between T and B cells. *Nature* 1985; 314:537.
  39. Luo W, Weisel F, Shlomchik MJ (2018) B cell receptor and CD40 signaling are rewired for synergistic induction of the c-Myc transcription factor in germinal center B cells. *Immunity* 48:313–326 e315
  40. Chan TD, Gatto D, Wood K, et al. Antigen affinity controls rapid T-dependent antibody production by driving the expansion rather than the differentiation or extrafollicular migration of early plasmablasts. *J Immunol* 2009; 183: 3139–3149.
  41. Young C, Brink R. Germinal centers and autoantibodies. *Immunology Cell Biology* 2020;98: 480–489. <https://doi.org/10.1111/imcb.12321>
  42. Victora GD, Nussenzweig MC (2012) Germinal centers. *Annu Rev Immunol* 30:429–457.
  43. Allen CD, Cyster JG. Follicular dendritic cell networks of primary follicles and germinal centers: phenotype and function. *Semin Immunol* 2008; 20:14.
  44. Stewart I, Radtke D, Phillips B, et al. Germinal center B cells replace their antigen receptors in dark zones and fail light zone entry when immünoglobulin gene mutations are damaging. *Immunity* 2018; 49: 477–489
  45. Liu D, Xu H, Shih C, et all. T-B-cell entanglement and ICOSL-driven feedforward regulation of germinal centre reaction. *Nature* 2015;517:214–218
  46. Javier M, Di Noia, Neuberger M.S. Molecular Mechanisms of Antibody Somatic Hypermutation. *Annu. Rev. Biomed.* 2007; 76:1–22
  47. Goodman MF, Scharff MD, and Romesberg FE (2007). AID-initiated purposeful mutations in immünoglobulin genes. *Adv Immunol* 94, 127–155
  48. Stavnezer J, Guikema JE, and Schrader CE (2008). Mechanism and regulation of class switch recombination. *Annu Rev Immunol* 26, 261–292.
  49. Kefei Yu, Michael R. Lieber. Current insights into the mechanism of mammalian immunoglobulin class switch recombination. *Crit Rev Biochem Mol Biol*. 2019 August ; 54(4): 333–351. doi:10.1080/10409238.2019.1659227.
  50. Harris RS, Sale JE, Petersen-Mahrt SK ve Neuberger MS. AID is essential for immünoglobulin V gene conversion in a cultured B cell line *Curr Biol*. 2002 Mar 5;12(5):435-8. doi: 10.1016/s0960-9822(02)00717-0.
  51. Muramatsu M, Kinoshita K, Fagarasan S, et all. (2000). Class Switch Recombination and Hypermutation Require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme. *cell* 102 , 541-544.
  52. Bransteitter R, Pham P, Scharff MD, and Goodman MF (2003). Activation-induced cytidine deaminase deaminates deoxycytidine on single-stranded DNA but requires the action of RNase. *Proc Natl Acad Sci* 100, 4102–4107.
  53. DiNoia J, and Neuberger MS (2002). Altering the pathway of immünoglobulin hypermutation by inhibiting uracil-DNA glycosylase. *Nature* 419, 43–48.
  54. Chaudhuri J, Basu U, Zarrin A, et al. (2007). Evolution of the immünoglobulin heavy chain class switch recombination mechanism. *Adv Immunol* 94, 157–214.
  55. Huang C. (2020) Germinal centers reaction. J.-Y. Wang (ed.), B Cells in Immunity and Tolerance, Advances in Experimental Medicine and Biology (pp 47-53) Springer Nature Singapore Pte Ltd. [https://doi.org/10.1007/978-981-15-3532-1\\_4](https://doi.org/10.1007/978-981-15-3532-1_4)
  56. Wan Z, Lin Y, Zhao Y, Qi H (2019) TFH cells in bystander and cognate interactions with B cells. *Immunol Rev* 288:28–36
  57. Nutt SL, Hodgkin PD, Tarlinton DM, Corcoran LM (2015) The generation of antibody-secreting plasma cells. *Nat Rev Immunol* 15:160–171
  58. Chang HD, Tokoyoda K, Radbruch A (2018) Immunological memories of the bone marrow. *Immunol Rev* 283:86–98.
  59. Krautler NJ, Suan D, Butt D, et.all. (2017) Differentiation of germinal center B cells into plasma cells is initiated by high-affinity antigen and completed by Tfh cells. *J Exp Med* 214:1259–1267
  60. Weisel F, Shlomchik M (2017) Memory B cells of mice and humans. *Annu Rev Immunol* 35:255–284