BIOLOGY REPORTS

Published: 25 March 2010

Epigenetic regulation of antigen receptor gene rearrangement

Salvatore Spicuglia[1,2,3], Joaquin Zacarias-Cabeza[1,2,3], Aleksandra Pekowska[1,2,3] and Pierre Ferrier[1,2,3]*

Addresses: [1]Centre d'Immunologie de Marseille-Luminy, Université Aix Marseille, Marseille, France; [2]CNRS, UMR6102, Marseille, France; [3]Inserm, U631, Marseille, France

* Corresponding author: Pierre Ferrier (ferrier@ciml.univ-mrs.fr)

F1000 Biology Reports 2010, **2**:23 (doi:10.3410/B2-23)

Abstract

V(D)J recombination assembles antigen-specific immunoglobulin and T-cell receptor variable region genes from germline V, D, and J segments during lymphocyte development. Regulation of this site-specific DNA rearrangement process occurs with respect to the cell type and stage of differentiation, order of locus recombination, and allele usage. Many of these controls are mediated via the modulation of gene accessibility to the V(D)J recombinase. Here, we summarise recent advances regarding the impact of nuclear organisation and epigenetic-based mechanisms on the regulation of V(D)J recombination.

Introduction and context

B and T lymphocytes form the adaptive arm of the immune system in jawed vertebrates and can specifically respond to an astounding number of foreign antigens. This property depends largely on a series of site-specific DNA rearrangement events between separate V, D, and J gene segments at antigen receptor (AR)-encoding loci, a process referred to as V(D)J recombination [1]. There are seven AR loci: the immunoglobulin heavy (IgH) and light (Igκ and Igλ) chain loci expressed in B cells and the T-cell receptor (TCR) α, β, γ, and δ loci expressed in T cells. For V(D)J recombination to occur, the presence of the lymphoid-specific proteins RAG1 and RAG2 and the ubiquitously expressed DNA repair factors from the non-homologous end joining pathway is required. Strict regulation of this process ensures B- or T-cell lineage specificity, dictates the temporal order of Ig or TCR rearrangements, respectively, and allows allelic exclusion at certain AR genes (for a recent review, see [2]). The lineage and temporal specificities of the common V(D)J recombinase are regulated primarily at the level of chromosomal accessibility. During the past decade, AR genes have served as tractable models to study the regulation of gene expression at complex genomic loci, using gene targeting technologies in particular [3,4]. These studies have notably led to a better appreciation of the hierarchical function of transcriptional *cis*-regulatory elements (enhancers and germline promoters) and their impact on the control of V(D)J recombination via the modulation of chromatin structure (e.g., [4-6]). Within a given AR locus, enhancer- or promoter-dependent chromosomal accessibility to the V(D)J recombinase generally correlate with the presence of several epigenetic marks synonymous with euchromatin (germline transcription [GT], accessibility to endonucleases, CpG demethylation, and enrichment in active histone marks) and the delocalisation from heterochromatic regions of the nucleus (the pericentromeric heterochromatin and nuclear periphery) [7]. How these epigenetic features are achieved at the molecular level is currently the focus of intense investigation.

Major recent advances

While we know that the presence of active epigenetic marks at AR loci generally correlates with tissue- and stage-specific V(D)J recombination events, its potential role in effectively targeting the recombinase to the individual loci remains unclear (reviewed in [7]). A first insight came

from studies demonstrating that the PHD (plant homeodomain) finger of RAG2 binds to histone H3 dimethylated or trimethylated at K4 (H3K4me2/3), with a preference for H3K4me3, and is enhanced by the presence of symmetrically dimethylated H3R2 (H3R2me2s) [8-10]. More recently, Lieber and colleagues [11] reported that H3K4me3 stimulates RAG-mediated *cis*-DNA cleavage *in vitro*, an effect that was also achieved by simply adding H3K4me3 peptide *in trans* to the reaction. This supports the notion of a direct impact of epigenetic environment on the recombinase catalytic activity. The authors also observed that most common cryptic recombination signals (RSs) known to be aberrantly used in acute T-cell leukaemia-transformed cells are located nearby H3K4me3-enriched domains in normal T cells. This could link translocation frequency at cryptic RSs with the epigenetic landscape in cells undergoing V(D)J recombination.

The RAG2-H3K4me3 connection raised the possibility that a specific histone code may restrict V(D)J recombination *in vivo*. However, H3K4me3 is not confined to the AR loci, and to date no particular combination of histone marks has been exclusively associated with these loci [12,13]. Irrespective of these concerns, the question of how active epigenetic marks are established through the recombining gene segments and associated RSs remains. One possibility could be that GT, either sense or antisense, impinges on epigenetic marking before AR assembly [14,15]. (Notice that the functional significance, if any, of antisense transcription at a given Ig/TCR locus or cluster [or both] still requires thorough investigation; also, see [16,17].) Accordingly, suppression of GT throughout the 5′ TCR-Jα region interferes with epigenetic marking and inhibits Vα-Jα rearrangements in this region [18]. Likewise, in an inducible pre-B cell line, GT at Igκ/λ loci appears to precede the establishment of active epigenetic marks [13]. In this context, targeted deletion of AR-associated enhancers generally results in reduced levels of germline transcripts and active histone marks [6], even though the magnitude of these effects may vary depending on the locus and, within a given locus, the particular region (i.e., the V versus D/J region) [19,20]. Ultimately, determining the precise enhancer function in chromatin remodelling may require mutational/deletional analysis of the discrete transcription factor (TF)-binding sites within these regulatory modules.

One arm of current research aims to decipher the gene expression programs that coordinate lymphoid cell differentiation and V(D)J recombination. An outstanding example is the dissection of the signalling pathways orchestrating the transition through the pre-B-cell receptor (pre-BCR) checkpoint during pro-B to pre-B cell differentiation and induction of Igκ recombination. On the one hand, pre-BCR signalling induces the expression of the TF interferon regulatory factor 4 (IRF4) and activation of the Ras-MEK-Erk phosphotyrosine kinase cascade, which in turn promotes cell cycle exit (via repression of cyclin Ccdn3) and modulates the expression of antagonist TFs E2A and Id3 – two features known to favour Ig gene assembly (notably, E2A is a direct activator of Igκ transcription and recombination) [21,22]. On the other hand, IL7R signalling acts, via the STAT5 TF, to inhibit Igκ recombination, in part by blocking E2A access to the intronic Igκ enhancer [21-23]. Finally, IRF4 also promotes the progressive loss of IL7R signalling, resulting in a full activation of Igκ recombination. Thus, intricate pre-BCR and IL7R signalling interplay regulates cell cycle exit, Igκ recombination, and B-cell differentiation.

Pioneering studies using fluorescence *in situ* hybridisation (FISH) have revealed large-scale locus contraction and chromosomal looping as novel processes that may be involved in the developmental regulation of V(D)J recombination at AR loci [7]. More recently, Jhunjhunwala and colleagues [24] used high-resolution microscopy to generate a statistical, three-dimensional (3D) description of the nuclear topology of the IgH locus within pre-pro- and pro-B cells. This 3D imaging revealed the existence of chromosomal domains displaying conformational changes during early B-cell development. It was suggested that the chromatin fibre, once poised for V(D)J recombination, folds into dynamic loops of variable sizes, which may depend on 'bridging' factors such as CCCTC-binding factor (CTCF). Indeed, the DNA-binding profile of CTCF throughout the IgH locus, together with that of Rad21 (a component of the cohesin complex that physically and functionally interacts with CTCF [25]), tends to support this assumption [26]. Intriguingly, another potential candidate, the TF Pax5, which is known to impinge on IgH locus contraction and rearrangements of distal V_H gene segments ([7] and references therein), may do so, at least in part, by promoting enrichment of the suppressive H3K27me3 mark at the proximal side of the V_H gene cluster [27].

FISH analyses of the subnuclear organisation of AR genes have, in addition, revealed a strong correlation between gene repression and positioning at the nuclear periphery or pericentromeric heterochromatin [7]. Using an inducible system, Singh and colleagues [28] demonstrated that recruitment of a chromosomal reporter to the nuclear lamina indeed results in its physical interaction with proteins associated with the inner nuclear membrane and transcriptional repression. Whether the

subnuclear organisation of Ig/TCR loci impacts on the initiation of allelic exclusion, a process that essentially relies on the dissociation of V-to-(D)J rearrangement between the two alleles, is a matter of debate. Experimental evidence supports both a deterministic (or instructive) and a stochastic (or probabilistic) model of gene activation (or a combination of both) to explain this phenomenon [29]. In the former scenario, AR alleles are believed to randomly display distinct epigenetic marking acquired during development such that, in individual cells, one will be preferentially used for initial rearrangement. Instead, stochastic models argue that allele dissociation results from inter-allelic competition and, usually, a low probability of locus activation. In this context, primary FISH-based studies have revealed a preferential mono-allelic association of Ig loci with pericentromeric heterochomatin, suggesting that a deterministic mechanism may in this way direct the inactivation of the non-functional allele ([30] and references therein). Conversely, a similar approach applied later on to the analysis of the TCRβ locus instead demonstrated high levels of biallelic association with the nuclear lamina or pericentromeric compartments (or both), arguing for a stochastic component in allelic primary choice [31]. In the meantime, however, re-examination of a GFP knockin mouse model long considered to provide strong evidence for probabilistic gene expression at Igκ alleles (hence supporting the stochastic view for initiation of allelic exclusion at this locus) has questioned the validity of this experimental system, thus casting doubt on prior interpretation [32,33]. Two novel observations regarding Ig locus intra-nuclear interaction fuelled the debate. First, the IgH and Igκ loci appear to frequently associate in pre-B cell nuclei [34]. This association requires the Igκ 3′ enhancer and contributes to the pericentromeric recruitment and decontraction of the IgH locus but appears dispensable for allelic exclusion. Second, the two alleles of the IgH and Igκ loci may at some point during B-cell differentiation also be paired in a stage-specific way [35]. This pairing would require the RAG1 protein, with the resulting DNA cut at one single allele then inducing the repositioning of the opposite allele toward pericentromeric chromatin, a process mediated by the DNA damage response protein ataxia telangiectasia mutated (ATM), which could thereby prevent biallelic recombination. Whether similar processes also occur at TCR alleles during T-cell development remains to be investigated. This could be relevant considering, for example, all the evidence that germline Vβ segments adjacent to a VβDJβ-Cβ domain maintain a chromosomal accessible configuration following TCRβ feedback signalling, and yet are not subjected to recombination [36,37].

Little is known about the epigenetic pattern or patterns that correlate with the late, DNA repair joining phase of V(D)J recombination. Recombinase-generated DNA double-strand breaks induce phosphorylation of the histone variant H2AX over long distances [38]. The aforementioned involvement of ATM in the nuclear positioning of Ig loci also suggests a link between the regulation of V(D)J recombination and DNA repair. Indeed, ATM appears to exhibit various effects on AR gene assembly [39,40], and additional DNA repair factors may also be involved [41]. Likewise, the 53BP1 protein that functions in a subset of ATM-dependent responses may also play a more specific role in long-range contraction of AR loci or the maintaining of genomic stability during their recombination (or both) [42,43]. Given all of these connections, it might also be interesting to investigate whether epigenetic marks contribute to the recruitment/spreading and activity of at least some DNA repair factors at V(D)J recombination foci.

Future directions

The sophisticated mechanisms behind the regulation of V(D)J recombination are progressively emerging. New concepts require further investigation, in particular regarding their generalisation to all Ig/TCR loci (and other immune loci). It will be equally important to decipher the precise links between epigenetic modifications, intergenic transcription, chomosomal organisation and connection with DNA-transacting machineries at these loci, and the precise mechanisms behind the establishment and enforcement of allelic exclusion. Significant progress may come from the thorough characterisation of TF and nucleoprotein complexes bound at AR loci, ideally in a developmental order, using high-throughput technologies (chromatin immunoprecipitation [ChIP]-on-chip, ChIP-Seq) [20,23,26,27,44]. Given the complexity of these biological systems in which the molecular/cellular outcome may not at first be obvious, mathematical models and simulations could also help in connecting hypotheses with experimental observations [7,45].

Abbreviations

3D, three-dimensional; AR, antigen receptor; ATM, ataxia telangiectasia mutated; BCR, B-cell receptor; ChIP, chromatin immunoprecipitation; CTCF, CCCTC-binding factor; FISH, fluorescence *in situ* hybridisation; GT, germline transcription; Ig, immunoglobulin; IgH, immunoglobulin heavy; IRF4, interferon regulatory factor 4; RS, recombination signal; TCR, T-cell receptor; TF, transcription factor.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

We thank members of the PF laboratory for critical reading of this manuscript. We apologise to those authors whose valuable contributions to this field were only referenced in the context of published reviews, due to space limitation. Work in the PF laboratory is supported by institutional grants from INSERM and the 'Centre National de la Recherche Scientifique' (CNRS) and by specific grants from the 'Fondation Princesse Grace de Monaco', the 'Association pour la Recherche sur le Cancer' (ARC), the 'Agence Nationale de la Recherche' (ANR), the 'Institut National du Cancer' (INCa) and the Commission of the European Communities. JZ-C is supported by a fellowship from ANR. AP is supported by a Marie Curie research training fellowship.

References

1. Jung D, Alt FW: **Unraveling V(D)J recombination; insights into gene regulation.** *Cell* 2004, **116:**299-311.
2. *V(D)J Recombination: Advances in Experimental Medicine and Biology*. Vol. 650. Edited by Ferrier P. Austin, TX: Landes Bioscience; 2009.
3. Bonnet M, Ferrier P, Spicuglia S: **Molecular genetics at the T-cell receptor beta locus.** *Adv Exp Med Biol* 2009, **650:**116-32.
4. Perlot T, Alt FW: **Cis-regulatory elements and epigenetic changes control genomic rearrangements of the IgH locus.** *Adv Immunol* 2008, **99:**1-32.
5. Krangel MS: **Mechanics of T cell receptor gene rearrangement.** *Curr Opin Immunol* 2009, **21:**133-9.
6. Thomas LR, Cobb RM, Oltz EM: **Dynamic regulation of antigen receptor gene assembly.** *Adv Exp Med Biol* 2009, **650:**103-15.
7. Jhunjhunwala S, van Zelm MC, Peak MM, Murre C: **Chromatin architecture and the generation of antigen receptor diversity.** *Cell* 2009, **138:**435-48.
8. Liu Y, Subrahmanyam R, Chakraborty T, Sen R, Desiderio S: **A plant homeodomain in RAG-2 that binds hypermethylated lysine 4 of histone H3 is necessary for efficient antigen-receptor-gene rearrangement.** *Immunity* 2007, **27:**561-71.

   f1000 Factor 6.6 *Must Read*
   Evaluated by Pierre Ferrier 05 Nov 2007, Patrick Matthias 04 Feb 2008, David Schatz 04 Feb 2008
9. Matthews AG, Kuo AJ, Ramon-Maiques S, Han S, Champagne KS, Ivanov D, Gallardo M, Carney D, Cheung P, Ciccone DN, Walter KL, Utz PJ, Shi Y, Kutateladze TG, Yang W, Gozani O, Oettinger MA: **RAG2 PHD finger couples histone H3 lysine 4 trimethylation with V(D)J recombination.** *Nature* 2007, **450:**1106-10.

   f1000 Factor 9.0 *Exceptional*
   Evaluated by David Schatz 31 Jan 2008
10. Ramon-Maiques S, Kuo AJ, Carney D, Matthews AG, Oettinger MA, Gozani O, Yang W: **The plant homeodomain finger of RAG2 recognizes histone H3 methylated at both lysine-4 and arginine-2.** *Proc Natl Acad Sci U S A* 2007, **104:**18993-8.

    f1000 Factor 3.0 *Recommended*
    Evaluated by David Schatz 31 Jan 2008
11. Shimazaki N, Tsai AG, Lieber MR: **H3K4me3 stimulates the V(D)J RAG complex for both nicking and hairpinning in trans in addition to tethering in cis: implications for translocations.** *Mol Cell* 2009, **34:**535-44.
12. Morshead KB, Ciccone DN, Taverna SD, Allis CD, Oettinger MA: **Antigen receptor loci poised for V(D)J rearrangement are broadly associated with BRG1 and flanked by peaks of histone H3 dimethylated at lysine 4.** *Proc Natl Acad Sci U S A* 2003, **100:**11577-82.

    f1000 Factor 3.0 *Recommended*
    Evaluated by Pierre Ferrier 16 Oct 2003
13. Xu CR, Feeney AJ: **The epigenetic profile of Ig genes is dynamically regulated during B cell differentiation and is modulated by pre-B cell receptor signaling.** *J Immunol* 2009, **182:**1362-9.
14. Abarrategui I, Krangel MS: **Germline transcription: a key regulator of accessibility and recombination.** *Adv Exp Med Biol* 2009, **650:**93-102.
15. Bolland DJ, Wood AL, Corcoran AE: **Large-scale chromatin remodeling at the immunoglobulin heavy chain locus: a paradigm for multigene regulation.** *Adv Exp Med Biol* 2009, **650:**59-72.
16. Zhao Y, Dunn-Walters DK, Barone F, Spencer J: **Antisense transcripts of V(D)J rearrangements; artifacts caused by false priming?** *Mol Immunol* 2009, **46:**2357-62.
17. Perlot T, Li G, Alt FW: **Antisense transcripts from immunoglobulin heavy-chain locus V(D)J and switch regions.** *Proc Natl Acad Sci U S A* 2008, **105:**3843-8.

    f1000 Factor 3.0 *Recommended*
    Evaluated by Janet Stavnezer 06 Mar 2008
18. Abarrategui I, Krangel MS: **Regulation of T cell receptor-alpha gene recombination by transcription.** *Nat Immunol* 2006, **7:**1109-15.

    f1000 Factor 3.0 *Recommended*
    Evaluated by Pierre Ferrier 05 Oct 2006
19. Chakraborty T, Perlot T, Subrahmanyam R, Jani A, Goff PH, Zhang Y, Ivanova I, Alt FW, Sen R: **A 220-nucleotide deletion of the intronic enhancer reveals an epigenetic hierarchy in immunoglobulin heavy chain locus activation.** *J Exp Med* 2009, **206:**1019-27.
20. Bonnet M, Huang F, Benoukraf T, Cabaud O, Verthuy C, Boucher A, Jaeger S, Ferrier P, Spicuglia S: **Duality of enhancer functioning mode revealed in a reduced TCRb gene enhancer knockin mouse model.** *J Immunol* 2009, **183:**7939-48.
21. Johnson K, Hashimshony T, Sawai CM, Pongubala JM, Skok JA, Aifantis I, Singh H: **Regulation of immunoglobulin light-chain recombination by the transcription factor IRF-4 and the attenuation of interleukin-7 signaling.** *Immunity* 2008, **28:**335-45.
22. Mandal M, Powers SE, Ochiai K, Georgopoulos K, Kee BL, Singh H, Clark MR: **Ras orchestrates exit from the cell cycle and light-chain recombination during early B cell development.** *Nat Immunol* 2009, **10:**1110-7.

    f1000 Factor 6.0 *Must Read*
    Evaluated by Pierre Ferrier 07 Oct 2009
23. Malin S, McManus S, Cobaleda C, Novatchkova M, Delogu A, Bouillet P, Strasser A, Busslinger M: **Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development.** *Nat Immunol* 2010, **11:**171-81.
24. Jhunjhunwala S, van Zelm MC, Peak MM, Cutchin S, Riblet R, van Dongen JJ, Grosveld FG, Knoch TA, Murre C: **The 3D structure of the immunoglobulin heavy-chain locus: implications for long-range genomic interactions.** *Cell* 2008, **133:**265-79.

    f1000 Factor 6.0 *Must Read*
    Evaluated by Patrick Matthias 29 Sep 2008
25. Parelho V, Hadjur S, Spivakov M, Leleu M, Sauer S, Gregson HC, Jarmuz A, Canzonetta C, Webster Z, Nesterova T, Cobb BS, Yokomori K, Dillon N, Aragon L, Fisher AG, Merkenschlager M: **Cohesins functionally associate with CTCF on mammalian chromosome arms.** *Cell* 2008, **132:**422-33.

    f1000 Factor 4.8 *Must Read*
    Evaluated by Albert La Spada 21 Feb 2008, Kenneth Zaret 13 May 2008

26. Degner SC, Wong TP, Jankevicius G, Feeney AJ: **Cutting edge: developmental stage-specific recruitment of cohesin to CTCF sites throughout immunoglobulin loci during B lymphocyte development.** *J Immunol* 2009, **182:**44-8.

f1000 Factor 3.3 *Recommended*
Evaluated by Amy Kenter 07 Apr 2009, Cornelis Murre 24 Apr 2009, Ranjan Sen 28 Apr 2009

27. Xu CR, Schaffer L, Head SR, Feeney AJ: **Reciprocal patterns of methylation of H3K36 and H3K27 on proximal vs. distal IgV_H genes are modulated by IL-7 and Pax5.** *Proc Natl Acad Sci U S A* 2008, **105:**8685-90.

28. Reddy KL, Zullo JM, Bertolino E, Singh H: **Transcriptional repression mediated by repositioning of genes to the nuclear lamina.** *Nature* 2008, **452:**243-7.

f1000 Factor 6.5 *Must Read*
Evaluated by Peter Scambler 13 Mar 2008, Lucio Comai 18 Mar 2008, Deborah Andrew 01 May 2008

29. Mostoslavsky R, Alt FW, Rajewsky K: **The lingering enigma of the allelic exclusion mechanism.** *Cell* 2004, **118:**539-44.

30. Cedar H, Bergman Y: **Choreography of Ig allelic exclusion.** *Curr Opin Immunol* 2008, **20:**308-17.

31. Schlimgen RJ, Reddy KL, Singh H, Krangel MS: **Initiation of allelic exclusion by stochastic interaction of Tcrb alleles with repressive nuclear compartments.** *Nat Immunol* 2008, **9:**802-9.

32. Amin RH, Cado D, Nolla H, Huang D, Shinton SA, Zhou Y, Hardy RR, Schlissel MS: **Biallelic, ubiquitous transcription from the distal germline Igk locus promoter during B cell development.** *Proc Natl Acad Sci U S A* 2009, **106:**522-7.

33. Taylor B, Cobb BS, Bruno L, Webster Z, Fisher AG, Merkenschlager M: **A reappraisal of evidence for probabilistic models of allelic exclusion.** *Proc Natl Acad Sci U S A* 2009, **106:**516-21.

34. Hewitt SL, Farmer D, Marszalek K, Cadera E, Liang HE, Xu Y, Schlissel MS, Skok JA: **Association between the *Igk* and *Igh* immunoglobulin loci mediated by the 3' *Igk* enhancer induces 'decontraction' of the *Igh* locus in pre-B cells.** *Nat Immunol* 2008, **9:**396-404.

35. Hewitt SL, Yin B, Ji Y, Chaumeil J, Marszalek K, Tenthorey J, Salvagiotto G, Steinel N, Ramsey LB, Ghysdael J, Farrar MA, Sleckman BP, Schatz DG, Busslinger M, Bassing CH, Skok JA: **RAG-1 and ATM coordinate monoallelic recombination and nuclear positioning of immunoglobulin loci.** *Nat Immunol* 2009, **10:**655-64.

36. Jackson AM, Krangel MS: **Turning T-cell receptor b recombination on and off: more questions than answers.** *Immunol Rev* 2006, **209:**129-41.

37. Yang-Iott KS, Carpenter AC, Rowh MA, Steinel N, Brady BL, Hochedlinger K, Jaenisch R, Bassing CH: **TCRbeta feedback signals inhibit the coupling of recombinationally accessible Vbeta14 segments with DJbeta complexes.** *J Immunol* 2010, **184:**1369-78.

38. Savic V, Yin B, Maas NL, Bredemeyer AL, Carpenter AC, Helmink BA, Yang-Iott KS, Sleckman BP, Bassing CH: **Formation of dynamic g-H2AX domains along broken DNA strands is distinctly regulated by ATM and MDC1 and dependent upon H2AX densities in chromatin.** *Mol Cell* 2009, **34:**298-310.

f1000 Factor 3.0 *Recommended*
Evaluated by Pierre Ferrier 17 Jun 2009

39. Yin B, Savic V, Bassing CH: **ATM prevents unattended DNA double strand breaks on site and in generations to come.** *Cancer Biol Ther* 2007, **6:**1837-9.

40. Callen E, Nussenzweig MC, Nussenzweig A: **Breaking down cell cycle checkpoints and DNA repair during antigen receptor gene assembly.** *Oncogene* 2007, **26:**7759-64.

41. Helmink BA, Bredemeyer AL, Lee BS, Huang CY, Sharma GG, Walker LM, Bednarski JJ, Lee WL, Pandita TK, Bassing CH, Sleckman BP: **MRN complex function in the repair of chromosomal Rag-mediated DNA double-strand breaks.** *J Exp Med* 2009, **206:**669-79.

f1000 Factor 3.0 *Recommended*
Evaluated by David Schatz 17 Mar 2009

42. Manis JP, Morales JC, Xia Z, Kutok JL, Alt FW, Carpenter PB: **53BP1 links DNA damage-response pathways to immunoglobulin heavy chain class-switch recombination.** *Nat Immunol* 2004, **5:**481-7.

43. Difilippantonio S, Gapud E, Wong N, Huang CY, Mahowald G, Chen HT, Kruhlak MJ, Callen E, Livak F, Nussenzweig MC, Sleckman BP, Nussenzweig A: **53BP1 facilitates long-range DNA end-joining during V(D)J recombination.** *Nature* 2008, **456:**529-33.

f1000 Factor 3.0 *Recommended*
Evaluated by Pierre Ferrier 30 Oct 2008

44. Agata Y, Tamaki N, Sakamoto S, Ikawa T, Masuda K, Kawamoto H, Murre C: **Regulation of T cell receptor b gene rearrangements and allelic exclusion by the helix-loop-helix protein, E47.** *Immunity* 2007, **27:**871-84.

45. Sepúlveda N, Boucontet L, Pereira P, Carneiro J: **Stochastic modeling of T cell receptor gamma gene rearrangement.** *J Theor Biol* 2005, **234:**153-65.