The Yin and Yang of RNA surveillance in B lymphocytes and antibody-secreting plasma cells

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INTRODUCTION

To ensure the fidelity of gene expression and prevent translation of truncated proteins, many cellular RNA surveillance pathways have been developed to distinguish between normal transcripts and those harboring premature termination codons (PTCs). RNA surveillance mechanisms

The random V(D)J recombination process ensures the diversity of the primary immunoglobulin (Ig) repertoire. In two thirds of cases, imprecise recombination between variable (V), diversity (D), and joining (J) segments induces a frameshift in the open reading frame that leads to the appearance of premature termination codons (PTCs). Thus, many B lineage cells harbour biallelic V(D)J-rearrangements of Ig heavy or light chain genes, with a productively-recombined allele encoding the functional Ig chain and a nonproductive allele potentially encoding truncated Ig polypeptides. Since the pattern of Ig gene expression is mostly biallelic, transcription initiated from nonproductive Ig alleles generates considerable amounts of primary transcripts with out-of-frame V(D)J junctions. How RNA surveillance pathways cooperate to control the noise from nonproductive Ig genes will be discussed in this review, focusing on the benefits of nonsense-mediated mRNA decay (NMD) activation during B-cell development and detrimental effects of nonsense-associated altered splicing (NAS) in terminally differentiated plasma cells. [BMB Reports 2019; 52(12): 671-678]

THE GENERATION OF ANTIBODY REPERTOIRE: A RISKY DIVERSITY

The error-prone V(D)J recombination process Ig genes are good candidates to study nonsense RNA surveillance because the generation of primary Ig repertoire in early B-cell development and the process of somatic hypermutations (SHM) in germinal center B cells frequently generate PTCs (1). The V(D)J recombination process of Ig genes takes place in the bone marrow and assembles the variable region from germline variable (V), diversity (D), and joining (J) gene segments. Control of V(D)J recombination
occurs at several levels, including cell-type specificity, intra- and inter-locus sequential rearrangements, and allelic exclusion (17). Although DNA rearrangements in the Ig heavy (IgH) and light (i.e., Igκ and Igλ) loci occur in a precise order, the selection of gene segments within each locus is random. It allows for combinatorial diversity. The mechanism used by lymphoid cells to successfully rearrange their antigen (Ag) receptor genes requires the use of recombinase enzymes RAG1 & RAG2 that are only active in lymphocytes (18, 19). Recombinases act at early stages of lymphoid cell development in order to bring two segments into close proximity, forming a loop of intervening DNA which can then be excised. The ends of these segments are annealed to form a newly rearranged DNA sequence. To increase diversity, joining of V, D, and J segments is imprecise with nucleotide deletions or insertions. Non-template (N) nucleotide additions are introduced by terminal deoxynucleotidyl transferase (TdT). Palindromic (P) insertions occur after asymmetric hairpin opening. Random N-additions cannot be attributed to any other genomic sequences. They rarely exceed a dozen nucleotides (20, 21). They are polymerized by TdT which is the third lymphoid-specific protein involved in V(D)J recombination besides RAG1 and RAG2 (22-25). P insertions rarely exceed two nucleotides and form a palindrome with respect to the sequence at the end of the coding strand (26-28). Although nucleotide deletions and insertions greatly enlarge the diversity of the Ig repertoire, only one third of all V(D)J junctions are in-frame, while the other two thirds are out-of-frame due to frameshift mutations that create PTCs.

Frequency of PTC-containing Ig genes in B-lineage cells

Clonal selection implies that each B cell clone expresses a unique receptor. Hence, one of the two inherited Ig alleles is functionally rearranged. This allelic exclusion associates asynchronous V(D)J recombination events at Ig loci with receptor-mediated inhibitory feedback control (29). At the pro-B cell stage, VDJ recombination is initiated by biallelic D to J rearrangements at IgH loci, followed by a monoallelic V to DJ recombination. A productive VDJ junction encodes the variable (V) region of the heavy chain that can associate with the surrogate light chain to form pre-BCR (pre-B cell receptor). Regulatory mechanisms mediated by pre-BCR signaling prevent further V to DJ rearrangements on the second IgH allele and initiates VJ recombinaton at Ig light chain loci lacking D segments. By contrast, when the VDJ junction on the first IgH allele is nonproductive, the lack of the pre-BCR inhibitory signal allows V to DJ recombination on the second allele. If this second attempt is successful, a pre-BCR-mediated proliferation wave will generate abundant B cell clones with biallelic VDJ rearrangements. Roughly half of mature B cells harbor biallelic VDJ-rearrangements with a nonproductively-recombined IgH allele (30-32). If another nonproductive VDJ junction occurs on the second IgH allele, cells are eliminated through apoptosis. As mentioned above, pre-BCR signaling stimulates recombination of Ig light chain genes. The presence of two Igκ and Igλ light chain isotypes permits multiple VJ recombination events. Again, the expression of a functional BCR precludes further recombination in immature B cells. In humans, ~50% of mature B cells express Igκ. However, in mice, recombination takes places preferentially at the Igκ locus and only 5% of B cells express Igλ isotypes (32). Hence, B cells harbor numerous nonproductive V(D)J-recombined Ig light chain alleles (Fig. 1).

After their exit from the bone marrow, alternative splicing of constant Cμ and Cδ exons ensures co-expression of IgM and IgD at the surface of naïve B cells (33). Upon antigen encounter, IgD expression is downregulated and activated B cells are subjected to a second wave of Ig gene diversification by SHM in germinal centers (GCs). Frequent nonsense mutations can arise during this affinity maturation process that requires transcription of the target region and enzymatic activity of B-cell-specific activation-induced deaminase AID (34). This process leads to the introduction of multiple nucleotide changes in the V exon (i.e., VDJ or VJ) and a few hundred base pairs in the downstream intron (35). Nucleotide insertions and deletions (indels) have also been observed (36, 37). SHM leads to the expression of a secondary repertoire from which B cells carrying a mutated BCR with improved Ag-binding affinity can be selected (38). We have previously observed that SHM occurs at similar levels on productive and nonproductive VDJ-rearranged IgH alleles (39). If a nonsense codon appears on the productive allele, the lack of Ag-binding activity provokes a rapid elimination of mutated B cell clones within GCs (40-42). The occurrence of SHM on nonproductive Ig alleles can introduce additional nonsense codons, modifying the PTC position within the V exon. Class switch recombination (CSR) also occurs in germinal centers. This second round of IgH intragenic rearrangements replaces the Cμ exons with a downstream constant gene (43). GC B cells can differentiate into memory cells or terminally differentiated PCs that secrete substantial amounts of antibody (44). The PC transcriptional program induces major changes including a transcriptional boost of Ig gene transcription and the activation of unfolded protein response (UPR) to ensure proper Ig folding (45). In PCs, the use of secreted polyadenylation signal (PAS) instead of downstream membrane PAS allows alternative IgH pre-mRNA processing to switch from membrane to secreted Ig isomers (46). Taken together, the vast majority of B-lineage cells harbor PTC+ Ig alleles in their genome with nonsense codons introduced in the V exon or in the adjacent constant exon during the V(D)J recombination process or SHM (Fig. 1).

Transcriptional control of PTC-containing Ig genes

The high frequency of PTC+ V(DJ)-rearranged Ig alleles in B-lineage cells needs additional mechanisms to downregulate these nonsense transcripts. A transcriptional silencing of PTC+ Ig genes has been proposed as a primary mechanism preventing their expression. This mechanism is called
Fig. 1. Abundance of nonproductive V(D)J rearrangements in B-lineage cells. (A) Schematic representation of productive and nonproductive V(D)J rearrangements during the generation of primary antibody repertoire. V(D)J recombination is initiated by a monoallelic V to DJ recombination at the IgH locus (biallelic D-J rearrangements are not depicted). If successful, then V to J recombination occurs at Ig light chain (IgL) loci. Successive IgL rearrangements are possible due to the fact that there are two Igκ and two Igλ alleles (not depicted). Pre-B cell receptor (pre-BCR) or BCR-mediated feedback signalling upon in-frame rearrangement of one IgH or IgL allele (i.e., VDJ+ or VJ+) prevents V(D)J recombination on the second allele (32). By contrast, a nonproductive V(D)J recombination on one Ig allele (i.e., VDJ- or VJ-) induces rearrangement on the second allele. The imprecise nature of V(D)J junctions generates ∼1/3 of productive and ∼2/3 of nonproductive V(D)J-rearranged alleles. Hence, most B-lineage cells harbour nonproductively-recombined Ig alleles in their genome (red parts in pie charts). If the two attempts on both Ig alleles are unsuccessful, the cell is programmed to die by apoptosis (dashed circles). (B) PTCs introduced during the error-prone V(D)J recombination process (red stars) or by somatic hypermutations (SHM; yellow stars) can activate different modes of NMD degradation. Frameshift V(D)J junctions can lead to the appearance of PTCs in the variable (V) exon or in the downstream adjacent constant exon. SHM can lead to the appearance of PTCs in the first leader exon (L1: L-part1) or in the V exon, with a greater abundance in the complement-determining regions (CDRs). For IgH mRNAs, PTC introduced by SHM or during V(D)J recombination can elicit exon junction complex (EJC)-dependent NMD. EJCs that remain bound to mRNAs after a pioneer round of translation are depicted (blue ovals). As good NMD candidates, PTC-containing IgH mRNAs are strongly degraded (up to 100-fold) (1, 9, 59). However, it has been demonstrated that some nonsense codons in the 5'-half of the VDJ exon could not elicit strong NMD degradation (73). Similarly, PTCs close to the initiation codon are NMD resistant in other models likely due to a critical interaction between PABPC1 with the translation initiation complex (74, 75). For nonproductive Igκ alleles, PTCs are located at the end of the V exon or within the last constant Cκ exon. Hence, these PTC-containing Igκ mRNAs could not elicit EJC-dependent NMD degradation, although they are likely to be targeted by a PTC-PABPC1 distance-dependent mode of NMD which induces a less efficient degradation (∼2-fold) (5).
"nonsense-mediated transcriptional gene silencing" (NMTGS). It involves chromatin remodelling and "heterochromatinization" of the PTC+ DNA sequence. NMTGS can be inhibited by the overexpression of exonuclease. However, the involvement of siRNA like molecules has not been elucidated yet (4). NMTGS is also impaired upon knock-down of the main NMD factor UPF1, suggesting a mechanistic link between NMD and NMTGS (47). Although NMTGS has been demonstrated in Hela cells transfected with minigenes constructs, the occurrence of such a quality control mechanism needs to be determined in B cells. Instead of active silencing, many studies including ours have shown a biallelic transcription pattern for productive and nonproductive Ig alleles in B cells (9, 39, 48-51). To study the transcription and RNA surveillance of PTC+ IgH alleles during B cell development, we introduced a nonsense V exon in the IgH locus to specifically mark each allele in heterozygous mutants. Consistent with previous observations in a pro-B cell line (52), productive and nonproductive IgH alleles exhibited equivalent transcription rates with similar RNAPII loading in LPS-stimulated B cells (9, 48). This also confirms our earlier study in germinal center B cells, demonstrating that the frequency of transcription-dependent SHM is similar for productive and nonproductive VDJ-recombined IgH alleles (39).

RNA SURVEILLANCE IN B-LINEAGE CELLS

The machinery of RNA surveillance is now known to include various pathways controlling the quality of pre-mRNA and mRNA to limit the translation of truncated proteins. The molecular mechanisms involved in the activation of RNA surveillance pathways have been extensively reviewed previously (13, 53, 54).

Accumulation of PTC-containing Ig pre-mRNAs

Despite their active transcription, PTC+ Ig genes can be controlled at pre-mRNA level. Previous studies (2, 6) performed in Milstein's lab have shown an accumulation of PTC+ Igc unspliced or splicing intermediate RNA precursors, supporting the idea that nonsense codons can be recognized in the nucleus by a mechanism independent of protein synthesis. In a simplified model of Igc transcripts containing only three exons, splicing intermediates can eliminate the first intron (IVS1) but retain the intervening sequence between VJ and C exons (IVS2). Upon transfection of B cell lines spanning the main developmental stages with PTC+ and PTC-free Igc minigenes, we have observed that the presence of PTC induces a ∼2-fold increase for each unspliced and splicing intermediate RNA precursors (5). Again, unspliced and partially spliced Igc RNAs were mainly confined in the nucleus (5). The accumulation of PTC+ precursors was not affected by protein synthesis inhibition (5). In agreement with these data, RNA-FISH experiments performed in Sp6-derived hybridoma cells further demonstrated that PTC+ Igc pre-mRNAs could accumulate near the site of transcription (55). Recent findings obtained in Drosophila have indicated that UPF1 can bind to nascent RNAs at RNAPII transcription sites to facilitate nuclear processes of gene expression (56). It has been demonstrated that UPF1 is needed for the release of poly(A) mRNAs from chromosomal transcription sites and for their export from the nucleus. It is tempting to speculate that these new nuclear scanning functions of UPF1 could be involved in the nuclear accumulation of nonproductive Ig RNA precursors or in NAS (see below). Interestingly, fluctuations in the steady state level of PTC+ IgH pre-mRNAs occurs during B cell development, with low accumulation in PCs compared to resting B cells (9). These observations indicate that a high level of transcription precludes splicing inhibition and accumulation of PTC+ Ig pre-mRNAs. Thus, efficient processing of PTC+ Ig transcripts in PCs needs additional RNA quality control to prevent the synthesis of truncated Ig polypeptides.

NMD of PTC-containing Ig mRNAs

NMD is tightly coupled to transcription. The molecular mechanisms of the two prevailing exon-junction complex (EJC-dependent and Poly(A) Binding Protein Cytoplasmic 1 (PTC-PABPC1) distance-dependent NMD activation models have been extensively characterized in the past decades (1, 13, 53, 54, 57, 58).

According to the "50-55 nucleotides rule" for EJC-dependent NMD activation, the presence of a PTC more than 50-55 nucleotides upstream of the 3′ UTR can trigger efficient mRNA degradation by NMD. This mode of NMD activation is elicited to downregulate the level of nonproductively-rearranged IgH mRNA that contains PTCs in the V or in the first constant exon (CH1) and several constant exons downstream. Up to 100-fold accelerated degradation of these NMD candidates has been documented in B cell lines (59-61). Consistent with a previous study using TCRβ as gene models (62), we found that the extent of NMD was closely correlated to the splicing rate during B-cell development, with ∼2 to 20-fold degradation of PTC+ IgH mRNAs in resting and LPS-stimulated B cells, respectively (9). Interestingly, levels of nonproductive IgH mRNAs remained constantly low in those B cell populations, suggesting compensatory effects between nonsense-mediated splicing inhibition and NMD. Hence, qualitative changes in the RNA surveillance machinery occur during B-cell development. The cooperation between RNA surveillance mechanisms controls the amount of PTC+ IgH mRNAs.

For Igc alleles, the situation is completely different because a frameshift at the VJ junction leads to the appearance of a PTC within the last Cc exon, or less frequently at 3 nucleotides upstream from the last exon-exon junction (50). Thus, the position of PTC on nonproductive Igc mRNAs does not meet the requirements for EJC-dependent NMD. Instead, it belongs to the PTC-PABPC1 distance-dependent NMD activation model. The latter pathway occurs when the 3′UTR of an
mRNA is abnormally long, as in the case of the presence of a PTC (53). NMD is activated when the 3'UTR structure precludes the normal interaction of PABPC1 with release factors (eRF1 and eRF3) involved in translation termination. The spatial rearrangement of 3'UTR controlling the proximity of the termination codon and the poly(A) tail is a critical determinant for NMD (63). Although UPF1 was previously assumed to be the essential player involved in the interaction with release factors (eRFs), in vitro translation termination assays recently performed by Neu-Yilik et al. (64, 65) indicate that UPF3B (also named UPF3X) directly interacted with both RNA and eRF3. This NMD mechanism is most likely to be involved in the uptake of nonproductive Ig mRNAs, inducing a modest (~2-fold) NMD degradation in mouse B cells (Fig. 1) (5).

NAS of PTC-containing Ig transcripts and production of deleterious truncated Ig polypeptides in plasma cells

Mutations within the sequence of exonic splicing enhancers (ESEs) and the presence of a PTC have been shown to elicit alternative splicing called class-I and class-II NAS, respectively (8, 11-13, 66, 67). As an additional RNA surveillance pathway, class-II NAS (hereafter called NAS) can prevent the maturation of full-length PTC-containing mRNAs by promoting alternative splicing to skip the offending PTCs. However, NAS can yield internally deleted mRNAs and proteins. Hence, it exhibits opposite effects compared to NMD with regard to the production of truncated proteins. Although NMD and NAS use the common factor UPF1, these processes are mechanistically different. Knockdown of several key NMD factors including UPF2, UPF3A, UPF3B, and SMG1 showed no significant effect on NAS (13). The intrinsic mechanisms responsible for the activation of NAS remain elusive. Conflicting results have been obtained with regard to the sensitivity of NAS to translation inhibition or frameshift mutations (5, 13). Future breakthroughs would indicate whether NAS, nonsense-mediated SOS, or splicing inhibition could be induced as a response to PTC recognition during translation, after nuclear degradation of spliced PTC-containing mRNAs, or by other nuclear-scanning mechanisms.

To study NAS of Ig transcripts, we transfected several B-cell lines with minigenes harboring frameshift mutations at the VJ junction that could lead to the appearance of PTCs at the end of the V exon (VPTC), or within the last C exon (CPTC) (5, 16). Consistent with a reading frame-dependent NAS activation, the presence of VPTC, but not of CPTC, strongly induced skipping of the V exon. We also confirmed that V exon skipping occurred in mouse B cells during splicing of both nonproductive Igk and IgH transcripts (5, 16, 48). Interestingly, we found that skipping of the PTC-containing V exon was greatly increased in PCs compared to B cells. This was correlated with a transcriptional boost of Ig genes during PC differentiation (48). Thus, a fast RNAPII elongation rate can enhance the skipping of PTC-containing V exons in PCs, whereas a slow elongation
rate authorizes their splicing as full-length mRNAs in B cells (or splicing inhibition as mentioned before). These observations are in agreement with the known influence of RNAPII elongation rate on alternative splicing (68), suggesting that PTC-independent and PTC-dependent exon skipping events can be governed by some similar rules.

Until recently, consequences of NAS with regard to the production of truncated Ig chains have been overlooked. Interestingly, we have observed that exon skipping of V\textsuperscript{\mu}Tκ Ig pre-mRNAs encodes V domain-less κ light chains (Δκ-lightCs) that can induce the death of PCs through endoplasmic reticulum (ER) stress-associated apoptosis (16). Revealing a new PC checkpoint referred to as Truncated Immunoglobulin Exclusion (TIE)-checkpoint, the production of Δκ-lightCs can dampen PC differentiation by eliminating cells expressing nonproductively-rearranged V\textsuperscript{\mu}Tκ-Igκ alleles (Fig. 2). In addition, conditional expression of Δκ-lightCs mRNAs in ‘inducible-TIE’ (iTIE) knock-in mice reproduced physiological TIE checkpoint and affected the survival of long-lived PCs and antibody production (16). Thus, the transcription of nonproductive Ig alleles is not as safe as previously assumed and the activation of NAS can drive the elimination of PC clones harbouring biallelic Igκ rearrangements. Remarkably, the TIE-checkpoint can reduce the magnitude of humoral responses and shape the antibody repertoire independently of classical constraints related to Ag specificity.

Closing remarks

Aberrantly rearranged Ig alleles are abundant in B-lineage cells. The cooperative action of nonsense-mediated splicing inhibition (or SOS) and NMD limits the amount of deleterious truncated Igκ polypeptides. However, activation of the NAS pathway exerts opposite effects with exon skipping-mediated production of V domain-less κ light chains. PCs with biallelic Igκ rearrangements, transcriptional boost of Ig genes can sustain massive Ig synthesis. However, it also promotes NAS activation and exon skipping during splicing of nonproductive transcripts. Because the survival of normal and malignant PCs is tightly controlled by ER stress and proteasome activity (69), high amounts of truncated Igκ can provoke PC death as a consequence of a deregulated proteostasis. According to an efficient TIE-checkpoint, alternatively spliced mRNAs encoding structurally abnormal Ig chains are hardly detectable in non-malignant PCs, although they can be observed in some lymphoproliferative disorders, including Multiple Myeloma and Burkitt lymphoma (70-72). Previous findings have indicated that the activation of the TIE checkpoint can eliminate ~20-25% of PCs, i.e., those expressing nonproductive V\textsuperscript{\mu}Tκ-Igκ alleles (16). If a similar disappearance of PC harboring nonproductive VDJ rearrangements is observed for the IgH repertoire, it could indicate a broad TIE-checkpoint blunting the terminal differentiation of many PCs with biallelic IgH and/or IgL rearrangements. Altogether, this should have major consequences in our classical mindset usually considering nonproductively V(D)J-rearranged Ig alleles as passengers rather than drivers.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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