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Adaptive Genetic Changes by Design: A Look at the DNA Editing by Activation-induced Cytidine Deaminase (AID)

Jean Lightner*

Abstract

According to evolutionary thinking, adaptive genetic changes are the result of random (non-purposeful) mutations and natural selection. While creationists do not need to account for the assumed changes that turn microbes into people, our model certainly points to a considerable amount of adaptive change that has occurred within created kinds. The naturalistic mechanisms proposed by evolutionists appear woefully inadequate to account for these.

A look at the immune system reveals several different enzymes that are used to edit DNA; one of them is activation-induced cytidine deaminase (AID). AID is involved in gene conversion, somatic hypermutation, and class-switch recombination in B lymphocytes. While each of these begins with AID converting a cytosine residue to a uracil residue, the different outcomes are a function of different proteins being recruited to process the lesion. Since the activity of AID could be disastrous if not kept in its proper place, it is well regulated and tightly controlled at many levels.

The well-designed DNA editing function of AID and other proteins in the immune system give reason to believe that adaptive alleles in various populations have similarly arisen by the providence of God, the Great Designer, and not by the naturalistic mechanisms proposed by evolutionists.

Introduction

According to popular evolutionary thinking, often referred to as neo-Darwinism or the modern evolutionary synthesis, the source of variation upon which natural selection supposedly acts arises from mutation. While the term "mutation" has changed over the last hundred years or so, it now generally refers to a change in the DNA sequence, primarily caused by unrepaired errors during replication (Mayr, 2001, pp. 96–98, 279–280). It is insisted that there is no teleology involved; that is, there is no design or purpose underlying mutations (Mayr, 2001, pp. 119–120, 275). They are believed to arise by chance and be random with respect to the needs of the organism (Huxley, 2010, p. 54). Natural selection is the mechanism given credit for rare adaptive genetic changes becoming fixed in various populations of organisms

* Jean Lightner, D.V.M., jklightner@gmail.com
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(Rensch, 1980, pp. 296–298; Mayr, 2001, 119–120).

Creationists approach the scientific evidence from a different vantage point. We reject the assumption of universal common ancestry, and instead recognize that creatures were created as various kinds (Genesis 1:11–12, 21, 24–25). Humans were created separately from all other animals (Genesis 1:26–28; 2:7, 19–24). In the process of analyzing biological data within a biblical framework, many have questioned two additional assumptions of neo-Darwinism: that mutations are always random errors without purpose, and that natural selection can really explain the almost magical transformations and adaptations in populations that evolutionists claim (Purdom and Anderson, 2009; Terborg, 2008; Lightner, 2015).

There is strong evidence that adaptive genetic changes do occur. The biblical history describing the global Flood makes it clear that limited genetic variability was present immediately after that event. This is especially true of unclean land animals, where only two individuals survived the Flood on the ark, but even clean animals and birds on the ark had a drastically reduced population. Certainly, much more genetic and phenotypic variability is present today compared to the time of the Flood (Lightner, 2006, 2009a; Wayne and vonHoldt, 2012). In some groups, such as birds, there is astounding diversity that has arisen within created kinds (Lightner, 2010b). Particularly impressive are the adaptive radiations of birds inhabiting islands, such as the radiations of the vangas of Madagascar, the honeycreepers in Hawaii, and the finches in the Galápagos (Reddy et al., 2012; Jønsson et al., 2012; Lerner et al., 2011; Lamichhaney et al., 2015).

A recent creationist review of high altitude adaptation shows that adaptation is a complex, multilevel process that ranges from short-term physiological adjustments in the individual to new adaptive alleles in populations (Lightner, 2014). Creationists have proposed various mechanisms for genomic change beyond the well-known shuffling that occurs during homologous recombination (i.e., crossing over and gene conversion in meiosis). Considerable attention has been given to transposable elements (Wood, 2002; Terborg 2009a, 2009b; Shan, 2009). Many transposable elements contain the genetic instructions for their own movement, and certain conditions seem to activate their movement (e.g., stress, hybridization). They can change the sequence of a gene, alter the regulation of one or more genes, and/or be involved in chromosomal rearrangements (Belyayev, 2014).

While transposable elements certainly appear to play a role, many detailed studies of genetic differences underlying phenotypic diversity have yielded few examples of where transposable elements appear to be involved in the genetic mutations that were identified (Lightner 2008, 2009b, 2010a). Therefore, within the creation model, a reasonable prediction is that other mechanisms are involved in many of these DNA changes. It has been pointed out that DNA changes in B cells are a normal part of mounting an antibody response and that all the necessary biological information required to induce appropriate variation is coded in the genome (Terborg, 2009a). Therefore, DNA editing enzymes involved in the immune system are worth considering in more detail, and recent reviews highlight advances in our understanding of the underlying mechanisms involved in the essential functions they perform (Zan and Casali, 2013; Kumar et al., 2014; Matthews et al., 2014; Moris et al., 2014; Chandra et al., 2015).

DNA Editing and the Immune System

Two enzymes known to be involved in DNA editing within the immune system are APOBEC3 (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3) and activation induced cytidine deaminase (AID). They belong to the AID/APOBEC family of DNA and RNA editing enzymes, which have important roles in a variety of important functions (Moris et al., 2014). This family is unique in possessing the ability to deaminate cytidine (C; the cytosine residue in RNA) or deoxycytidine (dC; in DNA) to uridine (U) or deoxyuridine (dU) (Figure 1). In many species, APOBEC3 varies in copy number and is polymorphic; it restricts the replication of many exogenous viruses and endogenous transposable elements (Harris and Dudley, 2015). At least some of this activity is based on its DNA editing ability, which essentially mutates the viral genome, destroying its ability to replicate.

While the best-known roles of APOBEC3 involve innate immunity, AID plays critical roles in various steps of adaptive immunity. Adaptive immunity involves an ingenious design that enables creatures to adapt to the challenges in their environment. Organisms are constantly exposed to a myriad of

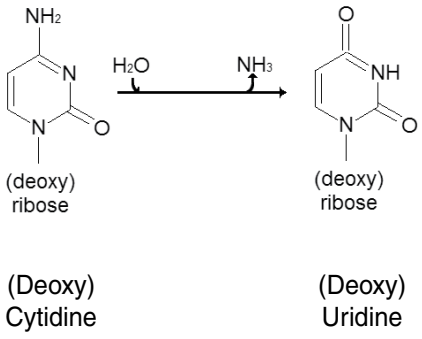

Figure 1. Activation-induced cytidine deaminase (AID) deaminates the cytosine residue deoxycytidine (dC) to deoxyuridine (dU) in DNA to enable adaptive immune responses. Other members of the AID/APOBEC family also catalyze this reaction in DNA or RNA for other purposes.

potentially harmful microorganisms, parasites, and toxins. They need to be able to identify them and properly dispose of them as necessary. Rather than being front-loaded with the exact code for every antibody to every possible antigen that could be encountered, the adaptive immune system is strategically designed to manufacture highly specific antibodies that can be used in several different contexts to effectively deal with potential pathogens.

The portion of the genome used for antibody (immunoglobulin, Ig) formation already contains some variability in many species. For example, in humans and mice, there are a number of different variable (V), joining (J), and diversity (D) regions coded on the DNA. Through V(D)J recombination, the recombination activating gene enzymes (RAG1 and RAG2) initiate double-stranded breaks in the DNA that are repaired to bring a single V, D, and J segment in apposition with each other (Jung et al., 2006). Other steps in Ig formation that involve DNA sequence modification are gene conversion, somatic hypermutation (SHM), and class-switch recombination (CSR). Each of these three steps uses AID to initiate the genomic changes (Arakawa et al., 2004; Matthews et al., 2014).

Gene conversion in lymphocytes was first described in the chicken, which has only one V region for both the light and heavy chain loci involved in Ig formation. However, it was found that there were numerous pseudogene V regions upstream that provide templates for intrachromosomal gene conversion, copying nucleotide tracts from the pseudogenes onto the V region to increase Ig diversity. In the rabbit, lymphocytes also undergo gene conversion to increase variability; however, some of the upstream sequences are potentially functional. Interestingly, in both species, this process can be used to diversify the primary antibody repertoire, or further increase diversity in an antigen-specific immune response (Lanning and Knight, 2015).

Somatic hypermutation (SHM) involves the rapid introduction of mutations, primarily single nucleotide changes, into the complementarity determining regions (CDRs) of the recombined V region. The CDRs code for the portion of the Ig molecule that contacts the antigen. SHM is best known for its role in an antigen-specific immune response, and there is a designed mechanism providing for the selection of B cells expressing Ig with the greatest affinity to the antigen. SHM enables the body to rapidly produce highly effective Ig to any conceivable antigen that is encountered from the more limited diversity of the primary antibody repertoire (Matthews et al., 2014).

Once an effective antibody has been produced, there is a need to use it in several different contexts to effectively deal with an infection. That is the purpose of class switch recombination (CSR); it is said to change the effector functions. To switch the class of Ig produced, a DNA segment needs to be excised to place the V(D)J region before an exon coding for a different constant (C) region (Figure 2). There are switch (S) regions containing repetitive DNA that precede most of the C regions, and these S regions are targeted by AID to induce several double-stranded breaks so the intervening region can be removed (Matthews et al., 2014).

AID: Gene Structure and Regulation

In humans, the enzyme AID is encoded by the *AICDA* gene on chromosome 12. The gene spans 11 kb, consists of 5 exons, and is primarily expressed in B cells. However, in mice it has also been detected in oocytes, embryonic germ cells, and embryonic stem cells; additionally, it has been detected in normal human spermatocytes. Occasionally, AID has been associated with pathology, as it has sometimes been detected in cells affected by chronic inflammation or cancer (though generally not testicular cancer). Since off-site activity of this DNA editing molecule can be disastrous, its expression is tightly controlled on multiple levels (Barreto and Magor, 2011).

In addition to a promotor region known to bind four different transcription factors, several other regions are involved in controlling transcription of the gene. Intron 1 contains an enhancer/silencer region, where two transcription factors bind to repress the gene, and two different transcription factors bind to de-repress it. A third downstream region binds a transcription factor to maintain physiologic levels of AID expression. A fourth enhancer region is located upstream of the promotor. Recently, three more enhancers were identified further (up to 50 kb) from the *aicda* locus in mice (on chromosome 6; Chandra et al., 2015; Kumar et al., 2014).

Once the gene is transcribed, stability of the mRNA is affected by two different microRNA (miRNA) molecules. These miRNAs bind to the 3' UTR, the untranslated region following the portion of mRNA specifying the amino acid sequence. One miRNA is down-regulated during B cell activation, while the other is up-regulated. It is not surprising, therefore, that experimentally induced mutation of the 3' UTR of the AID mRNA resulted in spatiotemporal dysregulation of AID and off-site mutations (Chandra et al., 2015; Kumar et al., 2014).

Enzyme Structure

The enzyme is 198 amino acids long in humans and consists of a number of functional domains, some of which overlap (pleiotropy) and a few of which are not well characterized. Like other cytidine deaminases, the catalytic region of AID (amino acid positions 56–90) includes two cysteines and a histidine that

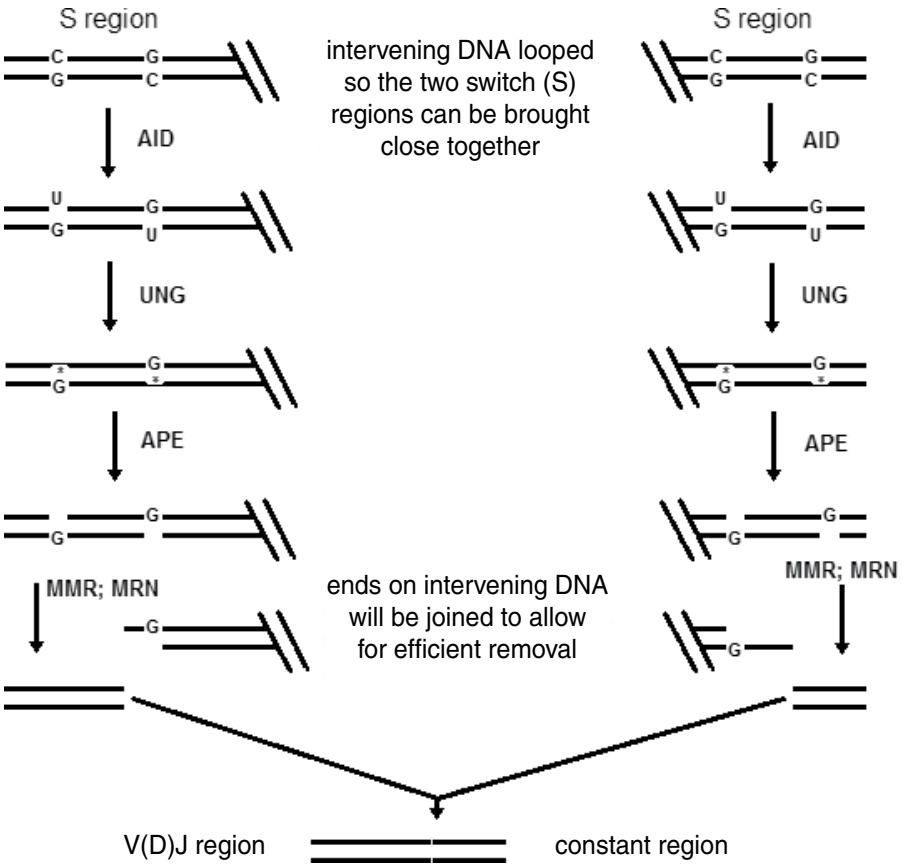

Figure 2. In class switch recombination (CSR), a segment of DNA must be removed to place the V(D)J region next to a different constant region. Activation-induced cytidine deaminase (AID) deaminates cytosine residues to uracil residues in the two switch (S) regions flanking the segment to be removed. The base excision repair enzyme uracil DNA glycosylase (UNG) removes the abnormal base leaving an abasic site. Apurinic/apyrimidinic endonuclease (APE) nicks the DNA at the abasic site. These single-stranded breaks can be converted to staggered double-stranded breaks. Mismatch repair (MMR) enzymes and the MRN complex (Mre11/Rad50/Nbs1) process the staggered ends so the V(D)J region can be joined to the constant region. The intervening DNA is circularized and removed.

coordinate a zinc ion to form the active site. Further downstream (113–123), though adjacent in the folded protein, is a critical hotspot recognition loop. This loop specifically targets a weak (W = A/T) nucleotide followed by a purine (R = A/G) in the 2' and 1' positions relative to the dC to be directed into the active site (Barreto and Magor, 2011; Nabel et al., 2014).

Interestingly, AID's preference for a DNA substrate appears to be related to the nucleotide's rotational conformation, sometimes known as sugar pucker. While AID targets a WRC motif (Figure 3), APOBEC3G (A3G) favors CCC. Experimental grafting of the recognition loop from one to the other will change the sequence specificity. When the AID loop was grafted into an A3G background, the chimeric enzyme was still efficacious in restricting effective HIV infection despite the difference in targeted sequence. In contrast, when the recognition loop of AID was changed, it adversely affected both SHM and CSR. Both the CDRs targeted in SHM and the S regions targeted in CSR are enriched with the WRC motif. This is accomplished within the CDRs by a preferential use of codons for serine (Ser), for example, that result in WRC hotspots, while in neighboring regions codons are preferentially used that do not create hotspots (Nabel et al., 2014; Kohli et al., 2010).

Among the other domains in the AID enzyme are a region required specifically for CSR (positions 190–198), another required for SHM (13–23), and a nuclear export signal (NES, 183–198). The latter plays an important role in maintaining AID in the cytoplasm, thus preventing it from damaging DNA when it has not been specifically recruited to provide an appropriate function (Barreto and Magor, 2011; Zan and Casali, 2013).

Keeping AID Where It Belongs

The hydrophilic residues in the NES (C terminal) portion of AID are essential for its active exclusion from the nucleus. It is retained in the cytoplasm, where it is complexed with other molecules to stabilize it until it is actively imported to the nucleus to perform its required function. It appears that there is a ubiquitin-dependent and independent pathway by which nuclear AID can be targeted for degradation (Barreto and Magor, 2011; Zan and Casali, 2013; Chandra et al., 2015). Phosphorylation of AID Ser3 is one factor that contributes to its degradation. Additionally, AID abundance in the nucleus is positively correlated with its catalytic activity (Matthews et al., 2014; Le and Maizels, 2015).

Somatic mutations in B cells are initiated during the G1 phase of the cell cycle. This is the growth phase that occurs prior to DNA replication (S phase), which precedes mitosis. When AID is experimentally sustained in the nucleus during the S phase, cell viability

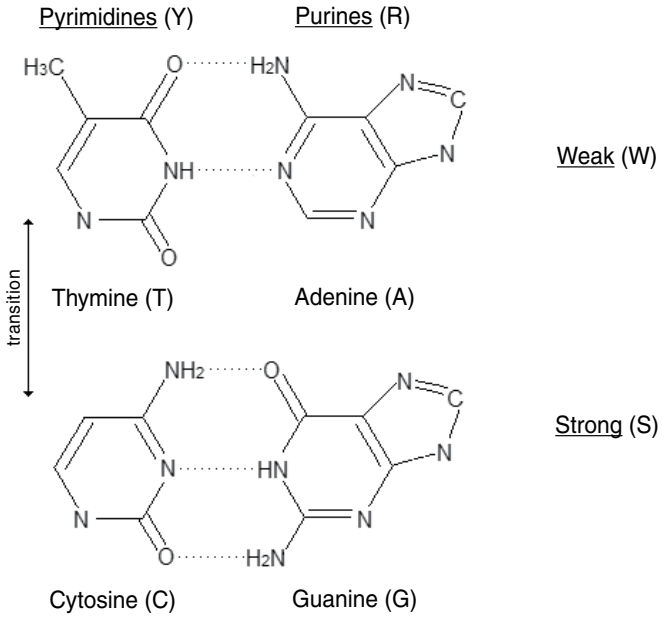

Figure 3. Nucleotides are classified as pyrimidines (Y) or purines (R) based on their ring structure. A mutation from one Y to another Y, or one R to another R is a transition; the ring structure stays the same. Mutations that result in a nucleotide with a different ring structure are called transversions. Nucleotides can also be classified as weak (W) or strong (S) based on the number of hydrogen bonds (2 or 3) in pairing. AID prefers the motif WRC (T or A; A or G; C)

is compromised; this explains why AID is normally rapidly degraded in the nucleus outside the G1 phase. It has been suggested that the nick left after the cellular machinery removes the foreign base, dU, may lead to double-stranded breaks if not repaired before replication. If so, this may account for the AID-dependent translocations characteristic of B-cell lymphomas where AID expression is no longer normally controlled (Le and Maizels, 2015).

Phosphorylation of AID Ser38 is necessary for somatic hypermutation (SHM) and class switch recombination (CSR), apparently to enable interaction with other molecules essential to these processes. In SHM, pS38-AID interacts with the single-stranded DNA (ssDNA) binding replication protein A (RPA), which stabilizes the ssDNA substrate that is the target of AID activity. In CSR pS38-AID recruits RPA and has been shown to interact with apurinic/apyrimidinic endonuclease (APE), which is required for making the breaks in the DNA. Interestingly, double-stranded breaks promote AID Ser38 phosphorylation, suggesting a positive feedback loop amplifies activity in S regions (Kumar et al., 2014; Matthews et al., 2014).

AID recruitment is transcription dependent. The transcripts through the V region (in SHM) or S region (CSR) are not translated, but in at least the latter case they are spliced. Deletion of a splice donor site was shown to interfere with CSR, suggesting that the transcripts might perform a regulatory function in some cases. During transcription, RNA polymerase II (Pol II) is stalled, and a factor involved in Pol II elongation and stalling, Spt5, has been shown to recruit AID. Additional adapter proteins have been found to recruit AID through their interaction with the abundant AGCT repeats (AGC being a subset of WRC) in the S region. Several other factors have been shown to be involved in recruiting AID as well. In fact, it has been commented that a surprisingly high number of cofactors are implicated despite the small size of the AID molecule, reflecting its tight regulation (Zan and Casali, 2013; Matthews et al., 2014; Chandra et al., 2015).

It is not difficult to understand how transcription allows AID access to the non-template strand; however, AID accesses both strands, which allows for the deaminated residues to be converted into double-stranded breaks for CSR. The RNA exosome complex has been shown to associate with AID and accumulate on S regions in an AID-dependent manner. This macromolecular complex removes and/or degrades nascent RNA on the template strand at stalled Pol II sites, exposing ssDNA for AID to access (Matthews et al., 2014; Chandra et al., 2015).

Epigenetic factors are also associated with AID recruitment. Methylated dCs make poor substrates for AID, and various histone modifications have been identified as playing a role in AID recruitment. A recent study evaluating patterns in both normal and off-site AID targeting found that regions enriched with chromatin modification typical of active enhancers, such as histone H3 acetylated at lysine 27 (H3K27Ac), as well as modifications typical of active transcription, such as trimethyl histone H3 lysine 36 (H3K36me3), mediate AID recruitment. Several transcription-factor binding sites are implicated in recruiting AID. Most AID targets are grouped within super-enhancers and regulatory clusters (Zan and Casali, 2013; Matthews et al., 2014; Chandra et al., 2015).

Diversity in Outcome via Different Repair Mechanisms

Despite the fact that gene conversion, SHM, and CSR in B cells all require

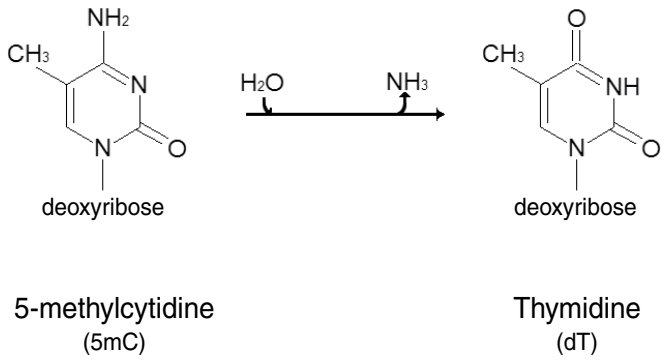

Figure 4. A methyl group (CH_3) can be added to deoxycytidine (dC; the cytosine residue in DNA) as an epigenetic tag to help regulate gene expression. At times the methyl group needs to be removed, and AID is sometimes involved. AID deaminates 5-methylcytidine (5mC) to thymidine (dT). This creates a T:G mismatch, which is subsequently repaired back to C:G, leaving an unmethylated cytosine residue

AID to initiate the process, the outcomes are very different. This is the result of recruiting a different array of proteins to process the dU lesion that AID creates.

In SHM, according to the current model, there are three possible pathways to repair the AID induced dU:dG mismatches. Replication prior to interaction with other repair enzymes results in transition mutations (CG → TA). Alternatively, removal of dU by the base excision repair (BER) enzyme uracil DNA glycosylase (UNG) prior to replication results in an abasic site. Subsequent repair during replication by error-prone DNA polymerases can lead to transition or transversion mutations. Otherwise, dU:dG mismatches can be processed by mismatch repair proteins, followed by filling in the gap with an error-prone polymerase, resulting in mutations at neighboring A:T residues and/or short indels (Matthews et al., 2014; Kumar et al., 2014).

It is important to recognize that error-prone polymerases are an essential part of the arsenal of polymerases used by cells to maintain genomic stability. They are specifically recruited to sites of DNA damage that the high processivity, high fidelity (i.e., fast, and accurate) polymerases cannot handle. In many (but not all) cases they accurately repair the lesions, though in the case of the immune system, they are recruited to induce changes (Saugar, et al., 2014; Yang, 2014).

According to the current model for CSR, dU introduced by AID is removed by the BER enzyme UNG (Figure 2). The abasic site is then converted to a ssDNA break by APE. A similar nick nearby on the opposite strand results in a staggered, double-stranded break. It has also been found that components of the mismatch repair pathway can act on dU:dG mismatches to form double-stranded breaks. These breaks are then repaired by nonhomologous end joining (Matthews et al., 2014; Kumar et al., 2014).

Theoretically, there are several ways the loose ends can be rejoined during CSR. For example, the intervening segment between the two S regions containing double-stranded breaks could be inverted, which would not result in a functional antibody. However, it appears there are certain features of the S region and AID designed to facilitate proper joining of the segments. The majority of the time the intervening segment is circularized, and the V(D)J region is correctly attached to the new C region (Dong et al., 2015).

Other Roles of AID

In addition to its roles in DNA sequence diversification in the immunoglobulin genes of B cells, AID appears to have other important functions. Methylation is a common epigenetic tag that helps define gene expression patterns essential to life. AID had been shown to deaminate 5-methylcytosine (5mC) to thymidine (dT), though the efficiency of this reaction is at least an order of magnitude lower than its normal substrate (Figure 4). When this reaction takes place, it results in a T:G mismatch that can be processed by glycosylases and downstream BER enzymes to restore an unmethylated C. Currently, there are conflicting conclusions on the relevance of this reaction in vivo based on studies. One recent summary suggests that there is no strong evidence for AID in genome-wide demethylation, but it appears to play a role in gene-specific demethylation that underlies cell differentiation (Ramiro and Berreto, 2015).

AID is also important in B-cell tolerance, and lack of the enzyme is associated with autoimmune disease. This is a rather paradoxical phenomenon, where humans lacking AID not only suffer from infections because they cannot mount a normal antibody response but also suffer autoimmune disease due to the inability to remove autoreactive B cells. In this role AID is expressed in immature B cells along with RAG2, though many details of how they eliminate autoreactive B clones remain to be elucidated (Cantaert et al., 2015).

Obviously, although AID has numerous crucial functions, loss of control over AID or the associated DNA repair

pathways can have disastrous results. Hypomethylation, point mutations, indels, and structural rearrangements are all features that are associated with cancer. Off-site activity of AID appears to be one factor that can contribute to carcinogenesis in certain malignancies such as lymphoma (Dominguez and Shaknovich, 2014; Pettersen et al., 2014).

Interestingly, in addition to mutations driving oncogenesis, cancer cells carry many thousands of passenger mutations not directly related to disease progression. With the increased availability of rapid-sequencing technologies, scientists have examined the patterns of mutations in a variety of cancer types to understand the factors involved. Different processes leave a different "mutational signature" depending on the exogenous or endogenous DNA damaging agents, as well as the repair or replicative pathways that follow (Helleday et al., 2014). Perhaps there are other places where endogenous enzymes are playing an important functional role as they alter the DNA sequence. If so, these signatures identified in cancer studies could help identify those places. It may be that the presence of AID in oocytes, spermatocytes, and embryonic cells is related to the induction of adaptive germ-line mutations.

AID: A Role in Adaptation?

Detection of AID in primordial germ cells, embryonic stem cells, and several other cell types was the impetus for investigating a possible role of AID in demethylation (Matthews et al., 2014). While AID does appear to sometimes play a role in demethylation, it could play another role in these cells. It has been suggested that it plays a role in meiotic recombination. SPO11 is an important enzyme that initiates double-stranded breaks during meiotic recombination. In some assays, AID appears to partially rescue SPO11 deficiency (Barreto and Magor, 2011). However, no statistical difference was noted in the average recombination events between normal and AID null mice (Cortesao et al., 2013). A third possibility that has been suggested is that AID may still play an APOBEC3-like role in controlling transposable element movement in some species (Barreto and Magor, 2011).

Another possibility exists: AID may be purposefully recruited to germ cells for DNA editing. In other words, enzymes such as AID and/or mutagenic repair pathways may be involved in the purposeful formation of adaptive alleles. It has already been noted that homologous recombination (crossing over and gene conversion) is mutagenic and that this is associated with adaptive mutations in bacteria. Error-prone TLS polymerases and/or error-prone repair pathways have been shown to play a role (Malkova and Haber, 2012). Given the purposeful nature of mutations induced by these mechanisms in adaptive immunity, it is quite plausible that genetic adaptation has a similar underlying basis.

If many germ-line mutations are purposeful, then it is expected that various factors will eventually be identified that govern the targeting of sites for mutagenesis and recruiting of appropriate proteins. Physiologic adaptation is characterized by changes in gene expression, which is mediated by epigenetic changes. Adaptive alleles often arise in the same genes as those targeted in physiologic adaptation (Lightner, 2014). Since transcription and associated epigenetic changes are important in recruiting AID, it may be that these factors play a role in targeting various regions of the genome for adaptive genetic changes.

Further, there may be purposeful mechanisms to increase the frequency of adaptive alleles in the population. Meiotic drive refers to any process that distorts Mendelian inheritance by preferentially transmitting one haplotype (or allele) over another when gametes are formed by meiosis. Biased gene conversion is one example; it can result from the break being preferentially induced on one strand of DNA over the other. Other downstream factors, such as the factors recruited to repair the break, can be involved as well. In some cases, this biased transmission is associated with, and perhaps influenced by, single nucleotide polymorphisms (SNPs; Odenthal-Hesse et al., 2014).

The existence of meiotic drive has significant implications for the evolutionary assumption that natural selection is a major player in adaptation. It has long been known, based on mathematical models that natural selection cannot account for diversity in vertebrates, even in an evolutionary time frame (Haldane, 1922; Kimura, 1968). Further, mathematical modeling suggests that genetic drift eliminates the majority of rare beneficial alleles. Finally, the phenotypically based prospective study of natural selection in Galapagos finches showed natural selection acted only at discrete times of harsh environmental conditions and was not consistent in direction (Lightner, 2015).

Despite this, there have been many genetic studies that have relied on statistical tests that suggest that natural selection has occurred, even within groups that creationists would say belong to the same kind. Yet these tests usually assume Mendelian inheritance, and the existence of meiotic drive violates those assumptions. Thus, meiotic drive is likely to be a well-regulated, designed mechanism (evolutionists currently assume it is random) that accounts for the statistical patterns normally attributed to natural selection (Lightner, 2015).

Summary

Historically, evolutionists have insisted that adaptation takes place by the naturalistic mechanisms of random genetic mutation and natural selection. These are philosophical assumptions based on a worldview that rejects a Designer, not something that was demonstrated scien-

tifically. In the creation model, universal common ancestry is rejected, but there is diversification and speciation that has obviously occurred within many created kinds. The appearance of adaptive alleles in various populations around the world suggests that there are designed mechanisms by which these alleles arise.

A look at the adaptive immune response indicates that the body has the ability to edit DNA in a variety of ways to meet environmental challenges. Several enzymes, including AID, are designed to initiate alterations in the DNA sequence. Then a variety of outcomes are possible depending on which proteins are recruited to resolve the aberrant base or DNA breaks that were induced. The whole process is well designed and tightly regulated. This bolsters the idea that similar designed mechanisms are involved in adaptive germ-line mutations.

Additionally, AID has been detected in ovaries, spermatocytes, and embryonic stem cells. While AID does appear to play a limited role in demethylation, which may at least partially explain its presence in these locations, this also leaves open the possibility that AID may play other roles. There is evidence it can partially cover for the loss of the enzyme SPO11, which is normally involved in meiotic recombination. AID, or other DNA editing enzymes, may be actively recruited during meiosis, which could help explain why homologous recombination is mutagenic beyond the normal crossing over and gene conversion.

Further, it is recognized that genes that are involved in physiologic adaptation are often the same genes involved in adaptive genetic mutations. Physiologic adaptation involves epigenetic changes that up- or down-regulate genes to compensate for an environmental challenge. AID can target regions where there is active transcription and other epigenetic signals, which suggests physiologic adaptation may plausibly be an important prerequisite if AID in fact does play a role in adaptive germ-line mutations. Since such mutations leave "signatures," it may be possible to bioinformatically screen for regions of the genome where adaptive mutations were induced by AID or a similar DNA editing enzyme.

Finally, when new adaptive alleles appear in a population, there needs to be an effective means for them to spread. Natural selection could play some role, but there are multiple lines of evidence suggesting that it is not particularly effective. The reality that meiotic drive, a type of non-Mendelian inheritance, exists suggests that it may play an important role in increasing the prevalence of adaptive alleles within a population.

All these considerations point to potentially fruitful lines of research. While the intelligent-design framework does recognize design is present in the genome, the history in Genesis provides background information suggesting several important places to look for this design. If AID and/or similar enzymes play a role in adaptive germ-line mutations, it would be one more line of evidence that adaptation occurs because of the Creator, the God described in the Bible, who cares for His creatures.

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