Genes and Protein Synthesis— Updating Our Understanding

TIMOTHY P. BRADY

Abstract

That genes are indispensable is indisputable but that they are the source of information for protein synthesis—to the extent reflected by statements such as "genes are blueprints for proteins" or "genomes constitute developmental programs"—is challenged by discoveries such as post-translational modification of protein and alternative splicing.

Key Words: *alternative splicing; post-translational modification of protein; mRNA editing; primary mRNA transcript; functional (mature) mRNA transcript; alternative transcript; protein isoforms.*

Introduction

I take it for granted that genetics teaching, at both the high school and undergraduate levels, pretty much reinforces the longstanding belief that genes are, ultimately, blueprints for proteins and, given the workhorse nature of proteins, that organisms' genomes constitute the blueprints for making organisms. The Next-Generation Science Standards' Disciplinary Core Ideas include L.S.1.A., "Genes are regions in the DNA that contain the instructions that code for the formation of proteins. . ." and L.S.3.A., "The instructions for forming species' characteristics are carried in DNA" (NGSS, n.d.). The premise of this paper, however, is that consideration of the influence post-translational modification of protein (PTM) and alternative splicing (AS) have on protein synthesis and consideration of the factors involved in regulating these processes cast doubt on the continued appropriateness of the gene-as-blueprint and genome-as-developmental-program metaphors. AP biology textbooks do discuss PTM and AS, over-looking, though, the

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possibility that these phenomena, properly considered, suggest the need to qualify the paradigm that insists genes largely dictate to cells and organisms via genetic influence on protein synthesis.

Post-Translational Modification of Protein

PTM provides for the covalent attachment of chemical groups such as phosphate or the acetyl group or sugar moieties, or even larger groups such as ubiquitin, to amino acid residues of proteins. Most eukaryotic proteins are post-translationally modified after their synthesis on ribosomes and these modifications are critical for the protein's functioning and for getting the protein to the site in the cell where it needs to be to in order to carry out its function (Reece et al., 2014, pp. 351–352). In the next section, examples of PTM are provided to show the extent to which modification status can influence protein function and to show the extent to which factors other than the nucleotide sequence of the associated gene can influence modification status. Any influence by a factor that is not itself a direct product of a gene is termed "non-genetic."

Evidence for Context-Dependence of PTM, Including Non-Genetic Context Dependence

PTM appears to be a very dynamic process. For instance, all of the examples of PTM mentioned above are reversible (Prabakaran et al., 2012, HHS Public Access Version, p. 28). These authors also stress the combinatorial possibilities associated with PTM as suggesting its dynamic nature and provide the following example to make clear their understanding of "combinatorial." If a particular lysine residue can bind an ubiquitin, and a second ubiquitin can bind to the first,

and this same protein has two serine residues, each of which can bind a phosphate group, then this one protein can exist in 12 different "mod-forms" (p. 24). A mod-form according to these authors is "a specific pattern of modifications on all modifiable residues in a protein" (p. 4). In Mohapatra et al. (2007; cited by Prabakaran et al., 2012), non-genetic and combinatorial control of a protein's functionality is illustrated along with a certain context-dependence. Evidence is presented that an increase in neuronal electrical activity triggers protein de-phosphorylation and that a cell-type specific correlation exists between extent of phosphorylation and membrane potential needed for protein activation (pp. 1064–1065). That this protein's functioning changes according to degree of phosphorylation, which depends on cell type, suggests that cell-specific factors and not just the nucleotide sequence of the associated gene influence the phosphorylation status and, hence, the function of this protein.

Tootle and Rebay (2005) provide several examples of the importance of context-dependent PTM for transcription-factor functioning. In one example, phosphorylation activates a transcription factor, this promoting transcription of a gene whose protein product is involved in lymphoid tissue differentiation; when a second type of kinase phosphorylates the same transcription factor, curtailment of activity occurs (pp. 290–291). Acetylation of this transcription factor causes it to play a role in the regulation of extra-cellular-matrix proteins (p. 291). These authors also discuss a transcription factor localized to the cytoplasm of T lymphocytes until the cell's differentiation status changes; then, the transcription factor is both phosphorylated and glycosylated and, as a result, moves into the nucleus (p. 294). Phosphorylation can only occur here if the transcription factor contains an amino acid residue with a hydroxyl group capable of binding a phosphate. For this, the transcription factor's biosynthetic gene plays a necessary role, as does the phosphorylating kinase and its biosynthetic gene. However, these are not sufficient to explain this phosphorylation event because this transcription factor is not always phosphorylated—it's only phosphorylated when there's a requirement that it move into the nucleus.

Brassinosteroids (BRs), plant steroid hormones, trigger phosphorylation of an enzyme, leading to activation of a transcription factor that turns on expression of BR-sensitive genes (Hill, 2015, pp. 4934–4935). I consider the BR influence here to be non-genetic because BRs, and steroid hormones in general, are not direct products of genes, and even though BRs do require gene-associated enzymes for their synthesis, BRs help regulate transcription of these genes (Vriet et al., 2013, p. 1749). Also, auxin, another hormone, triggers a rate-determining step in BR synthesis (Chung et al., 2011a, p. 575), and auxin synthesis, or getting auxin where it needs to go to exert its effects, can be influenced by gravity, light, or yet another hormone, ethylene (Vanneste & Frimi, 2009, p. 1013), and ethylene can control its own synthesis by a positive-feedback mechanism (Vandenbussche et al., 2012, p. 897).

Nitrogen incorporation in plants requires the nitrate reductase (NR)-catalyzed reduction of nitrate to nitrite; light is an indirect catalyst for the de-phosphorylation/activation of NR (Lillo et al., 2004, pp. 1275–1277), with plant-sugar level functioning as a direct catalyst (Kaiser & Huber, 2001, p. 1984).

Glucocorticoid (GC) binding to its receptor engenders receptor phosphorylation, facilitating this complex's movement into the nucleus, where it functions as a transcription factor (Gupta et al., 2007). As with the BR-mediated influence just discussed, I consider GC's influence on phosphorylation here to be non-genetic. Steroid hormones are not direct products of genes, and even though gene-associated proteins are needed for GC synthesis, GCs can, in negative-feedback fashion, down-regulate plasma levels of two of them, corticotrophin-releasing factor (CRH) and adrenocorticotropic hormone (ACTH) (Oakley & Cidlowski, 2013, p. 1033). Additionally, bloodstream GC levels vary in circadian fashion (Chung et al., 2011b), this suggesting a role for day/night cycling in the regulation of GC synthesis. Finally, different types of stress trigger CRH and concomitant GC synthesis (Chung et al., 2011b, p. 583).

The cytoplasmic moiety of a B_2 adrenergic receptor must be phosphorylated for receptor coupling to occur, and prior palmitoylation of the cytoplasmic moiety is required for phosphorylation (Chini & Parenti, 2009, p. 374). Although the information stored in the receptor's biocynthetic gene is necessary for synthesis of this protein, it would seem apparent that knowledge of *when* to attach a palmitic acid to the receptor, and *when not* to, would have to reside elsewhere than in that gene.

Implications of PTM for Conceptualizing the Role of Genes in Protein Synthesis

A serine residue on protein A can be phosphorylated while that same residue on another molecule of A can be glycosylated (Prabakaran et al., 2012, p. 4). Light-engendered photosynthesis triggers an enzyme's dephosphorylation. A transcription factor's function changes depending on which kinase phosphorylates it and changes again if it's acetylated. The extent of neuronal electrical activity dictates the phosphorylation status of a channel protein associated with that neuron. Of course, there would be no proteins to modify without genes. Still, the reversible nature of PTM, its context-dependence, and its combinatorial aspect, suggest PTM occurs according to the dictates of a regulatory web whose information store must greatly exceed that of the associated gene. Indeed, it would not have been possible to predict any of the protein modifications discussed above solely from the nucleotide sequence of the relevant gene. This is not contradicted by the fact that software exists (Chen et al., 2016) that can infer from the nucleotide sequence of a region of a gene and that region's modification status what the likelihood will be of that same modification occurring in other proteins. Software such as this can only predict the likelihood that a particular modification can occur, not that it will occur. To achieve the latter, for modifications that are context-dependent, relevant context would have to be taken into consideration.

Prabakaran et al. write,

> PTM . . . is nature's escape from genetic imprisonment. Gene sequences change on an evolutionary time scale but not on one appropriate for organismal development, adult physiology . . . PTM allows amino-acid properties to be changed "on the fly" in response to requirements on a developmental or physiological time scale. (2012, p. 1)

It would seem, then, that it's precisely the capacity of a cell or organism to respond to the context-dependent, fluctuating data informing modification decisions, so different from the quality of information encapsulated in genes, that explains the tremendous usefulness of PTM to cells and organisms.

Most proteins are not functional until after PTM, and changing a protein's modification status changes it function; thus, PTM

should not be considered mere editing. Furthermore, the context-dependence of a modification event suggests that the information needed for it resides in a realm wider than that of the associated gene, and context-dependence appears to be the rule, rather than the exception, as regards PTM. So, if by "protein" one means "*functional* protein," it would appear that referring to genes as blueprints for proteins undervalues the significance of PTM for protein synthesis. Additionally, the involvement of non-genetic factors in regulating PTM suggests that the genome-as-developmental-program metaphor requires qualification.

○ Alternative Splicing

Three decades ago, it was discovered that the coding function of some eukaryotic genes was broken up into smaller, discrete coding segments called exons, these separated from one another by long stretches of non-coding DNA, called introns. Both intron and exon nucleotides are transcribed, this yielding a primary mRNA transcript, or pre-mRNA molecule, from which RNA nucleotides complementary to intron nucleotides are excised, this constituting RNA splicing. RNA nucleotides complementary to *some* exon nucleotides can also be spliced out of a primary mRNA molecule; these RNA nucleotides, though, can vary, depending on, for instance, cell type, this constituting AS. Primary-transcript exons ending up in all the functional mRNAs derivable from a particular primary transcript are commonly referred to as constitutive exons. Excisable exons are commonly referred to as alternative exons. Evidence suggests 95 percent of human genes are alternatively spliced (Chen & Manley, 2009, p. 741). The end-result of RNA processing—the RNA that leaves the nucleus to undergo translation—is called mature, or functional, mRNA.

To illustrate RNA splicing and AS,[1] imagine a eukaryotic structural gene A comprised of 10 exons and 9 introns. (From this point on, I will be using "intron" and "exon" in the context of RNA molecules, also.) In one cell type, intron removal and selective exon removal might yield a functional mRNA containing exons 1, 2, 3, 4, 7, 8, and 10, all the introns and exons 5, 6, and 9 having been removed from the primary transcript. In a different cell type, the functional mRNA might contain exons 1, 4, 5, 6, 7, and 9. Somewhat obviously, these two different mRNAs are going be translated into two different protein isoforms (hereafter referred to as isoforms), which might have different functions, as suggested by Yang et al. (2016). These authors determined the number of binding partners shared between members of an isoform pair. In a majority of cases, members of a pair shared fewer than 50 percent of binding partners, Yang et al. concluding, "In the global context of interactome network maps, alternative isoforms tend to behave like distinct proteins rather than minor variants of each other" (p. 805).

AS, then, to the extent that isoforms are functionally different, allows for an expanded proteome relative to a fixed genome, but also, the outline of AS provided so far might already provoke doubt that the information for protein synthesis resides solely in genes. A structural gene should certainly be considered a template for the associated primary mRNA. Should a structural gene, though, also be considered the template for a functional mRNA arising only after considerable processing of the primary transcript, if this processing involves *variable* excision of exons? The primary transcript does contain structural cues identifying excisable exons, and this

information is necessary for functional mRNA synthesis. Additionally, every exon found in any of the functional mRNAs derivable from a particular primary transcript *was*, originally, part of that primary transcript. However, there is one category of information, critically important for splicing outcomes, that the primary transcript, and by extension, the gene, does not appear to contain. The primary transcript, alone, does not appear to contain the information for *which* excisable exons to leave in and *which* excisable exons to splice out during a *particular* splicing event. The information stored in a structural gene, so necessary for a protein's primary amino acid sequence, appears at the same time insufficient as regards specifying that sequence to the extent that more than one such sequence can result from splicing of the primary transcript. The information in a primary transcript, alone, can only indicate which exons *might* be excised, not which exons *will* be excised, as the result of a splicing event, when more than one isoform can result. Next, evidence that factors other than the associated gene can influence splicing outcomes is presented, but that such factors *must* exist seems implicit, already, in the very fact of AS; any influence not due to a direct product of a gene will be termed non-genetic.

Evidence for the Role of Context, Especially Non-Genetic Context, in the Regulation of AS

That AS can lead to synthesis of isoforms with opposite functions is illustrated by an example from Yang et al. (2016): one isoform promotes apoptosis, while the other inhibits it (p. 806). An article cited by Yang et al., Schwerk and Schulze-Osthoff (2005), provides other examples of isoform pairs exhibiting opposite functions, but these authors also write, "Accumulating data have shown that splicing patterns can already be determined at the promoter of a gene, evidencing a coupling between transcription and alternative splicing" (p. 8, citing Goldstrohm et al., 2001). This statement appears to be saying that a gene *is* capable of wholly influencing the outcome of a splicing event. Schwerk and Schulze-Osthoff go on to summarize research, however, showing that a gene for which the aforementioned connection between transcription and splicing outcome is established has five promoters, and that selection of one of them *is* associated with a particular splicing outcome, but that the trigger for this is a steroid hormone (p. 8). It would appear that the information for this splicing outcome, its "blueprint," due to this splicing outcome's dependence on a non-genetic factor, must lie in a realm wider than that of just the gene.

Pre-mRNA secondary structure can influence alternative-splicing outcomes. Buratti and Baralle (2004) discuss several examples of this, one (p. 5) being a pre-mRNA's-secondary-structure's influence on expression of two mutually exclusive exons, the tissue-specific manner of exon expression here suggesting a role in secondary-structure determination, and hence, splicing outcome, for factors other than just the relevant gene. The *Drosophila* gene *Dscam*, which can generate over 38,000 isoforms, all or most of which may be required for normal fruit fly central nervous system development (Yue et al., 2013, p. 1822), has 115 exons, 20 of which are not alternatively spliced. The remaining 95 are bundled into 4 groups or clusters (exon clusters 4, 6, 9, and 17 containing 12, 48, 33, and 2 exons, respectively), with a single exon from each cluster ending up in a particular functional mRNA (May et al., 2011, p. 222). Of *Dscam*'s 115 exons, then, only 24 will be represented in any of 38,000 possible functional-mRNA transcripts and, hence, only 24 in any one isoform. Graveley (2005) proposed a mechanism for splicing of cluster 6, containing 48 exons,

which relied on different secondary structures for each AS outcome. May et al. provided experimental evidence for the existence of these structures, and their importance, but concluded that other factors were also important (p. 227). Whether one focuses on the large number of different secondary structures involved in the many different alternative-splicing outcomes possible or on the ". . .larger integrative system" within which these authors believe the secondary-structure influence is embedded, it should still be apparent that the information required for splicing outcomes here must far exceed that capable of being supplied by *Dscam* itself.

The capacity of endogenous zinc levels, in *Arabidopsis*, to skew splicing of the primary transcript of a gene coding for a zinc-sequestration protein toward an alternative transcript with enhanced "translation efficiency" (Remy et al., 2014, p. 1) is another example of the influence of a non-genetic factor on AS.

A second example of a steroid-hormone's influence on a splicing outcome and, at the same time, a second example of transcription-AS linkage is provided by Dowhan et al. (2005). This article summarizes research showing that binding of progesterone to its receptor, in addition to influencing transcription, triggers recruitment of co-regulatory molecules that influence downstream splicing events. This second example of a steroid-hormone's influence on a splicing outcome provides somewhat explicit evidence of the capacity of a non-genetic factor, progesterone, to regulate a key splicing regulator molecule, the splicing factor. (AS *regulation* is generally attributed to the interaction of splicing factors [proteins and RNA molecules] with primary-mRNA nucleotide sequences, splicing factors thus filling a role in AS analogous to that filled by specific transcription factors in transcription; importantly, because splicing factors are proteins or RNA molecules, their genesis, too, can involve AS.) This is noteworthy because implicit in the notion of a genetic program driving development is that regulator-gene products, such as the *lac operon's* repressor protein, control transcriptional and post-transcriptional events to an extent that obviates the need to look for factors outside of the genome to explain control of cellular processes (Keller, 2000, pp. 56–57). Thus, one might agree that the discovery of AS should provoke movement away from the characterization of single genes as blueprints for proteins but insist that because splicing factors are direct products of genes, the information for splicing outcomes still lies within the genome as a whole. However, in this splicing outcome, we see regulation by a non-genetic factor, not of transcription but, still, of the identity of the final product of a regulator gene.

An example of an external-environmental influence on AS also manifesting as an influence on the same category of regulator gene as in the previous example is, in *A. thaliana*, the effect of long-term exposure to cold on which of two splicing factors predominates (Shang et al., 2017, p. 2 of online version).

Syed et al. (2012), in examining the importance of AS to plant physiology, stress the role of splicing factors in AS but then point out the importance of non-genetic factors in the splicing outcomes that dictate the identity of the splicing factors themselves, these non-genetic factors including "temperature, light, salt, hormones, etc." (p. 3 of online version).

Implications of AS for Conceptualizing the Gene

Prior to the discovery of AS, it seemed reasonable to conceive of structural genes as blueprints for proteins to the extent that genes appeared to be straightforward templates for mRNA molecules, with these appearing to be straightforward templates for the amino-acid sequence of proteins. However, the nature of the processing that primary mRNA undergoes on the way to becoming functional mRNA insures that there is no one-to-one correspondence between DNA nucleotides and *translatable* mRNA nucleotides in eukaryotes. Additionally, there is the problem, already discussed, of trying to imagine how the information in the gene/primary transcript, alone, is sufficient to dictate *which* excisable exons are to be spliced out when these can vary in a situation-dependent manner. Genes appear very much to be blueprints for primary mRNA molecules but not blueprints for the functional mRNA molecules resulting from AS. Information of a different sort seems required in going from primary to functional mRNA. Furthermore, that this information, whether manifesting as cell-specific secondary structure or hormone or mineral levels, or temperature or light intensity, is not always of a merely ancillary nature is indicated, again, by the fact that AS can result in isoforms with opposite functions.

According to Tress et al. (2017), there is scant evidence, in mammals at least, that anywhere near the same number of isoforms is being generated as are alternative transcripts (functional mRNAs), and when multiple isoforms do result, there is not always accompanying evidence that each is functionally distinct from the other(s). Howver, a splicing outcome non-productive in the sense that one of a pair of alternative transcripts is never translated can still exert a profound regulatory influence on protein synthesis via the orchestrated linkage of nonsense-mediated decay (NMD), a process that results in the degradation of functional mRNA molecules, to AS (Soergel et al., 2000, p. 13). Makeyev et al. (2007) provide an example of this. In mice non-neuronal cells, a splicing factor influences splicing of a second splicing factor's primary transcript in such a way that the resulting alternative transcript is shunted into the NMD pathway and degraded. However, in nervous system (NS) cells, where the second splicing factor is needed, a small regulatory RNA represses the first splicing factor's synthesis to a degree that allows for synthesis of the second splicing factor. Thus, splicing of the second splicing factor's primary transcript, in *non-NS* tissue, is non-productive; the alternative transcript is never translated. Splicing in NS tissue, however, is productive; the alternative transcript is translated.

Intron retention (IR) is a type of AS. One IR variant results in the retention of an intron in the 5′ un-translated region of a functional mRNA, this altering the ease of translation of the transcript and thus providing a means for regulating gene expression. We saw an example of this in Remy et al. (2014) as regards *Arabidopsis*. Translation of each of two alternative transcripts results in synthesis of exactly the same protein. However, there is a greater need for this protein in root cells. In *these* cells, zinc-mediated IR results in an alternative transcript with enhanced translation efficiency.

Regulation of gene expression by shuttling alternative transcripts down the NMD pathway, prior to translation, and intron retention, thus, are two mechanisms by which AS can regulate protein synthesis, and in a tissue-specific manner, even though neither results in the synthesis of more than one protein per gene.

The starting point for this article's analysis of PTM was an already "complete" protein, from where PTM's role in protein synthesis was seen to lie in its capacity to influence protein functioning. The starting

point for this article's analysis of AS was the primary transcript, from where AS's influence on protein synthesis was seen to lie in its capacity to provide for the generation of more than one functional mRNA and, *presumably*, more than one functionally distinct protein. To the extent that this happens and to the extent that non-genetic factors are involved in regulating AS, the gene-as-blueprint and genome-as-developmental-program metaphors seem called into question. However, as just mentioned, there are doubts in some circles about the degree to which alternative transcripts are translated or, when translated, translated into functionally distinct proteins. We have just seen though, that AS can influence protein synthesis even when two different functional mRNAs, derived from the same primary transcript, do not lead to synthesis of two different proteins. AS can influence protein synthesis, not just by providing the basis for generating more than one functionally distinct protein from the same gene but also by regulating the *extent* of synthesis of a protein that might be the only one associated with a particular gene. (This latter capacity of AS does not challenge the gene-as-blueprint metaphor; it does challenge the genome-as-developmental-program metaphor.)

○ Discussion

Biologists have long recognized that the environment, not just the genotype, plays a role in the genesis of phenotype. In their AP biology text, Hillis et al. (2014), with the stated desire to distance themselves from anything resembling extreme genetic determinism, write,

> The phenotype of an individual does not always result from its genotype alone. Genotype and environment often interact to determine the phenotype of an organism . . . Common knowledge tells us that environmental variables such as light, temperature, and nutrition can affect the phenotypic expression of a genotype. For example, in humans, body weight is determined not only by multiple genes but also by nutrition and activity. (p. 160)

However, these authors, after discussing PTM (p. 212) and AS (pp. 229-230), might still be thought to overemphasize the role of genes in protein synthesis, given the extent to which PTM and AS appear capable of influencing this process. Their statement that "Genetics shows that genes code for proteins" (p. 196), if intended to mean that the information for a protein's synthesis resides solely in the associated gene, would seem to be contradicted by the discoveries of PTM and AS, at least in eukaryotes.

Because any PTM and AS pertaining to the eventual product of a structural gene occur after transcription, it might be argued that these processes represent editing, only, of the products of a more fundamental process, transcription. Trying to minimize the influence of PTM and AS in this way, however, ignores the roles PTM and AS play in the genesis of, for instance, specific transcription factors, without which transcription is impossible.

mRNA editing is a type of post-transcriptional modification different from AS. It involves replacing a functional mRNA's adenosine with an inosine, read by the translation machinery as a guanosine, or a cytosine with a uracil, thus possibly altering a codon's identity and the corresponding amino acid's identity from that intended by the gene. In mammals, mRNA editing is rare but also very important. For instance, mRNA editing allows a glutamate-receptor subunit to undergo a glutamine-to-arginine substitution that is critical for survival; mice for which this event is not possible die shortly after birth (Rosenthal, 2015, p. 1814). Gene-associated enzymes catalyze mRNA editing, but non-genetic factors can play key roles in regulating the expression and activity of these enzymes (Gan et al., 2006, p. 33387); fasting, a high-fat diet, and glucose levels influence the expression and activity of the enzyme that catalyzes A-to-I editing in mouse pancreatic tissue (p. 33387). mRNA editing is thus a third phenomenon, in addition to PTM and AS, suggesting an important role for factors other than the associated genes, or even the genome as a whole, in protein synthesis. Meyer et al. (2013), in a section entitled, "The Crisis of the Gene Concept," point to AS and mRNA editing as being among the reasons why some philosophers of science and biologists have lost confidence in the intelligibility of the orthodox view of the gene to a degree that has seen alternative conceptualizations of the gene propounded (pp. 346–347). One such alternative conceptualization is Eva M. Neumann-Held's "process molecular gene concept" (discussed in Meyer et al., p. 349) that a gene is best understood today not so much as a site on a chromosome but, rather, as an *activity* a cell engages in to procure needed proteins. Meyer et al. believe Neumann-Held has a valid point, writing,

> The process nature of this concept arguably makes it possible to accommodate anomalies which the classical molecular gene has difficulties in facing, such as alternative splicing or mRNA editing. These phenomena are simply included in the gene, when interpreted as a process, dissolving the anomalies at stake. (p. 349)

Space constraints preclude going further into Neumann-Held's "process molecular gene concept" or at all into the other alternative conceptualizations of the gene discussed by Meyer et al.; they are mentioned to highlight the extent to which some biologists and philosophers of science have grown dissatisfied with the orthodox conceptualization of the gene. Meyer et al. (p. 367) point out, however, that discussion of processes such as AS and mRNA editing in university-level textbooks has not served to alter the way the gene is portrayed in these—the orthodox, decades-old, understanding still prevails. Additionally, that the orthodox conceptualization of the gene is in trouble to a degree that warrants alternative conceptualizations is, no-doubt, a minority view.

The focus of this article has been somewhat narrow: to examine some of the molecular biology behind 21st century science's evolving awareness of the context-dependent, multi-factorial nature of protein synthesis. If this article provokes discussion about the material covered and/or stimulates outside reading on the subject,[2] especially among secondary science teachers, it will have served, I believe, a useful purpose.

○ Acknowledgments

NOTES

1. There is more than one type of AS. The type illustrated here, exon skipping, is the most common.

2. I recommend Evelyn Fox Keller's very readable *The Century of the Gene* for a much broader examination of the factors driving modern biology's growing recognition of the limitations of genetic reductionism.

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TIMOTHY BRADY (timbra717@yahoo.com) has been a science teacher at North Hollywood High School in Los Angeles since 2001.