Commentary: Past, present, and future of epigenetics applied to livestock breeding — Hard versus Soft Lamarckian Inheritance Mechanisms

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A commentary on

Past, present, and future of epigenetics applied to livestock breeding
by González-Recio, O., Toro, M. A., and Bach, A. (2015). Front. Genet. 6:305. doi: 10.3389/fgene.2015.00305

The article by González-Recio et al. (2015) claims to “review the concept of Lamarckian inheritance and the use of the term epigenetics in the field of animal genetics.” I began reading with interest as I am involved in selective livestock improvement (Williamson et al., 2011) using the ancestral haplotype approach to establish associations with desirable beef quality traits (Dawkins, 2015). I was curious where the epigenetics field was situated in this regard. However, in the introductory section, “The Old Ideas,” I considered their comments on an earlier book of mine (Steele et al., 1998) were incorrect. Further, the rest of their article had, in my view, a major omission on what constitutes Weismann’s Doctrine and the Central Dogma of Molecular Biology (below). Having said this the review by Gonzalez-Recio et al is an otherwise thoughtful and informative article on the application of transgenerational epigenetic ideas and phenomena to livestock improvement. Indeed I have no argument with accurate recounting of the difficulties documenting "hard" epigenetic inheritance in mammals (the transmission of an epigenetic character beyond three generations).

Understanding the genetic rules for how a reversible (erasable and thus “soft”) epigenetic trait can be made into a “hard” genetic transmission process involving modifications to germline DNA sequences, is a worthy research goal. Given the current state of immunological knowledge I am persuaded by the data that “hard” types of soma-to-germline transfer are ongoing at very high frequency in human immune system germelines, and, by extension, other mammalian germlines (below).

I have been developing Lamarckian soma-to-germline concepts and reverse transcriptase (RT) - based feedback mechanisms—“hard” Lamarckian Inheritance—since 1978 (Steele, 1979, 2009a; Rothenfluh and Steele, 1993; Rothenfluh et al., 1995; Blanden et al., 1998; Steele et al., 1998; Zylstra et al., 2003; Steele and Lloyd, 2015). This research has run parallel to investigations on similar RT-based mechanisms in the antigen-driven somatic hypermutation (SHM) of rearranged immunoglobulin (Ig) variable genes, so called VDJs (Steele and Pollard, 1987; Blanden et al., 1998; Weiller et al., 1998; Franklin et al., 2004; Steele et al., 2006; Steele, 2009b). This has led to studies showing that RT-based strand-biased mutation mechanisms, and recently
to Robyn Lindley’s codon-contexted targeted mutagenesis, apply
to dysregulated SHM as a general causal mechanism in all cancers
(Steele and Lindley, 2010; Lindley, 2013; Lindley and Steele, 2013).

Given that reverse transcription is at the heart of any modern
“hard” Lamarckian inheritance mechanism I was surprised that
“reverse transcription” is not mentioned by Gonzalez-Recio et al.
This is curious because the RNA to DNA step has been embodied
in the Central Dogma of Molecular Biology since the discovery
of reverse transcription by Temin and Mizutuni (1970) and
Baltimore (1970). Crick, who like Temin anticipated it enshrined
it in his famous “modification” of the Central Dogma in Nature
in 1970 (Crick, 1970; summarized in Figure 1A).

Indeed the rigid dictum DNA -> RNA -> Protein is the earlier
1960s rendition which is often mistakenly confused with
Weismann’s Doctrine (Figure 1B). It must be made clear that
Weismann’s Barrier enshrines a cellular theory of information
flow whereas the Central Dogma is a theory of information
flow at the molecular level. I found it necessary to draw these
clear distinctions when the Somatic Selection Hypothesis was
first formulated 37 years ago (Steele, 1979). In that theory the
data were marshaled to advocate that for the immune system at
least, Weismann’s Barrier was selectively permeable to somatic
immunoglobulin V gene mutants (Figure 1C).

I draw out these historical threads as they were not made clear
in the Gonzalez-Recio et al article.

My primary reason for writing this invited Commentary is
the statement by the authors: “In immunology, Steele et al.
(1998) claimed that environment could make the immune
system to change its DNA structure, and these changes could
be transmitted to the offspring, assertions that have yet to be
cirmed.” Apart from anything else I might add our work ca.
1998 was more than just an “assertion,” as it summarized 20 years
of work and experimental data (note: “Basic Books” as mentioned
in the authors’ reference list were not the publishers of Lamarck’s
Signature in the US, it was Perseus Books).

Extensive DNA sequence data shows that the signature of
antigen-driven somatic hypermutation of somatically rearranged
VDJ genes is embedded within all vertebrate unrearranged
germline V segment arrays examined (Rothenfluh et al., 1995;
Blanden et al., 1998; Steele, 2009a; Steele and Lloyd, 2015). This
striking fact requires a rational explanation—we have provided
that explanation and this has never been challenged by molecular
immunologists over the past 25 years (at least since our first
published report on such patterns in Rothenfluh and Steele,
1993). The logic of this interpretation is outlined in our many
papers and the 1998 book, Lamarck’s Signature.

Certainly as Fogarty (2002) and the group of Corrado
Spadafora have repeatedly shown (Zoraqi and Spadafora, 1997;
Spadafora, 2008; Cossetti et al., 2014) there is no physical
barrier preventing somatic RNA/DNA sequences entering the
mammalian germline. Sperm developing in the epididymis
are most susceptible to this uptake. The transfer of somatic
regulatory miRNAs may well use the same soma-to-germline
channel for epigenetic transfers in male mice (Rassoulzadegan
et al., 2006). This is now emphatically underlined by the
recent work of Oliver Rando and colleagues which clearly
shows that “small RNA biogenesis and its dietary regulation
during post-testicular sperm maturation” linking these “tRNA
fragments to regulation of endogenous retroelements active in
the preimplantation embryo” (Sharma et al., 2016). Thus vesicles
identified as “epididymosomes” carrying RNA payloads matching
those of mature sperm, clearly fuse with spermatozoa during epididymal transit and can also be shown to deliver these somatic RNAs to immature sperm in vitro (Sharma et al., 2016). What is lacking in all this is a reverse transcription step to lock in these somatic RNAs into germline DNA. Likely RT candidates are the Y family of DNA polymerases (eta, kappa, and iota) or LINE retropseudogenes—can be characterized by testing for putative haplotype segregation in three generation families (Steele and Lloyd, 2015).

**AUTHOR CONTRIBUTIONS**

The author confirms being the sole contributor of this work and approved it for publication.

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**NOTE ADDED IN PROOF**

The earlier demonstrations by the author of soma-to-germline inheritance should have been cited (Gorczynski and Steele, 1980, 1981). Further, a recent paper was overlooked in referencing. This demonstrated the soma-to-germline feedback phenomenon for regulatory double stranded RNA triggering RNA interference (RNAi) in C. elegans (Devanapally et al., 2015).

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**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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