Rethinking the Central Dogma: Protein Amyloids acting as Transgenerational Epigenetic Memory Carriers

Commentary on "Noncanonical Inheritance of Phenotypic Information by Protein Amyloids" by Matthew Eroglu et al. (September 2, 2024)

Repenser le dogme central : les amyloïdes protéiques agissant comme vecteurs de mémoire épigénétique transgénérationnelle

Commentaire sur « Hérédité non canonique de l'information phénotypique par les amyloïdes protéiques » par Matthew Eroglu et al. (2 septembre 2024)

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Abstract | Résumé

Nucleic acids remain the primary mechanism for transmitting hereditary information across generations. Despite advances in genome-wide association studies and epigenetic reprogramming mechanisms, many familial traits and disease susceptibilities remain unexplained, a gap known as "missing heritability" (1). Conventionally, epigenetic inheritance is attributed to small RNA or chromatin/histone modifications. However, a revolutionary finding by Matthew Eroglu and colleagues identified amyloid-like protein aggregates in *Caenorhabditis elegans* (*C. elegans*) that persist across generations to influence developmental phenotypes. This suggests proteins can act as independent carriers of transgenerational epigenetic memory. This commentary examines how these findings challenge the Central Dogma, expand inheritance models, and redefine amyloids beyond disease pathology.

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Les acides nucléiques restent le principal mécanisme de transmission d'informations héréditaires à travers les générations. Malgré les avancées dans les études d'association à l'échelle du génome et les mécanismes de reprogrammation épigénétique, de nombreux traits familiaux et susceptibilités aux maladies restent inexpliqués, un écart connu sous le nom de « manque d'héritabilité » (1). Conventionnellement, l'hérédité épigénétique est attribuée à de petits ARN ou à des modifications de chromatine/histones. Cependant, une découverte révolutionnaire de Matthew Eroglu et de ses collègues a identifié des agrégats protéiques amyloïdes chez *Caenorhabditis elegans* (*C. elegans*) qui persistent à travers les générations pour influencer les phénotypes développementaux. Cela suggère que les protéines peuvent agir comme porteuses indépendantes de la mémoire épigénétique transgénérationnelle. Ce commentaire examine comment ces résultats remettent en question le dogme central, élargissent les modèles d'hérédité et redéfinissent les amyloïdes au-delà de la pathologie des maladies.

Keywords: Protein amyloids, epigenetic inheritance, central dogma, prions, transgenerational memory, noncanonical inheritance

Introduction

The phenomenon of "missing heritability" arises from puzzling relationships in heritable conditions that cannot be justified by known transmissible molecular mechanisms. While transgenerational epigenetic inheritance can transmit adaptive traits independently of DNA sequence, most epigenetic marks are extensively erased during gametogenesis and embryonic development. This eradication limits their long-term stability across generations, suggesting that additional inheritance mechanisms exist beyond conventional nucleic acid-based models.

Additionally, sexually reproducing organisms transmit parental factors such as gametic proteins to progeny during early embryogenesis. The dynamic regulation of a balanced, functional proteome, encompassing the cellular mechanisms that control protein synthesis, folding, trafficking, and degradation, is referred to as proteostasis. These protein quality control systems are highly upregulated in stem and germline cells, suggesting that proteostasis is crucial for self-renewal.

Amyloids are solid-phase fibrillar protein oligomers characterized by cross β-sheets that allow them to self-propagate by transferring their structure onto native proteins. A notorious sub-class of amyloids called prions can convert native proteins into distinct prion conformations, disrupting normal cellular functions and infecting nearby cells (2). However, amyloids are not solely pathogenic; they play essential roles in hormone regulation, such

as facilitating storage and secretion of peptide hormones (3). Furthermore, controlled transitions between amyloid aggregation and disaggregation are strictly required for proper embryonic development in yeast, worms, and flies (4). Despite these developmental functions, this specific mechanism of heritability was not likely to be investigated further, as higher-order organisms clear such aggregates during embryogenesis, allowing for no method of transmission (5).

During early development, most parental epigenetic information, including DNA methylation and chromatin modifications, is erased and replaced by zygotic material, thereby limiting the long-term stability of inherited epigenetic states (6). Consequently, amyloid-like aggregates observed in metazoan germ cells and embryos were generally assumed to be transient structures that are cleared during development. However, this paper challenged this assumption by demonstrating that amyloid-like protein aggregates in *C. elegans* persist beyond the maternal-to-zygotic transition and are stably inherited across generations (7).

Structural findings

The authors identified cytoplasmic amyloid-like puncta within developing oocytes that subsequently travel into embryos and spread throughout somatic and germline tissues during development (7). Unlike transient protein aggregates associated with cellular stress or degeneration, these structures persist across generations, producing distinct developmental phenotypes. This transgenerational persistence challenges the long-standing assumption that protein aggregates are fully cleared during embryogenesis, suggesting instead that proteins can carry heritable biological memory independent of genomic DNA sequences.

To investigate their functional significance, the authors examined two conserved AN1-domain proteins, mstr-1 and mstr-2, which regulate 26S proteasomal selectivity to maintain proper amyloid homeostasis. Absence of MSTR proteins disrupted normal proteasomal regulation, allowing heritable amyloid aggregates to progressively accumulate and gradually transform sperm-producing germ cells into functional oocytes over multiple generations. Remarkably, this phenotype intensified gradually across generations and could be reversed under permissive environmental conditions — hallmarks that are highly consistent with epigenetic inheritance rather than irreversible genomic mutation (7). The reversibility of the phenotype strongly supports a dynamic, transmissible, protein-mediated inheritance system rather than a purely genetic mechanism.

Among the most compelling findings in the study were the aggregate injection experiments, which provided strong evidence for protein-mediated inheritance. Injection of amyloid-like aggregates isolated from mstr-deficient feminized worms into naïve hermaphrodites caused reduced fertility and progressive feminization that persisted for at least five generations. In contrast, aggregates isolated from wild-type worms maintained under normal conditions produced minimal developmental effects, suggesting that the heritable influence of the aggregates depends not only on their presence, but also on their conformational or compositional state (7). The self-propagating behavior of these aggregates resembles fungal prions, in which protein conformations template similar structural states onto native proteins. However, unlike pathogenic prions associated with neurodegenerative disease, the amyloid-like structures identified in this study appear to function physiologically in developmental regulation and reproductive fitness.

Importantly, the feminization phenotype intensified progressively across generations yet reverses when worms return to permissive growth conditions following maintenance at elevated temperature. Worms propagated for multiple generations at 25°C gradually regained normal spermatogenesis and fertility after being shifted back to 20°C, demonstrating that the phenotype was not permanently fixed (7). This reversibility represents one of the strongest pieces of evidence supporting an epigenetic rather than genetic mechanism of inheritance. If the phenotype were caused solely by irreversible genomic mutation, restoration of normal spermatogenesis across subsequent generations would not be expected. Instead, the gradual accumulation and subsequent reversal of the phenotype suggest that the inherited factor is dynamic, environmentally responsive, and capable of being remodeled over time. These observations support the authors' proposal that amyloid-like protein aggregates function as transmissible epigenetic memory carriers whose abundance or conformational state can be altered by environmental conditions such as temperature. Collectively, the findings demonstrate not only the heritability of protein-mediated phenotypes, but also the remarkable plasticity of this inheritance system, a defining characteristic of epigenetic regulation.

Under normal conditions, proteasomes selectively degrade misfolded or damaged proteins to preserve cellular proteostasis. However, mutations affecting MSTR proteins disrupted proteasomal selectivity, leading to altered amyloid accumulation and compensatory activation of proteasomal pathways (7). Genetic suppressors targeting 26S proteasomal regulatory subunits restored normal phenotypes, further supporting the conclusion that regulated proteostasis is central to maintaining this protein-based epigenetic memory system.

Mechanism of Action for MSTR Proteins in Proteasomal Selectivity

Further investigation of how MSTR proteins regulate sex-determining pathways through proteasomal activity demonstrated the regulatory function of MSTR proteins. The MSTR proteins maintained a critical balance between the sex-regulatory proteins GLD-1 and TRA-1 by controlling selective protein degradation through the 26S proteasome. In wild-type worms, MSTR-1 expression was highest in spermatogenic germ cells, while GLD-1 expression remained restricted to regions associated with oogenesis (7). However, in mstr mutant worms, GLD-1

accumulated abnormally in spermatogenic regions and progressively increased over generations, coinciding with increasing germline feminization (7). Simultaneously, expression of TRA-1 progressively declined across generations, further shifting germ cells toward oocyte differentiation.

Pharmacological inhibition of proteasomal activity partially restored TRA-1 expression and spermatogenesis in early generations, supporting the conclusion that altered proteasomal regulation drives the inherited phenotype (7). The progressive nature of these molecular changes provides additional evidence that the observed feminization is mediated by an epigenetically inherited factor rather than irreversible genetic mutation. By linking protein homeostasis to transgenerational developmental regulation, the study strengthens the argument that amyloid-associated protein states may function as stable carriers of heritable biological information.

Amyloid-Like Aggregates as Epigenetic Memory Carriers

A major strength of the study is that the authors systematically eliminated several established mechanisms of transgenerational epigenetic inheritance before proposing amyloid-like protein aggregates as the heritable factor responsible for germline feminization. In *C. elegans*, inheritance is commonly mediated through chromatin modifications or small RNA (sRNA)-dependent pathways (8). However, expression levels of the sex-determining genes gld-1 and tra-1 remained unchanged across generations and environmental conditions, suggesting that transcriptional regulation through DNA methylation, histone modifications, or direct mRNA inheritance was unlikely to explain the observed phenotype (7). Furthermore, disruption of multiple endogenous sRNA pathways, including miRNA, piRNA, 22G RNA, and 26G RNA systems, failed to suppress germline feminization in mstr mutant worms (7). These findings support the conclusion that the inherited developmental effects observed in the study occur independently of currently established epigenetic inheritance pathways.

While imaging feminized worms, the authors identified prominent green autofluorescent puncta within the germline that progressively accumulated over generations. These were colocalized with multiple amyloid-specific dyes, including Proteostat, Thioflavin T, and Amytracker, indicating that the structures possessed amyloid-like properties (7).

To determine whether amyloid accumulation directly contributed to germline feminization, the researchers treated worms with structurally distinct anti-amyloid compounds, including curcumin, baicalein, and epigallocatechin-3-gallate (EGCG) (7). These treatments reduced amyloid accumulation and restored self-fertility in MSTR worms, providing functional evidence that amyloid formation contributes to the inherited phenotype. Further investigation into the composition and inheritance of these structures revealed proteins previously associated with aggregation-prone assemblies, including RHO-1 and vitellogenins, alongside proteasomal subunits implicated in proteostasis regulation (7). Although wild-type and MSTR worms displayed similar amyloid compositions, aggregates isolated from MSTR mutants exhibited altered structural properties and greater resistance to proteolytic digestion, suggesting that differences in aggregate conformation, rather than protein identity alone, may underlie the inherited phenotypic effects observed across generations.

Using fluorescently tagged VIT-2 reporters and photoconversion experiments, the authors demonstrated that maternally derived amyloid-associated proteins persisted throughout embryogenesis and larval development in offspring (7). Similar persistence was observed following injection of fluorescently labelled amyloids into wild-type germlines, providing direct evidence that physiological amyloid-like proteins are physically inherited and remain stable across developmental stages.

To directly trace inheritance of these structures, the authors generated fluorescently tagged VIT-2 reporters that colocalized with amyloid-like bodies in the germline. Through irreversible photoconversion experiments, maternally derived VIT-2 aggregates were visualized persisting throughout embryogenesis and into larval development in offspring. Importantly, these inherited protein puncta remained detectable in the germline during later stages of gametogenesis, where newly synthesized amyloid-associated proteins accumulated around pre-existing parental aggregates (7). Similar persistence was observed following injection of fluorescently labelled isolated amyloids into wild-type germlines, with labelled aggregates subsequently detected in both somatic and germline tissues of progeny. Collectively, these experiments provide direct evidence that physiological amyloid-like proteins are physically transmitted between generations and remain stable throughout development.

Limitations

Despite the study's strengths, the precise molecular composition of the amyloid-like structures remains incompletely defined, and it is unclear whether a single core aggregate species is responsible for inheritance or whether multiple heterogeneous protein assemblies contribute collectively. Similarly, the injection experiments utilized mixed amyloid populations, preventing definitive identification of the minimal factor required for phenotypic transmission. The anti-amyloid compounds used in the study also possess antioxidant activity, introducing the possibility that some observed effects may partially arise from altered oxidative stress rather than amyloid disruption alone. Nevertheless, the convergence of genetic, biochemical, imaging, pharmacological, and inheritance-based evidence supports the authors' central conclusion that amyloid-like protein aggregates participate in transgenerational epigenetic regulation.

Implications for Current Scientific Perspective

Perhaps most importantly, the study demonstrates that inherited protein aggregates can coexist with newly synthesized proteins in progeny and influence developmental outcomes long after fertilization. This persistence challenges the long-standing assumption that protein-based cellular states are transient and erased during embryogenesis. Instead, the work supports a model in which proteins may store conformational information capable of acting as a stable epigenetic memory system. While additional research is necessary to determine whether similar mechanisms operate in vertebrates or humans, the findings presented by Eroglu and colleagues substantially broaden current understanding of inheritance beyond nucleic acids and suggest that regulated amyloid formation may represent an evolutionarily conserved mechanism for transmitting adaptive phenotypic information across generations.

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