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VIRAL FOSSIL GENOMES: JUNK DNA OR LIVING DINOSAURS?

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The term junk DNA became popular at the end of the twentieth century to describe those genetic sequences that, apparently, did not influence the functionality of an organism[1]. The idea arose from observing that, after gene cloning and massive DNA sequencing, the genome appeared to be constituted by "islands" of functional sequences (genes) surrounded by vast oceans of silent, dormant DNA[2]. However, this definition was almost immediately called into question, as the mere existence of these regions suggested that they might have some as-yet-unidentified purpose, a hypothesis that began to gain support with subsequent evolutionary and expression studies.

In 2012, the ENCODE consortium revolutionized the field by demonstrating that about 80% of the human genome presents biochemical evidence of activity[1]. That is, many sequences are transcribed or interacted with proteins in different cellular contexts. However, this finding does not imply that all these regions have a clear and defined biological function.

A paradigmatic example of genome complexity is the human endogenous retroviruses (HERV). These "viral fossils" were inserted into the DNA of ancestral mammals millions of years ago and, since then, they have been transmitted from generation to generation following Mendel's classical laws[3]. Most HERV have accumulated mutations and/or have been silenced by epigenetic mechanisms, but some can still encode functional proteins.

The role of syncytins in placental and reproductive physiology

Two HERV-encoded proteins, called syncytins, play key roles in the placenta. *ERVW-1*, located on human chromosome 7, produces syncytin-1, a membrane glycoprotein that facilitates cell-cell fusion to form the syncytiotrophoblast. This protein also maintains the proliferative capacity of progenitor cells and regulates the cell cycle of mature ones. *ERVFRD-1*, on chromosome 6, is expressed in the villous cytotrophoblast and encodes syncytin-2, and possesses fusogenic activity, too. Its most prominent function is maternal immunosuppression, improving tolerance towards the developing fetus. Both proteins are present in gametes, and their correct expression is crucial for their maturation and fertilization. In addition, the aberrant expression of syncytins is associated with pathologies such as preeclampsia and delayed embryonic development, which makes them emerging biomarkers and potential therapeutic targets[3].

Chronology of human endogenous retroviruses insertion and placental evolution

HERV insertions relevant to human physiology are dated to around 20-25 million years for *ERVW-1* (encoding for syncytin-1) and 40-45 million years for *ERVFRD-1* (syncytin-2). This period coincides with the evolutionary divergence between the apes of the New World and those of the Old World[3]. The development of the placenta in mam-

mals is much older, estimated at 160-180 million years ago. It is proposed that viral syncytins replaced previous genes related to cell fusogenesis, modifying trophoblast functionality and allowing new placental configurations associated with the reproductive success of placental mammals[4].

The surprising usefulness of these "stowaway retroviruses" –which snuck into the genome of our ancestors a very long time ago– is still manifested today in embryonic and placental physiology. Paraphrasing the Argentinian actress and renowned television host, Susana Gimenez[5], these "dinosaurs" are alive and take care of our descendants, contributing to the perpetuation of contemporary species (Fig. 1).

Figure 1 | Dinosaur with a collar that says HERV (human endogenous retroviruses), representing junk fossil genes holding a baby

Image generated by Gemini (2025)

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