

Evolution Did Not Eliminate Aggregation: Functional Amyloids Enable Hormone Storage and Signaling

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A functional reservoir with a molecular cost

Members of the PACAP–glucagon hormone family play pleiotropic roles in human physiology, regulating metabolic, nervous system, endocrine, and developmental processes. Their synthetic derivatives, including today's **blockbuster GLP-1 receptor agonists**, have consequently become highly **important pharmaceutical agents**.

These peptides, however, share an **intrinsic propensity** to self-assemble and **form amyloid structures**. This property presents a particular challenge for the production and formulation of peptide-based active ingredients, where aggregation is generally regarded as undesirable.

From a biological perspective, however, aggregation is not necessarily pathological. Following post-translational maturation, peptide hormones awaiting secretion can exist in a self-assembled state within acidic secretory granules. This transient amyloid state is thought to provide a compartmentalized reservoir, allowing large amounts of peptide to be stored in a dense, stabilized form and released when required. This raises a fundamental question: **why do** peptide **hormones possess a molecular architecture** that **simultaneously supports biological recognition and amyloid assembly?**

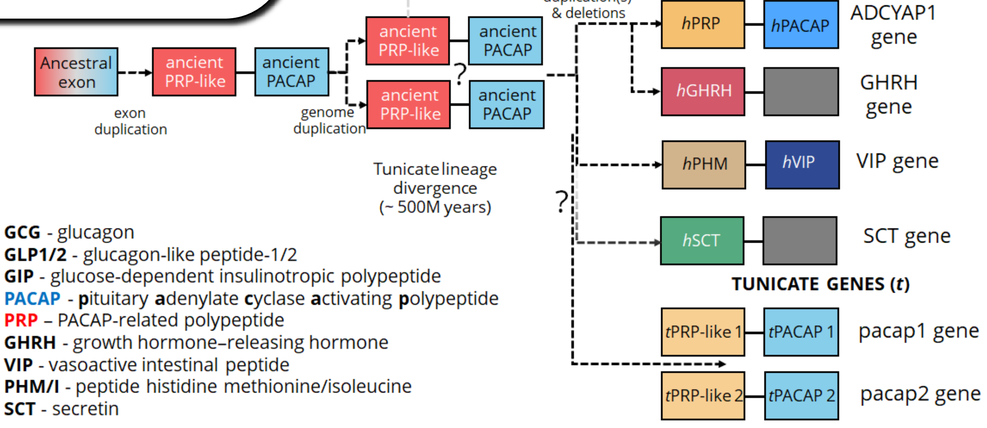
An evolutionary perspective

If this relationship is intrinsic to peptide architecture, it raises a further question: **how has the balance** between **biological function** and **aggregation** been shaped during evolution?

The PACAP–glucagon family provides an unusually informative system in which to address this question. Its members have been **conserved throughout hundreds of millions of years of** vertebrate **evolution**, while their individual receptor specificities and biological functions have diversified substantially.

We therefore asked whether the intrinsic propensity of these hormones to aggregate has remained conserved alongside their biological functions, and which structural features determine this propensity.





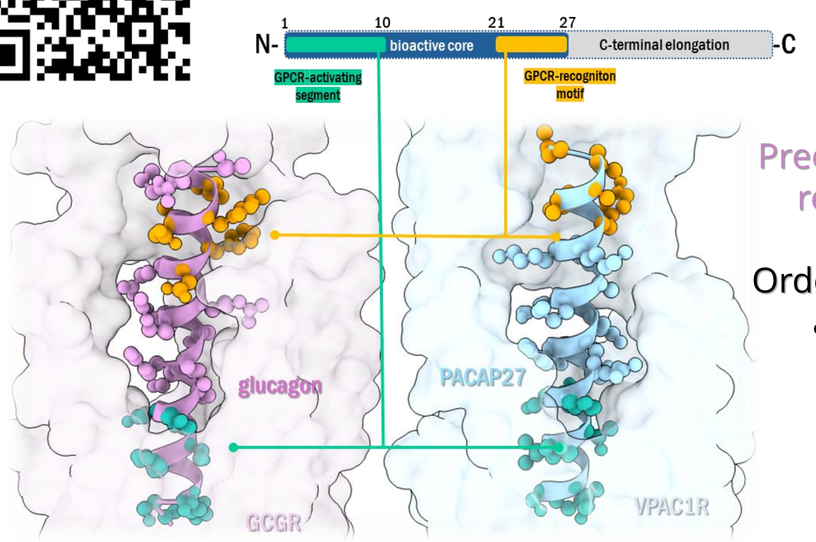
GCG - glucagon
GLP1/2 - glucagon-like peptide-1/2
GIP - glucose-dependent insulinotropic polypeptide
PACAP - **p**ituitary **a**denylate **c**yclase **a**ctivating **p**olypeptide
PRP – PACAP-related polypeptide
GHRH - growth hormone–releasing hormone
VIP - vasoactive intestinal peptide
PHM/I - peptide histidine methionine/isoleucine
SCT - secretin

From receptor recognition to amyloid assembly

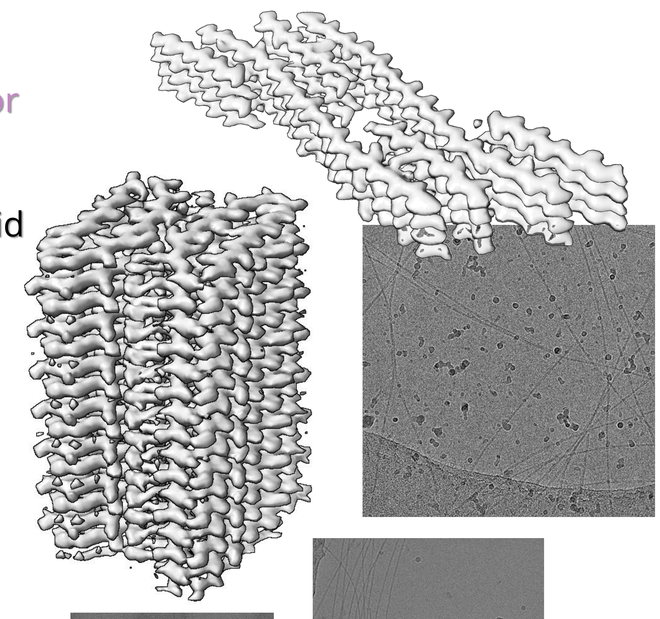
Peptide hormones of the PACAP–glucagon family recognize their cognate G-protein-coupled receptors (GPCRs) through highly specific molecular interactions. Their biological activity therefore depends on **precise recognition of receptor surfaces**, involving complementary shapes, electrostatic interactions, hydrogen bonds, and hydrophobic contacts.

Remarkably, many of the same molecular features can also promote self-association. The side chains required for specific intermolecular recognition can establish complementary interfaces between peptide molecules, **enabling ordered assembly into amyloid structures**.

Thus, receptor recognition and amyloid aggregation may represent two different structural manifestations of the same molecular interaction landscape.



Precise receptor recognition
↔
Ordered amyloid assembly

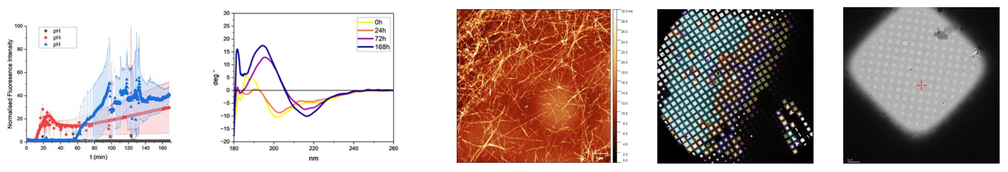


The role of molecular environment

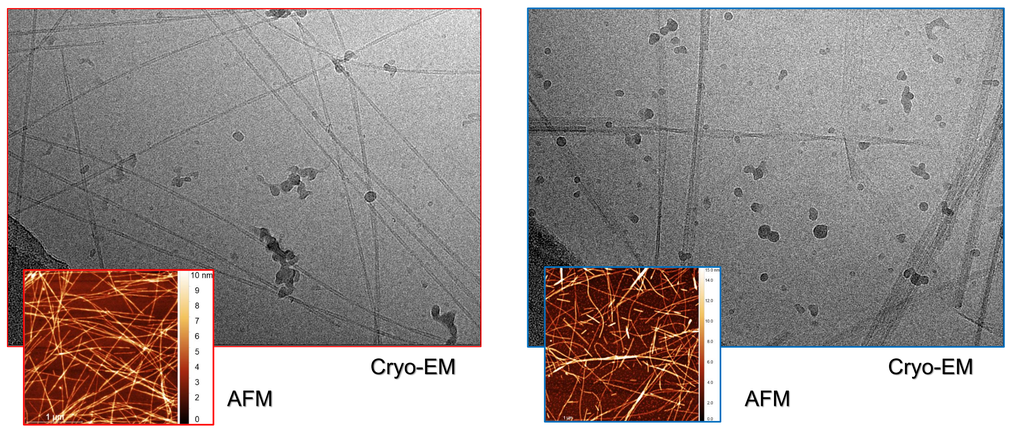
Amyloid formation is not determined **by sequence alone**. The conformational landscape of a peptide and the interactions between assembling molecules are strongly **influenced** by their **molecular environment**. In secretory granules, for example, pH, ionic strength, and macromolecular components create conditions that can profoundly alter the balance between soluble and assembled states.

Understanding this environment-dependent structural landscape is **essential for distinguishing** functional and regulated self-assembly from uncontrolled aggregation.

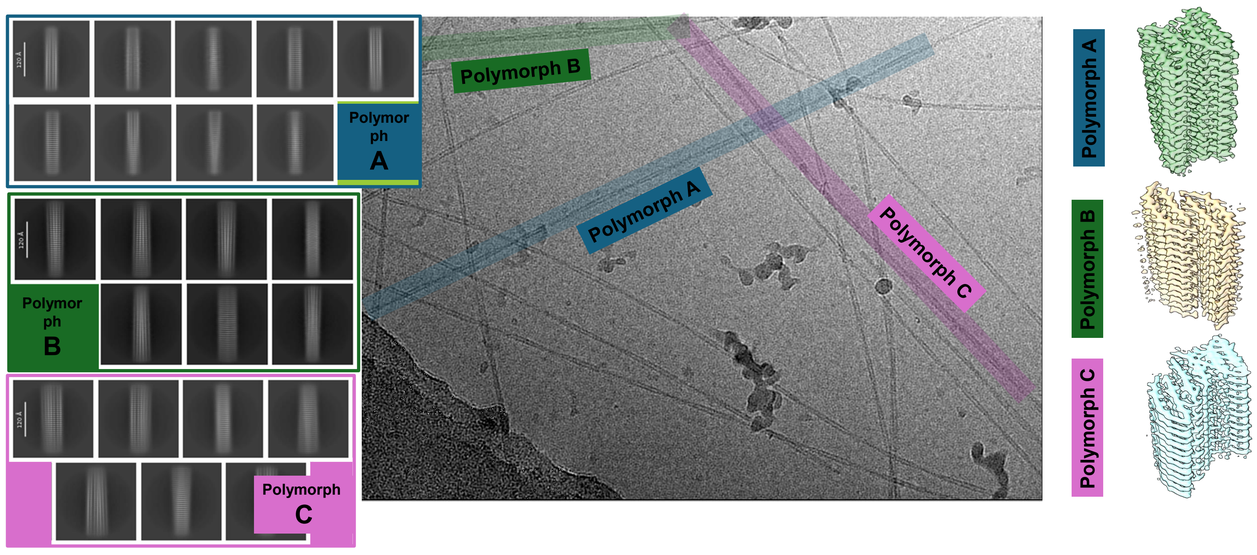
peptide	pH	c_{NaCl}	Agitation-period	dilution
GLP-1	A or B	0mM	168h	1x



Sample A (pH A) ⟷ **Sample B (pH B)**







From Aggregation to Function

Amyloid architecture can be both stable and reversible. Our results show that this apparent paradox is resolved at the level of higher-order interface organization. Functional amyloids are therefore not failed soluble proteins, but programmable molecular reservoirs

