Catalytic DNA Degradation by Pancreatic β-cell Peptide Hormone: A New Pathway Towards Amylin Pathology

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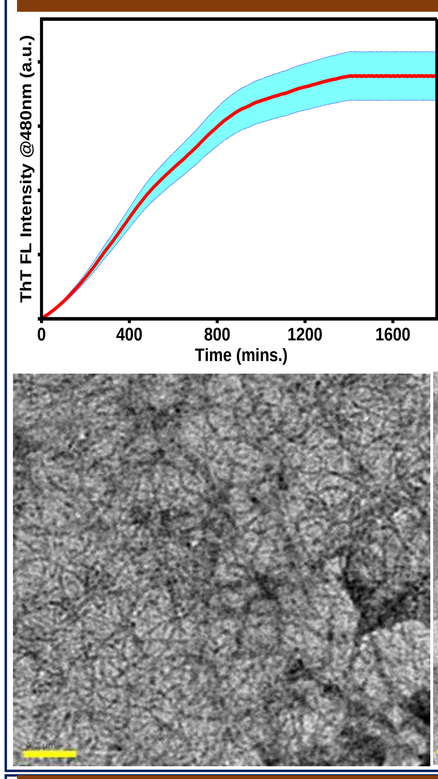
Motivation

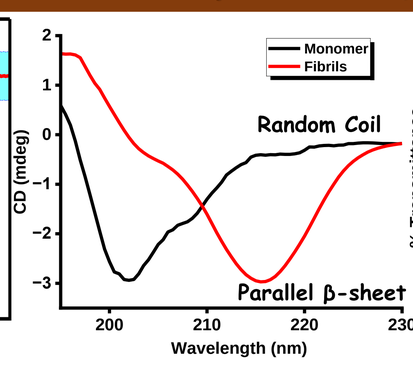
- Amylin or human islet amyloid polypeptide (hIAPP) is a 37 amino acid residue amyloidogenic hormone, co-secreted with Insulin from the β-cells of pancreas.
- Aggregation of Amylin to toxic amyloids is central to ~90% cases of T2DM causing β-cell death and consequent disease progression.
- DNA damage drives the dysfunction of pancreatic β-cells, senescence and deaths, in T1DM and T2DM.
- Important to envisage on the DNA damage ability of the Amylin fibrils as a possible mechanism of β-cell death and subsequent T2DM progression.

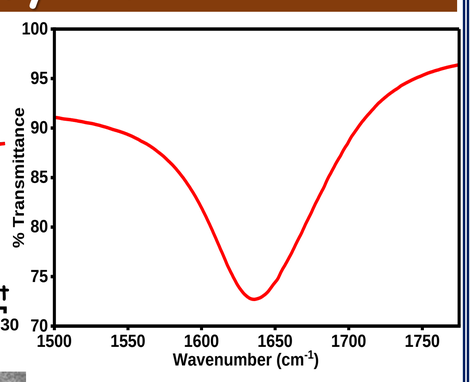
Objectives

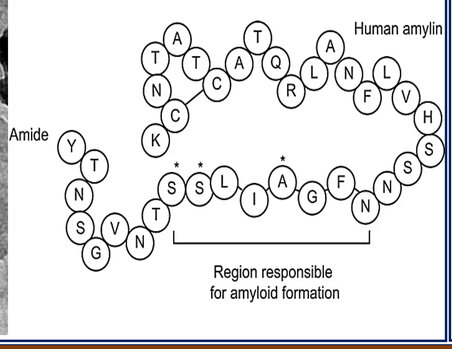
- Catalytic phosphodiester hydrolysis of the DNA model substrate bis(p-nitrophenyl) phosphate (BNPP) in diabetic mimic conditions (33mM glucose) by Amylin fibrils.
- Catalytic DNA degradation of a model single stranded DNA (ssDNA) and a model double stranded DNA (dsDNA) by Amylin fibrils.
- Theoretical validation of the binding and degradation by MD Simulation.
- The ability of the Amylin fibrils to induce replication slowdown in yeast cells using a CFP-tagged hIAPP overexpressed yeast plasmid (IAPP-CFP).

Characterization of the Amylin Fibrils

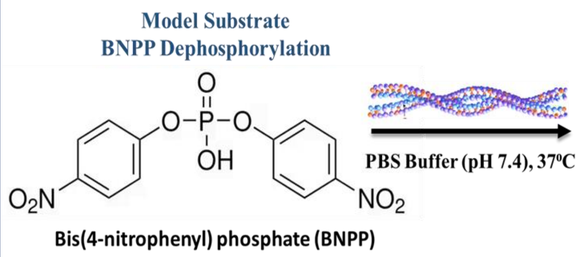


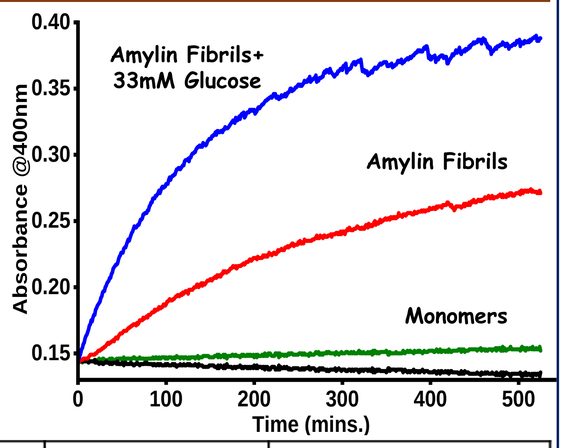


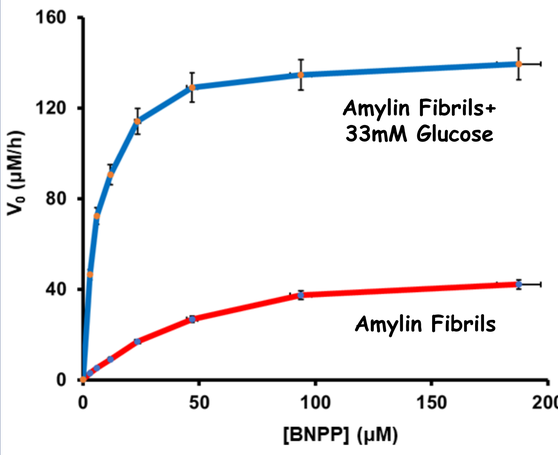




Phosphodiester Hydrolysis (DNAse mimic)





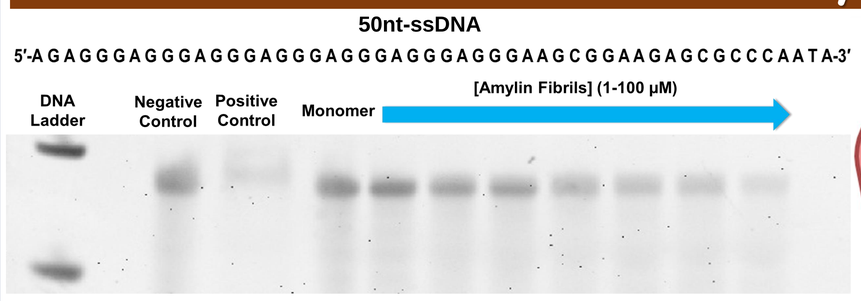


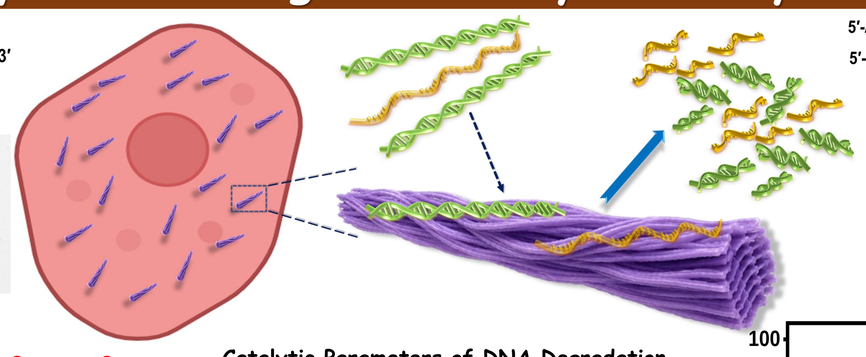
	– Glucose	+ Glucose
V_{max} (μM/h)	55 ± 2	144 ± 0.8
k_M (μM)	50 ± 5	6 ± 0.3
k_{cat} (s^{-1})	$9x10^{-4}$ ± $3x10^{-5}$	$3x10^{-3}$ ± $1x10^{-5}$
ε (Mol^{-1} s^{-1})	18 ± 0.7	502 ± 4

Catalytic DNA Degradation by the Amylin Fibrils

50nt-ssDNA

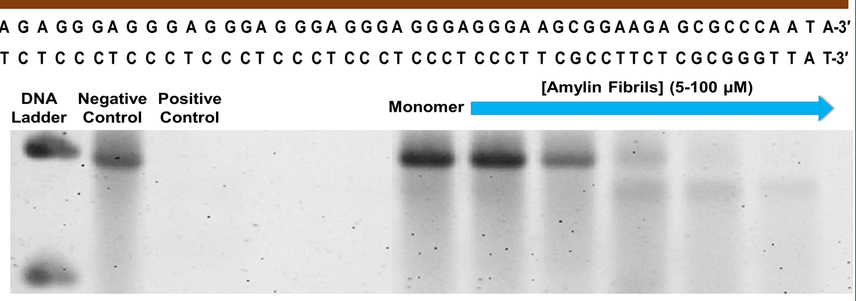
5′-A G A G G G A G G G A G G G A G G G A G G G A G G G A G G G A A G C G G A A G A G C G C C C A A T A-3′

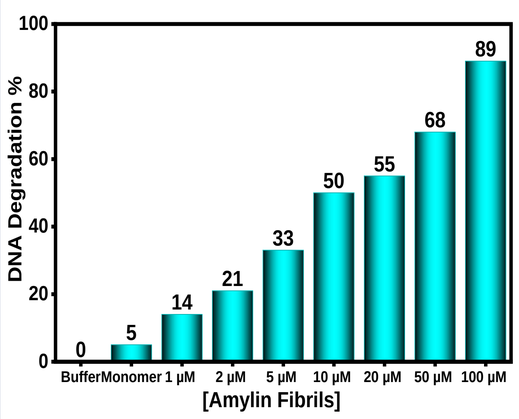


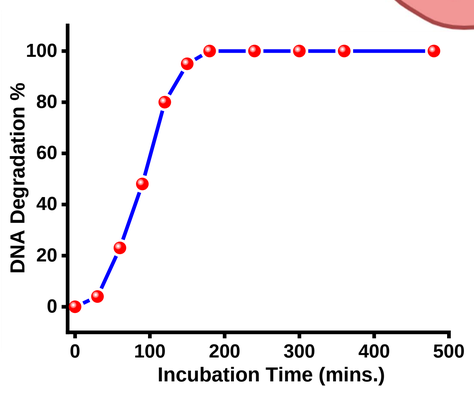


5′-A G A GG GA G G G A G GGA G GGA GGGA GGGAGGGA A GCGGAAGA GCGCCCA A T A-3′

5′-T C T C C CT C C C T C C CT C C CT CC CT CCCT CCCT T CGCCTTCT CGCGGGT T A T-3′

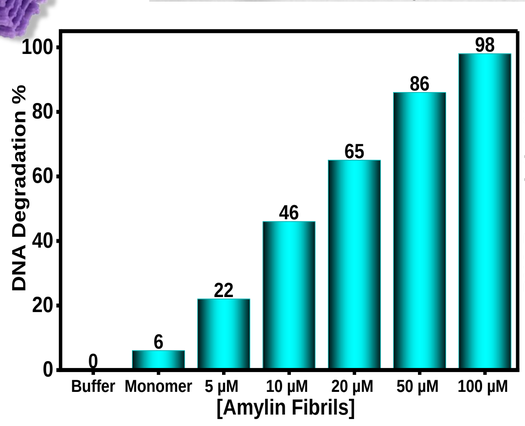


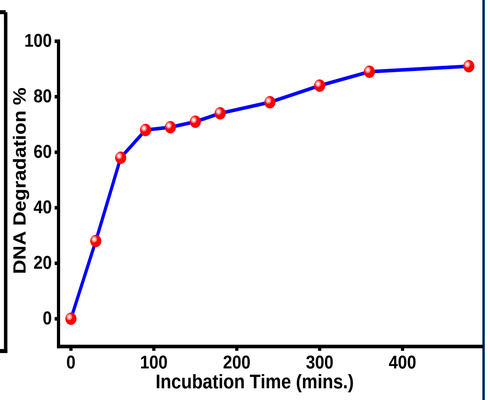




Catalytic Parameters of DNA Degradation
(Pseudo-first order MM kinetics)

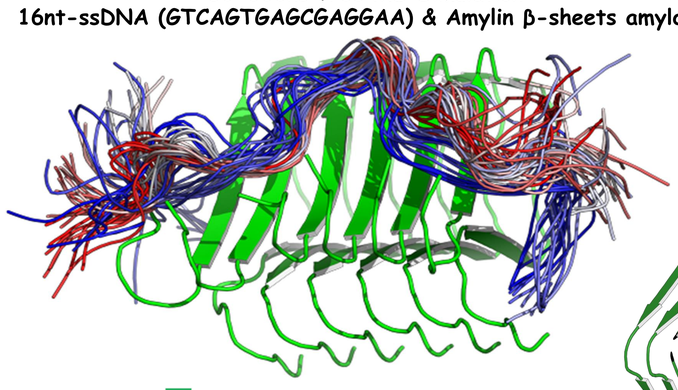
	ssDNA	dsDNA
K_M (μM)	71 ± 5	16 ± 4
K_{cat} (h^{-1})	$3x10^{-1}$ ± $2x10^{-5}$	$7x10^{-1}$ ± $3x10^{-5}$
ε (Mol^{-1} s^{-1})	13 ± 0.7	12 ± 0.4

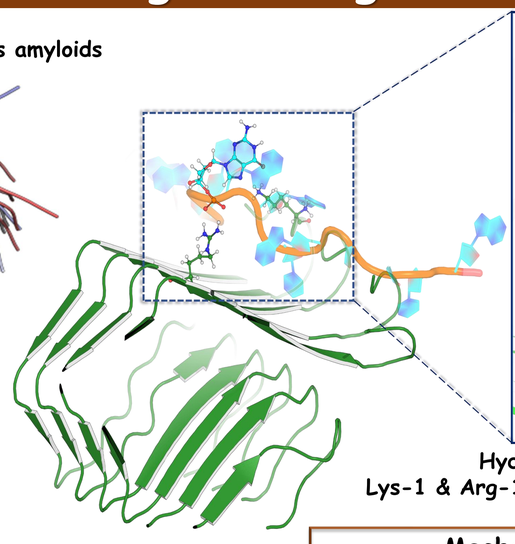


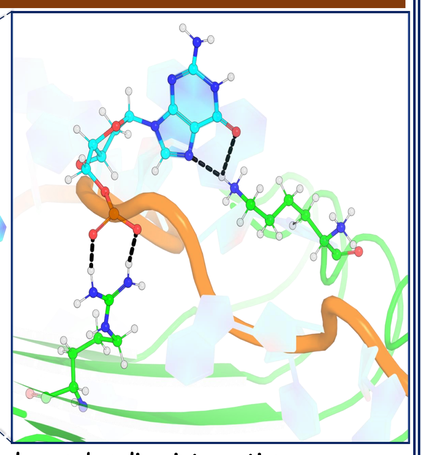


Validation of Binding and Degradation

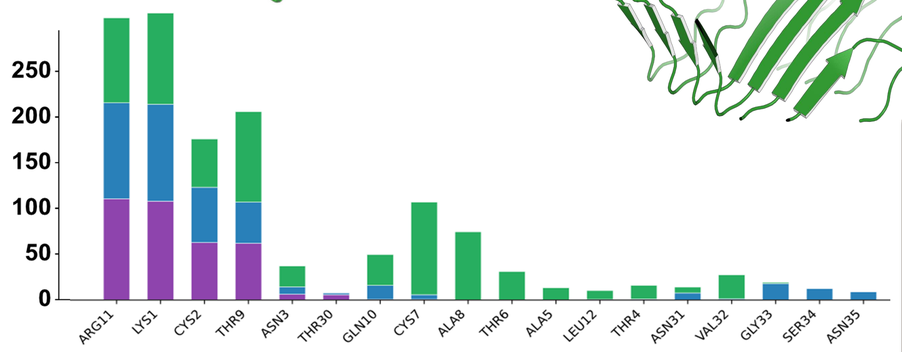
50-300ns free MD Simulation
16nt-ssDNA (GTCAGTGAGCGAGGAA) & Amylin β-sheets amyloids







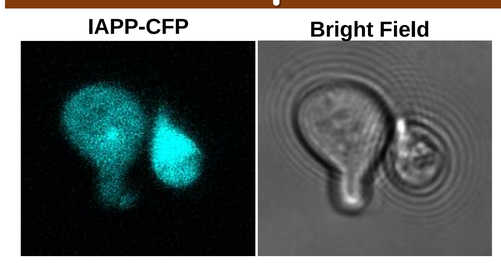
Hydrogen bonding interaction
Lys-1 & Arg-11 with phosphate backbone of DNA



Mechanism of Degradation

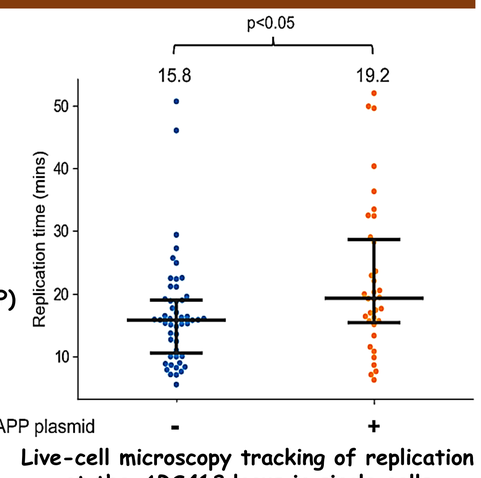
- The guanidinium group (of ARG11) binds and polarizes the negatively charged DNA phosphate
- A water molecule initiates a nucleophilic attack on the phosphate
- Resulting in DNA cleavage

DNA Replication Slowdown in Yeast



Confocal microscopy images of yeast cells expressing human IAPP fused to CFP (IAPP-CFP)

- Replication fork progression is monitored by quantifying the duplication of *lacOx128* and *tetOx160* arrays, located downstream of *ARS413*
- Replication time represents the time delay between the duplication of the lacO and tetO arrays



Live-cell microscopy tracking of replication at the *ARS413* locus in single cells expressing IAPP (+) and in control cells (–)

Conclusions:

- Toxic Amylin amyloid fibrils can catalyze BNPP hydrolysis.
- Catalytic activity is enhanced in diabetic mimic condition.
- They can catalytically damage DNA.
- Due to H-bonding of Arg 11 & Lys1 residues with DNA.
- Amylin fibrils can slowdown DNA replication in yeast cells.
- Catalytic DNA degradation by Amylin fibrils is a new pathway towards Amylin pathology

Acknowledgement:

SCAN ME!