Amyloid-β aggregation affected by Oxidized Aβ

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Role of Amyloid-β in Alzheimer's Disease

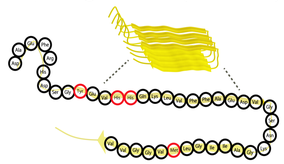
Altzheimer's disease (AD)

- Age-related disease destroys brain cells.
- It is difficult to predict the development of AD.
- In 2050, 16% of people older than 65 will suffer from AD.

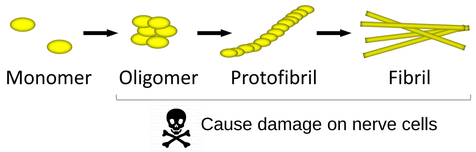
Healthy Brain AD's brain

Amyloid beta (Aβ)

- Aβ is observed as the dominant component in AD patients' brain.
- Aβ monomers aggregate into oligomers, protofibrils, and fibrils.
- Aβ oligomers (soluble) Aβ fibrils (insoluble) are toxic

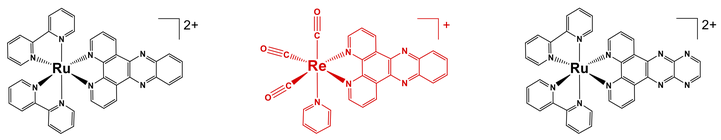


$Aβ_{40}$ peptide



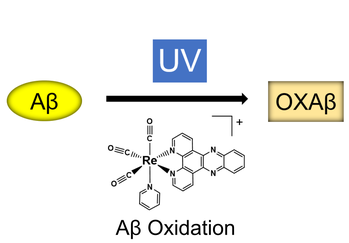
Metal Complex as a Probe of Aβ Aggregation

- Metal complexes have been developed as the probes of Aβ aggregation.
- The advantages: red fluorescence, large Stokes shifts, relatively long lifetime.

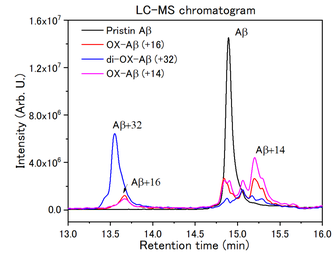


$[Ru(bpy)_2(dppz)]^{2+}$ $[Re(CO)_3(dppz)(Py)]^{+}$ $[Ru(bpy)_2(dpqp)]^{2+}$

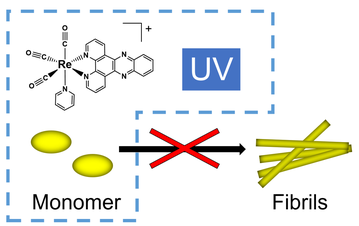
- Aβ can be oxidized by $[Re(CO)_3(dppz)(Py)]^{+}$ upon UV irradiation.



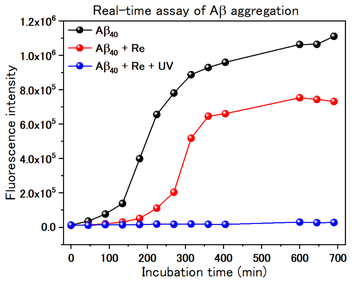
Aβ Oxidation



- In the presence of $[Re(CO)_3(dppz)(Py)]^{+}$, after UV irradiation, $Aβ_{40}$ monomers do not show aggregation.

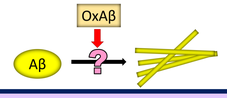


Inhibition of Aβ aggregation



Research Goal

Investigate the inhibition effect of Aβ aggregation by OXAβ.



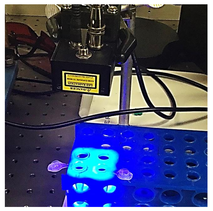
Sample Preparation and Real Time Assay

Aβ samples preparation

- Purify $Aβ_{40}$ and $Aβ_{42}$ by HPLC.
- Measure the concentration by UV-Vis spectrometer.

OXAβ preparation

- Irradiate Aβ monomers by 365 nm UV light in the presence of $[Re(CO)_3(dppz)(Py)]^{+}$
- Use PD10 column to remove Re complexes
- Use HPLC to separate OXAβ



UV irradiation for oxidation

Real time assay

- Use thioflavin T (ThT) to detect the aggregation of Aβ.
- Incubate Aβ sample at 37 ℃, 700 rpm.
- Monitor the fluorescence of ThT every 45 min.

Two experiments:

1) Monitor the $Aβ_{42}$ aggregation

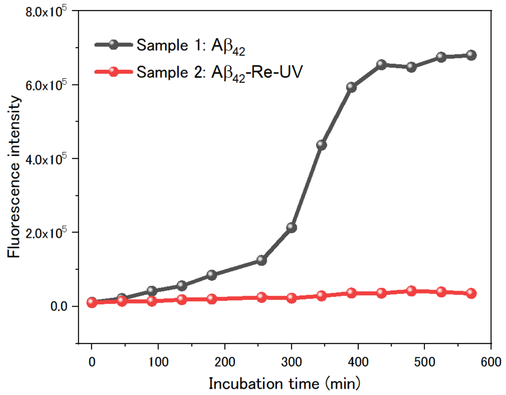
	$Aβ_{42}$	ThT	NaCl	Re	UV
Sample 1	50 μM	20 μM	20 mM		
Sample 2	50 μM	20 μM	20 mM	20 μM	3 min

2) Monitor the aggregation of $Aβ_{40}$-OXAβ mixture

	$Aβ_{40}$	OXAβ	ThT	NaCl
Sample 3	50 μM		20 μM	20 mM
Sample 4	37.5 μM	12.5 μM	20 μM	20 mM
Sample 5		50 μM	20 μM	20 mM

Real Time Assay Results

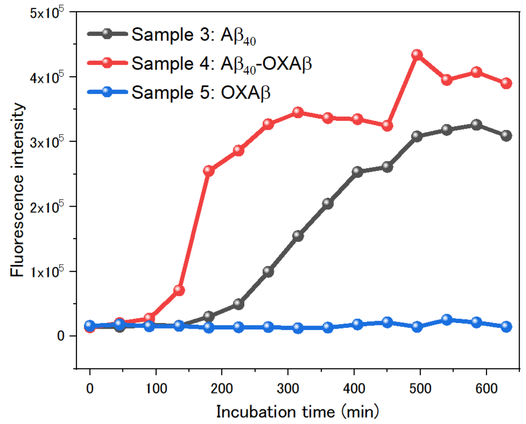
1) Real time assay of $Aβ_{42}$



Excitation = 440 nm
Emission = 450 - 500 nm

- In the presence of $[Re(CO)_3(dppz)(Py)]^{+}$ after UV irradiation for 3 min, $Aβ_{42}$ does not aggregate.

2) Real time assay of $Aβ_{40}$-OXAβ mixture



- Pure $Aβ_{40}$ does aggregate.
- Pure OXAβ does not aggregate.

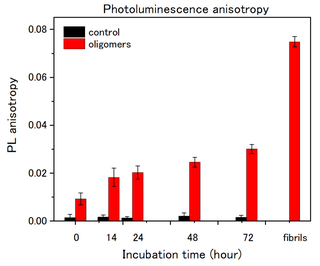
Discussion & Future Work

Discussion

- $[Re(CO)_3(dppz)(Py)]^{+}$ can prevent the $Aβ_{42}$ aggregation with UV irradiation
- OXAβ itself does not aggregate.
- The interaction between OXAβ and Aβ is still not clear.

Future Work

- Do real time assay of different samples(e.g. $Aβ_{42}$ with OXAB)
- Discover the mechanism that Aβ aggregation is inhibited.
- Monitor the oligomerization of $Aβ_{42}$ by anisotropy measurement.
- Investigate the inhibition effect of $Aβ_{42}$ oligomerization.



Reference & Acknowledgement

1. Aliyan, A., Kirby, B., Pennington, C. and Martí, A.A. "Unprecedented Dual Light-Switching Response of a Metal Dipyridophenazine Complex toward Amyloid-β Aggregation" Journal of The American Chemical Society, 2016, 138, 8686.
2. Aliyan, A.; Paul, T. J.; Jiang, B.; Pennington, C.; Sharma, G.; Prabhakar, R.; Martí, A. A. " Photochemical Identification of Molecular Binding Sites on the Surface of Amyloid-β Aggregates", CHEM, 2017, 3, 898-912.

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