M35 oxidation induces Aβ40-like Structrual and Dynamical changes in Aβ42

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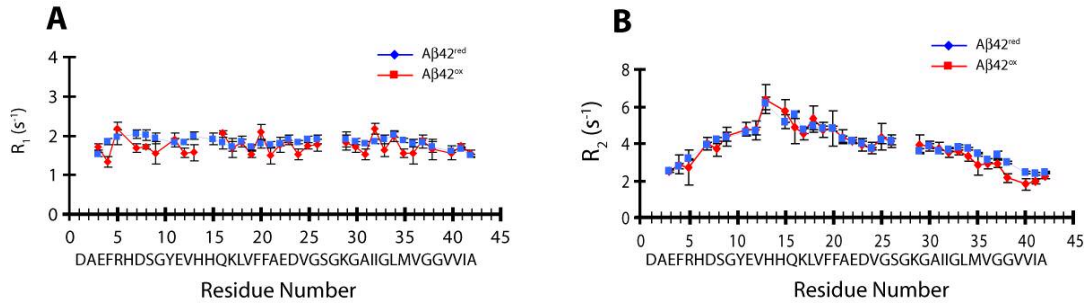
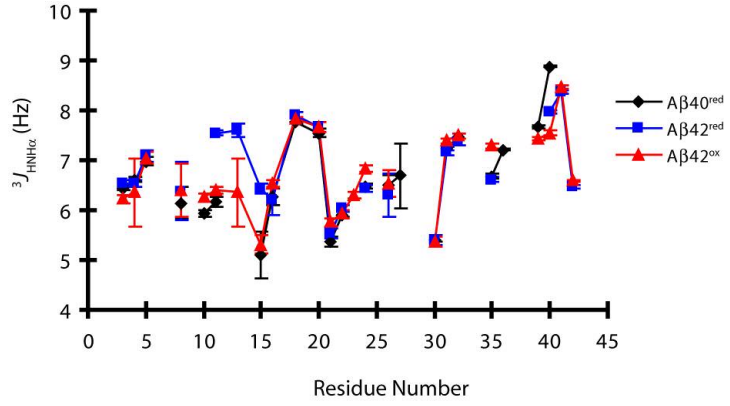
Supporting figure1



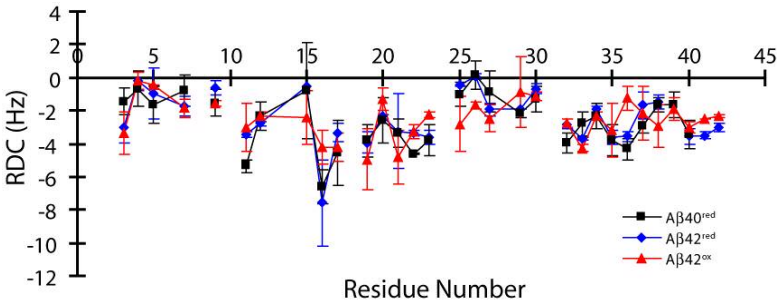
Supporting figure 1. R_1 (A) and R_2 (B) indicated that Aβ42^{red} and Aβ42^{ox} monomers have similar global motions. Aβ42^{ox} displays a slight decrease of R_2 values towards the C-terminus suggesting enhanced mobility.

Supporting figure2



Supporting figure 2. $^3J_{HNH\alpha}$ values comparison of Aβ40^{red}, Aβ42^{red}, and Aβ42^{ox}. Residues E11 and Q15 of Aβ42^{red} has a bigger $^3J_{HNH\alpha}$ values than those of Aβ40^{red}. After M35 oxidation, Aβ42^{ox} displays decrease of J-coupling values of those two residues as compared to Aβ42^{red}.

Supporting figure3



Supporting figure 3. RDC comparison of Aβ in 10% polyacrylamide gels with a stretch ratio d_o/d_N of 1.29. The overall pattern of RDC is similar between Aβ40^{red}, Aβ42^{red}, and Aβ42^{ox}. The C-terminus of Aβ42^{ox} displays a slight decrease in the absolute value of RDC as compared to that of Aβ42^{red}, consistent with the increased dynamics and less structure towards the C-terminus upon M35 oxidation. S26 and V36 also show significant differences in RDC between Aβ42^{red} and Aβ42^{ox}. The RDC was measured with 30 μM Aβ (pH 7.2) using IPAP-HSQC pulse sequence at 273.3 K. Errors were estimated from three measurements. The potential differences in alignment magnitude of individual Aβ40^{red}, Aβ42^{red}, and Aβ42^{ox} samples in stretched gel are corrected by preparing samples of Aβ40^{red}/ Aβ42^{red} monomer mixture and Aβ40^{red}/ Aβ42^{ox} monomer mixture. The scaling factors were obtained by comparing the RDC of V40 in all samples and were found to be close to 1.

Supporting table 1.

^{15}N relaxation data of Aβ42^{ox}

Residue	R_1 (s^{-1})	ΔR_1 (s^{-1})	R_2 (s^{-1})	ΔR_2 (s^{-1})	NOE	ΔNOE	$J(0.87\omega_H)$ (ns)	$\Delta J(0.87\omega_H)$ (ns)
3	1.72	0.08	2.51	0.07	0.16	0.03	0.023	0.001
4	1.3	0.1	2.9	0.5	0.26	0.02	0.015	0.002
5	2.2	0.2	2.7	0.9	0.38	0.03	0.021	0.002
7	1.7	0.1	4.0	0.3	0.44	0.04	0.015	0.001
8	1.71	0.06	3.7	0.4	0.56	0.07	0.012	0.002
9	1.6	0.3	4.4	0.5	0.57	0.06	0.010	0.002
11	1.9	0.2	4.8	0.4	0.5	0.1	0.014	0.004
12	1.6	0.1	4.7	0.5	0.5	0.1	0.013	0.003
13	1.6	0.2	6.4	0.8	0.56	0.05	0.011	0.002
16	2.08	0.05	4.9	0.8	0.41	0.05	0.015	0.001
17	1.7	0.2	4.5	0.3	0.48	0.08	0.014	0.003
18	1.8	0.1	5.3	0.7	0.6	0.1	0.012	0.003
19	1.52	0.08	4.7	0.4	0.44	0.09	0.013	0.002
20	2.1	0.2	4.8	0.9	0.46	0.06	0.015	0.002
21	1.5	0.2	4.4	0.4	0.50	0.08	0.012	0.003
22	1.8	0.2	4.2	0.2	0.40	0.02	0.016	0.002
23	1.9	0.1	3.9	0.3	0.37	0.03	0.019	0.001
24	1.5	0.1	3.8	0.3	0.50	0.06	0.012	0.002
25	1.74	0.09	4.4	0.7	0.43	0.02	0.015	0.001
26	1.8	0.2	4.1	0.3	0.41	0.01	0.016	0.001
29	1.8	0.2	4.0	0.5	0.47	0.04	0.015	0.002
30	1.7	0.1	3.9	0.3	0.46	0.03	0.014	0.001
31	1.5	0.1	3.8	0.3	0.41	0.09	0.014	0.002
32	2.2	0.1	3.5	0.3	0.33	0.08	0.017	0.003
33	1.6	0.2	3.6	0.2	0.47	0.06	0.013	0.002
34	2.0	0.1	3.3	0.3	0.38	0.08	0.017	0.003
35	1.5	0.1	2.8	0.5	0.40	0.04	0.014	0.001
36	1.6	0.3	2.9	0.3	0.34	0.05	0.016	0.003
37	1.9	0.1	2.9	0.2	0.32	0.08	0.020	0.003
38	1.7	0.3	2.1	0.2	0.36	0.02	0.017	0.003
40	1.6	0.2	1.8	0.3	0.14	0.06	0.021	0.003
41	1.75	0.06	2.0	0.1	0.22	0.05	0.021	0.001
42	1.55	0.08	2.3	0.2	-0.37	0.06	0.033	0.002

Supporting table 2.

^{15}N relaxation data of Aβ42^{red}

Residue	R_1 (s^{-1})	ΔR_1 (s^{-1})	R_2 (s^{-1})	ΔR_2 (s^{-1})	NOE	ΔNOE	$J(0.87w_H)$ (ns)	$\Delta J(0.87w_H)$ (ns)
3	1.52	0.06	2.53	0.09	0.31	0.02	0.0175	0.0008
4	1.86	0.08	2.8	0.1	0.32	0.03	0.019	0.001
5	2.0	0.2	3.16	0.06	0.42	0.03	0.0158	0.0008
7	2.0	0.1	3.9	0.1	0.43	0.03	0.0147	0.0009
8	2.0	0.1	4.2	0.2	0.62	0.07	0.01	0.002
9	1.9	0.1	4.4	0.2	0.57	0.04	0.012	0.001
11	1.8	0.1	4.6	0.2	0.45	0.08	0.014	0.002
12	1.83	0.08	4.7	0.2	0.44	0.01	0.0138	0.0006
13	2.0	0.1	6.2	0.4	0.58	0.05	0.01	0.002
16	1.8	0.2	5.6	0.2	0.52	0.05	0.012	0.001
17	1.7	0.1	4.7	0.2	0.50	0.03	0.0117	0.0009
18	1.9	0.1	4.9	0.2	0.52	0.01	0.0114	0.0005
19	1.71	0.07	4.8	0.1	0.51	0.01	0.011	0.0008
20	1.8	0.1	4.8	0.1	0.52	0.06	0.011	0.002
21	1.77	0.08	4.2	0.2	0.52	0.03	0.011	0.001
22	1.80	0.06	4.14	0.09	0.34	0.02	0.015	0.0005
23	1.91	0.09	4.0	0.1	0.53	0.06	0.012	0.002
24	1.83	0.04	3.73	0.04	0.44	0.03	0.0131	0.0006
25	1.90	0.08	4.2	0.2	0.52	0.05	0.013	0.001
26	1.9	0.1	4.1	0.2	0.51	0.06	0.012	0.002
29	1.9	0.2	3.6	0.1	0.46	0.03	0.0143	0.0008
30	1.85	0.08	3.9	0.1	0.51	0.05	0.013	0.001
31	1.80	0.05	3.6	0.1	0.55	0.03	0.0112	0.0008
32	1.86	0.06	3.66	0.07	0.35	0.03	0.016	0.001
33	1.9	0.1	3.8	0.1	0.48	0.02	0.0142	0.0006
34	2.02	0.07	3.72	0.06	0.46	0.05	0.014	0.001
35	1.88	0.06	3.49	0.06	0.50	0.03	0.0134	0.0009
36	1.81	0.08	3.1	0.1	0.31	0.02	0.0176	0.0006
37	1.8	0.1	3.4	0.2	0.50	0.07	0.014	0.002
38	1.7	0.1	2.97	0.07	0.40	0.01	0.016	0.0006
40	1.61	0.02	2.43	0.05	0.47	0.02	0.0133	0.0005
41	1.67	0.05	2.37	0.05	0.40	0.04	0.015	0.001
42	1.49	0.05	2.43	0.05	-0.27	0.06	0.03	0.002

Supporting table 3

Methyl dynamics of Aβ42

	Aβ42^{ox}						Aβ42^{red}	
Residue	S^2_{axis}	ΔS^2_{axis}	R_1 (s^{-1})	ΔR_1 (s^{-1})	Γ (s^{-1})	$\Delta\Gamma$ (s^{-1})	S^2_{axis}	ΔS^2_{axis}
V12γ	0.66	0.02	2.48	0.07	1.87	0.05	0.58	0.04
V12γ'	0.69	0.02	3.1	0.2	1.89	0.06	0.61	0.03
L17δ	0.31	0.01	2.5	0.1	0.86	0.03	0.3	0.03
L17δ'	0.51	0.01	2.37	0.07	1.46	0.04	0.33	0.02
V18γ	0.68	0.01	2.36	0.06	1.95	0.04	0.45	0.03
V18γ'	0.82	0.02	3.2	0.2	2.25	0.05	0.67	0.03
V24γ	0.49	0.01	2.2	0.1	1.4	0.03	0.51	0.01
V24γ'	0.402	0.006	2.31	0.06	0.93	0.03	0.48	0.02
I31γ	0.59	0.02	2.21	0.06	2	0.05	0.51	0.01
L34δ	0.36	0.02	2.6	0.1	0.99	0.04	0.43	0.04
L34δ'	0.34	0.01	2.33	0.04	0.95	0.04	0.33	0.03
M35ε	0.17	0.03	1.1	0.3	0.5	0.07	0.073	0.007
V36γ	0.33	0.01	2.37	0.05	1.13	0.02	0.35	0.02
V39γ	0.414	0.004	2.67	0.02	1.14	0.01	0.43	0.01
V40γ	0.36	0.01	3.1	0.1	0.94	0.03	0.36	0.02
V40γ'	0.36	0.01	2.95	0.09	0.94	0.03	0.34	0.03
I41δ	0.34	0.01	1.17	0.04	1.01	0.04	0.38	0.02
A42β	0.224	0.006	2.2	0.03	0.61	0.02	0.24	0.01

Note: The stereospecific assignments of the methyl groups of Leu and Val were not known and were arbitrarily named as, δ and δ', and γ and γ', respectively.

Supporting table 4

Aβ42 Methyl groups with significant changes after M35 oxidation and their comparison with Aβ40.

	S^2_{axis}		
Residue	$A\beta42^{red}$	$A\beta42^{ox}$	$A\beta40^{red}$
L17δ'	0.33 ± 0.02	0.51 ± 0.01	0.43 ± 0.01
V18γ	0.45 ± 0.03	0.68 ± 0.01	0.72 ± 0.01
V18γ'	0.67 ± 0.03	0.82 ± 0.02	0.79 ± 0.01
V24γ'	0.48 ± 0.02	0.402 ± 0.006	0.362 ± 0.004
I31γ	0.51 ± 0.01	0.59 ± 0.02	0.64 ± 0.01
L34δ	0.43 ± 0.04	0.36 ± 0.02	0.43 ± 0.01

NMR relaxation measurement:

The backbone ^{15}N R_1, R_2, and ss-NOE of Aβ42^{ox} monomer were measured at 273.3 K on a Bruker 800 MHz spectrometer equipped with a cryogenic probe in an interleaved manner and side chain methyl dynamics of Aβ42^{ox} monomer were measured at 273.6 K as described.[1-3] For ^{15}N relaxation measurements, delays (t) are 100, 200, 300, 400, 500, 600, and 700 ms for R_1, and 44, 84, 164, 204, 244, 324, and 404 ms for R_2. NOE values were measured by interleaving the proton-saturation experiment and no-proton-saturation experiment at each t_1 point. Recycle delay was 3 s and proton saturation was achieved by applying 120 degree proton pulse at 5 ms delay. For ^{13}C relaxation measurements, delays were set to 50, 100, 200, 300, 400, and 500 ms for R_1 measurement. The dipole-dipole cross-correlated relaxation rate (Γ) was obtained with the relaxation delays set to 0.6, 1.2, 1.8, 2.4, 3.0, 3.6, 4.2, 4.8, 5.4, 6.4, 7.2, 8.0, 10, 12, 14, 16, 18, and 20 ms. Data were processed with NMRPipe and Sparky. Methyl order parameters were extracted from the ^{13}C relaxation rate R_1 and dipole-dipole cross-correlated relaxation rates (Γ) assuming the global correlation time $\tau_m = 4$ ns.

Reference

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(3) Zhang, X.; Sui, X.; Yang, D. *J Am Chem Soc* **2006**, *128*, 5073-81.