Electronic supplementary information (ESI)

Internalized Compartments Encapsulated Nanogels for Targeted Drug Delivery

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Experimental section

Synthesis of methacrylate HA (*m*-HA)

m-HA was synthesized following the previous reported reference[1]. Briefly, 1.0 g of HA was dissolved in 50 mL of DI water at 4 ^{o}C, and then 0.8 mL of methacrylic anhydride (MA) was dropwise added. The reaction solution was kept at pH 8 - 9 by the addition of 5N NaOH and stirred at 4 ^{o}C for 24 h. After precipitation in acetone, the resulting polymer was washed 3 times with ethanol, re-dissolved in DI water, and then dialyzed against DI water for 48 h. *m*-HA was achieved by lyophilization with a yield of 87.5 %. The degree of modification was calculated to be 15 % by comparing the ratio of the areas under the proton peaks at 5.74 and 6.17 ppm (methacrylate protons) to the peak at 1.99 ppm (*N*-acetyl glucosamine of HA) after performing a standard deconvolution algorithm to separate closely spaced peaks. *m*-HA: 1H NMR (D_2O, 300 MHz, δ ppm): 1.85-1.96 (m, 3H, CH_2=C(CH_3)CO), 1.99 (s, 3H, NHCOCH_3), 5.74 (s, 1H, CH^1H^2=C(CH_3)CO), 6.17 (s, 1H, CH^1H^2=C(CH_3)CO).

Synthesis of rhodamine-HA derivative

m-HA (120 mg) was mixed with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) (50 mg/30 mg) for the activation of carbonyl groups on HA in pH 5.0 acetic buffer for 30 min, followed by additional 1,6-diaminohexane (60 mg) for another 4 h. The mixture was precipitated in 2-propanol (IPA) to remove unreacted diamine. The HA-amine derivative was reacted with rhodamine-NHS (0.4 mg) in sodium bicarbonate solution (50 mM; pH=8.5) for 4 h and precipitated in acetone to remove the unreacted rhodamine. The resulting rhodamine-HA derivative was dissolved in DI water.

Reference

1. J. Yu, Y. Zhang, Y. Ye, R. DiSanto, W. Sun, D. Ranson, F. S. Ligler, J. B. Buse and Z. Gu, *Proc Natl Acad Sci*, 2015, **112**, 8260-8265.

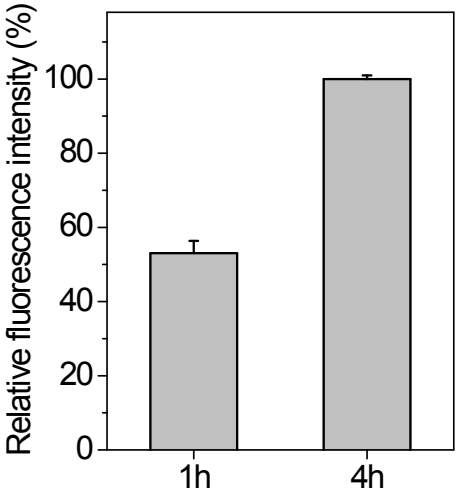

Fig. S1 Relative fluorescence intensity of DOX-EM-NGs on HeLa cells after incubation of 1 h and 4 h determined by flow cytometry.