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Instructed-Assembly as Context-Dependent Nanoscale Signals for Death and Morphogenesis of Cells

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Context-dependent signaling, as a ubiquitous phenomenon in nature, is a dynamic molecular process at nano- and microscales, but how to mimic its essence using non-covalent synthesis in cellular environment has yet to be developed. Here we show a dynamic continuum of non-covalent filaments formed by instructed-assembly (iA) of a supramolecular phosphoglycopeptide (sPGP) as context-dependent signals for controlling death and morphogenesis of cells. Specifically, while enzymes (i.e., ectophosphatases) on cancer cells catalyze the formation of the filaments of the sPGP to result in cell death, damping the enzyme activity induces 3D cell spheroids. Similarly, relying on the ratio of stromal and cancer cells in a co-culture to modulate the expression of the ectophosphatase, the iA process enables cell spheroids. The spheroids act as a mimic of tumor microenvironment for drug screening. As the first demonstration of iA as multifunctional processes according to local enzyme activity for controlling cell behavior, this work illustrates context-dependent biological functions of non-covalent synthesis in cellular environment.

File list (2)

Instructed-Assembly as Context-Dependent Nanoscale Signals for Death and Morphogenesis of Cells

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Contents

1. Materials

Materials

Fmoc-OSu, Fmoc-amino acid with protected group on the side chain and 2-Cl-trityl chloride resin (1.0 mmol/g) were purchased from GL Biochem (Shanghai, China); N, N-diisopropylethylamine (DIPEA), HBTU, trimethylsilyl chloride and other chemical reagents and solvents were obtained from Fisher Scientific; alkaline phosphatase was purchased from Biomatik (Cat. No. A1130, alkaline phosphatase [ALP], >1300 U/mg, in 50% glycerol.). All chemical reagents and solvents were used as received from commercial sources without further purification. Water was purified using a Millipore system. Dulbecco's Modified Eagle's medium (DMEM) and McCoy's 5A medium obtained from ATCC, fetal bovine serum (FBS) and penicillin/streptomycin from Gibco by Life Technologies, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) from ACROS Organics. Cell culture related dishes, 96 cell well and confocal dish, were purchased from Corning Inc. Water Delta600 HPLC system, equipped with an XTerra C18 RP column, was used to purify the compound. LC-MS spectrum was obtained on Waters Acquity Ultra Performance LC with Waters MICROMASS detector, and ^{1}H-NMR spectra on Varian Unity Inova 400, and TEM images on Morgagni 268 transmission electron microscope. Carbon-coated copper grids (400 meshes) from Pacific Grid-Tech.

2. Supplementary figures

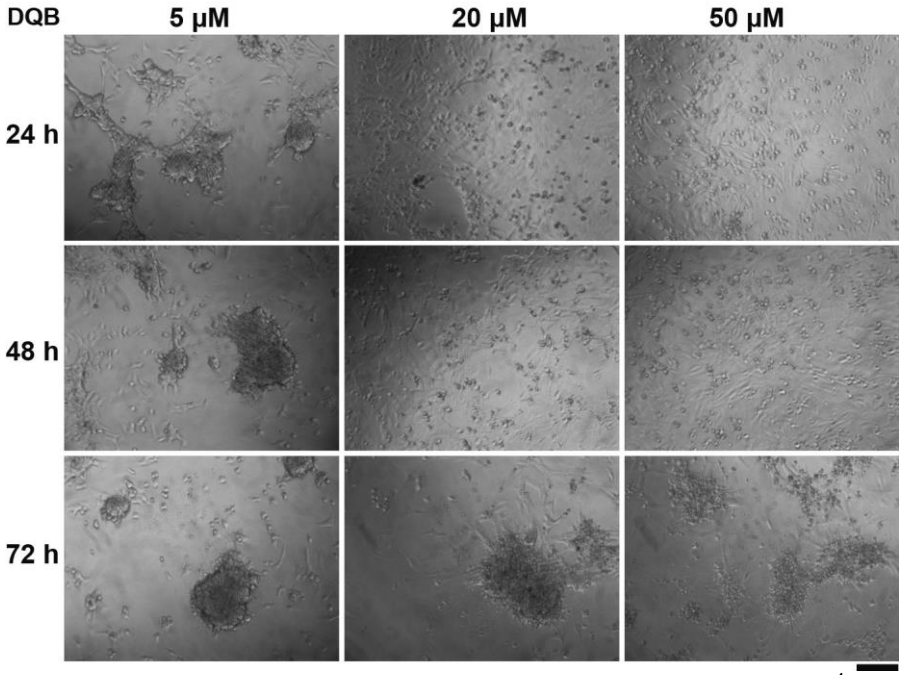

Figure S1. Optical microscopic images of Saos-2 cells at the density of 3×10^4 with the treatment of **1P:2** (300 μM) and different concentrations of DQB for 24, 48 or 72 h. Scale bar is 150 μm.

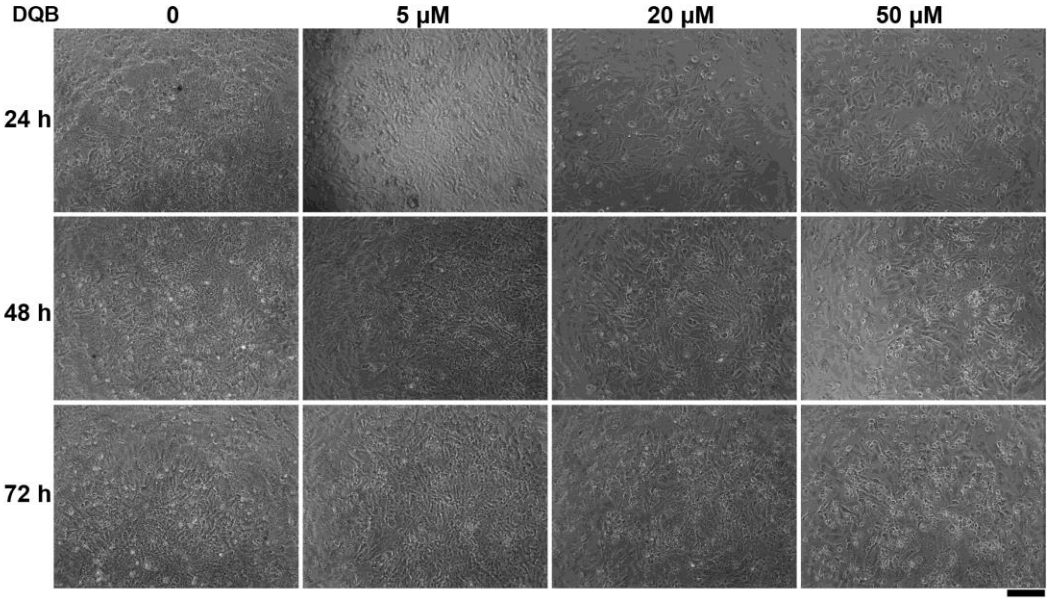

Figure S2. Optical microscopic images of Saos-2 cells at the density of 3×10^4 with the treatment of **1P** (300 μM) and different concentrations of DQB for 24, 48 or 72 h. Scale bar is 150 μm.

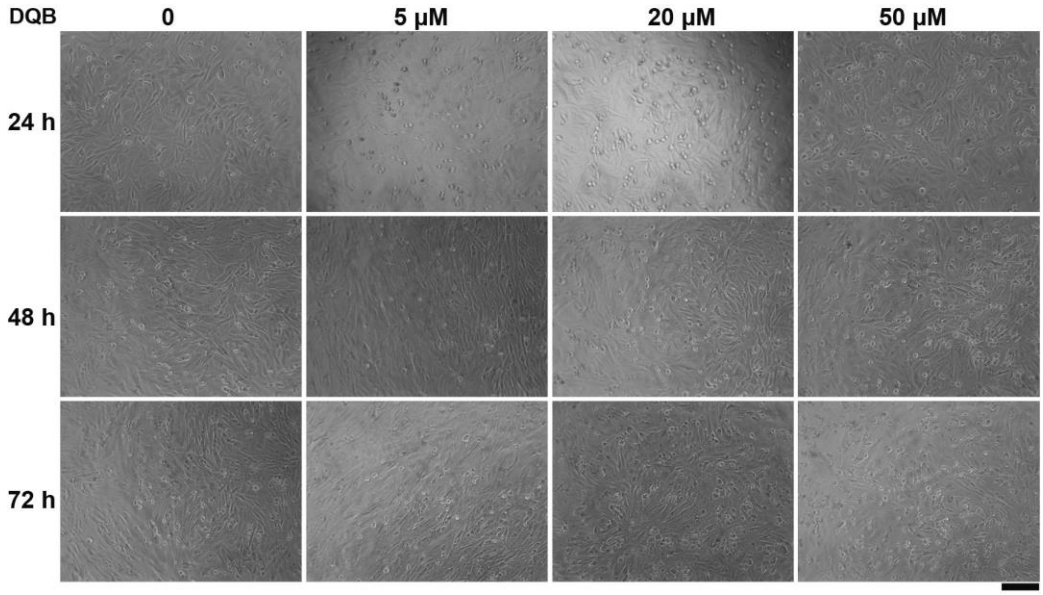

Figure S3. Optical microscopic images of Saos-2 cells at the density of 3×10^4 with the treatment of **2** (300 μM) and different concentrations of DQB for 24, 48 or 72 h. Scale bar is 150 μm.

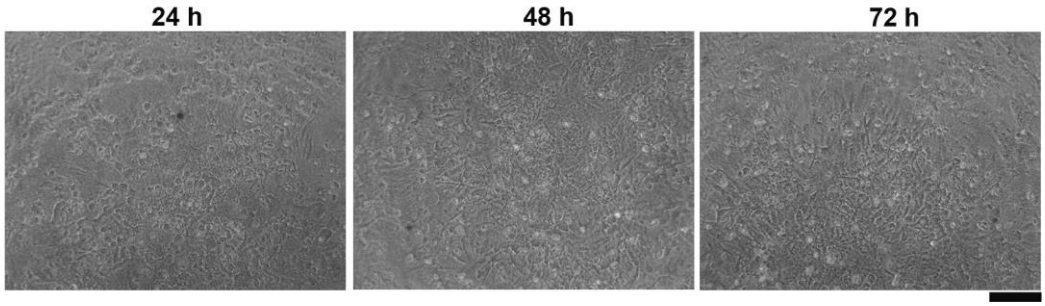

Figure S4. Optical microscopic images of Saos-2 cells at the density of 3×10^4 with the treatment of **1:2** (500 μM) for 24, 48 or 72 h. Scale bar is 150 μm.

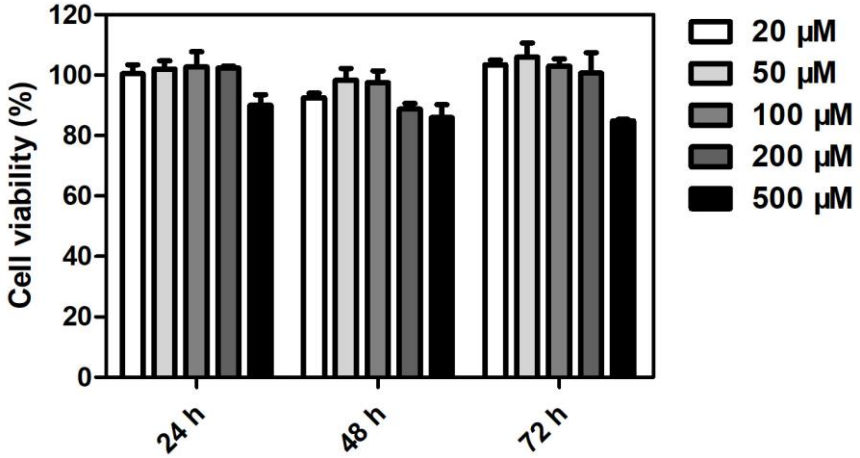

Figure S5. Cytotoxicity of **1:2** against Saos-2 cells for 24, 48 and 72 h.

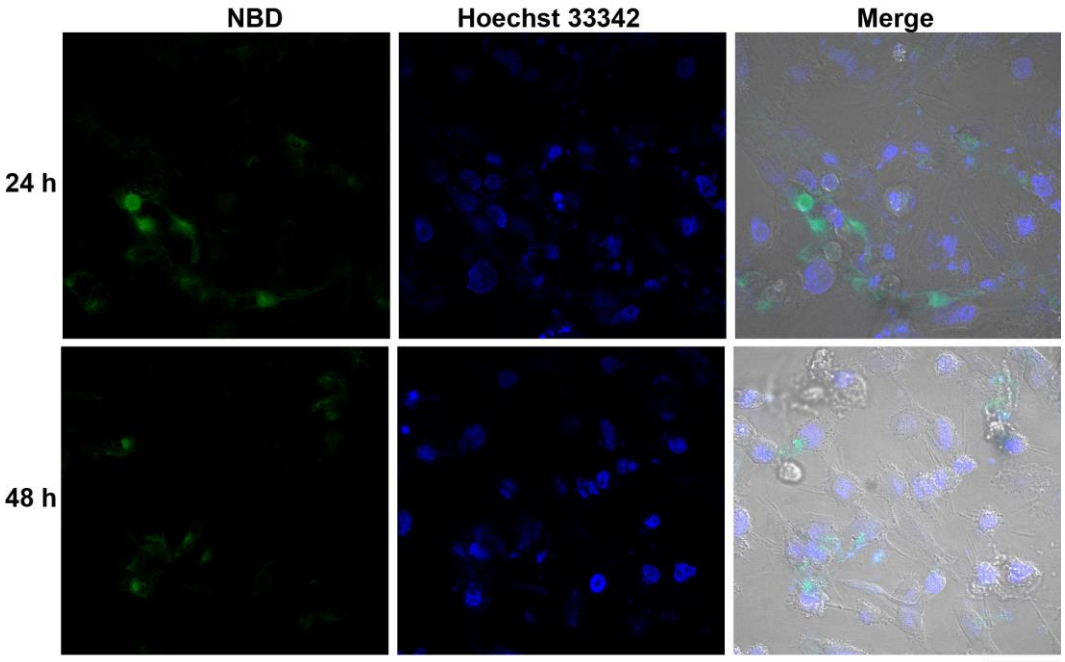

Figure S6. Confocal images of Saos-2 cells treated with **NBD-1P** (300 μM) for 24 and 48 h. Scale bar is 50 μm.

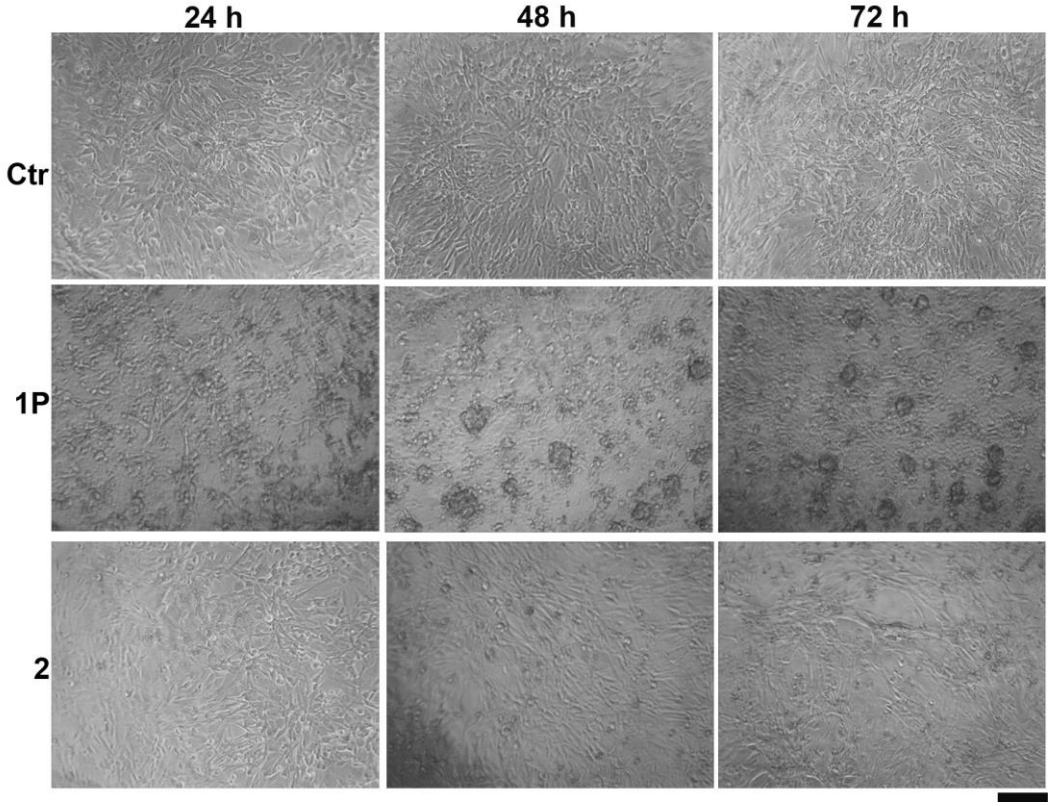

Figure S7. Microscope images of the co-culture of HS-5 and Saos-2 (ratio is 1:1) cells at the density of 3×10^4 treated with culture medium (control), **1P** or **2** for 24, 48 and 72 h.

3. Supplementary movies

Movie S1
Constructed Z-scan of Saos-2 cells treated with (**NBD-1P:2**) at concentration of 300 μM for 48 h.

Movie S2
Constructed Z-scan of Saos-2 cells treated with (**NBD-1P:2**, 300 μM) and DQB (5 μM) for 48 h.

Movie S3
Constructed Z-scan of co-cultured HS-5 and Saos-2 cells treated with (**1P:2**, 300 μM) and DQB (5 μM) for 48 h and then stained with live-dead assay.

Movie S4
Constructed Z-scan of co-cultured HS-5 and Saos-2 cells treated with (**1P:2**, 300 μM) and DQB (5 μM) for 48 h. HS-5 cell lines was firstly treated with Hochest 33342 (red) for 10 minutes and then co-cultured with the Saos-2 cell firstly treated with membrane probe (green)[1] for 1 h.

1. H. Wang, Z. Feng, S. J. Del Signore, A. A. Rodal, B. Xu,Active probes for imaging membrane dynamics of live cells with high spatial and temporal resolution over extended time scales and areas *J. Am. Chem. Soc.* **140**, 3505-3509 (2018).

Other files

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