Supporting Information

In situ imaging of live-cell extracellular pH during cell processes with SERS

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SUPPLEMENTARY FIGURES

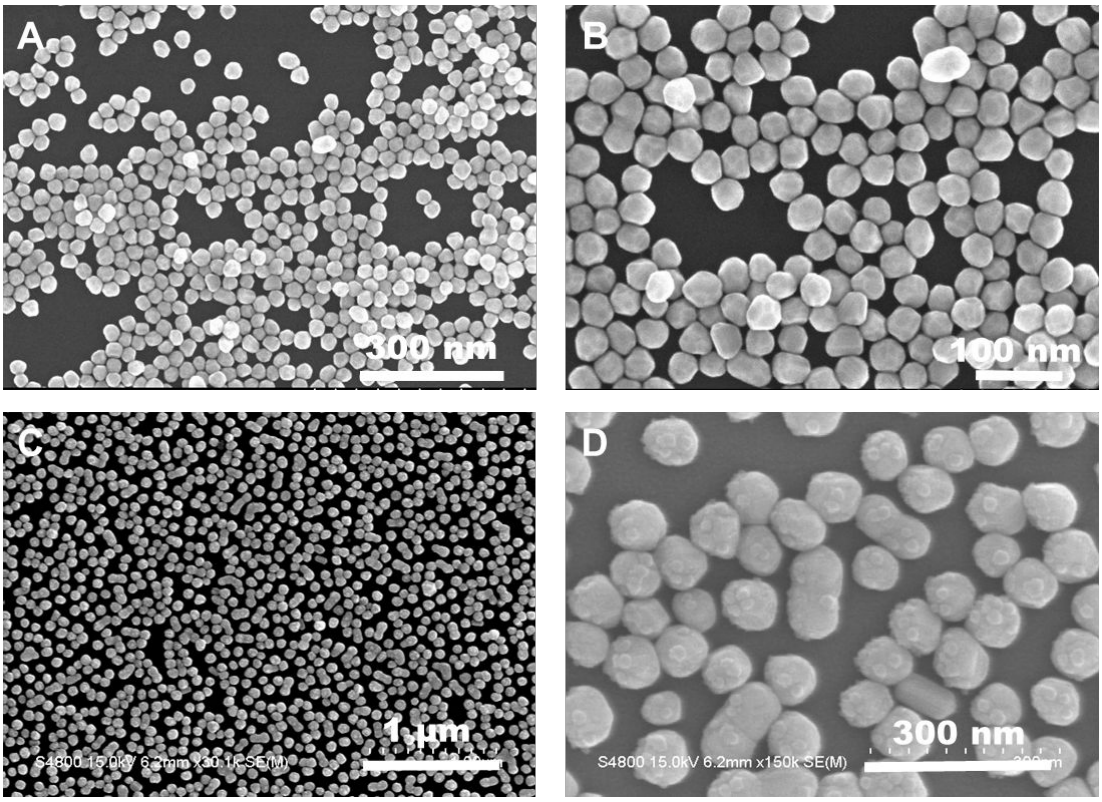

Figure S1. SEM images of AuNPs with a diameter of 40 nm (A, B) and 80 nm (C, D) with different magnifications.

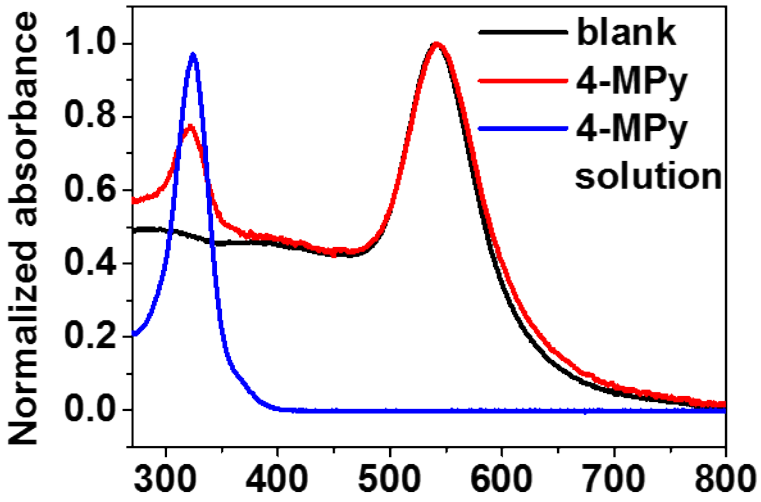

Figure S2. Typical UV-Vis absorption spectra of gold nanoparticle-assembled substrates before (black line) and after (red line) adsorption of 4-MPy molecules. The blue line is the absorption spectrum of 4-MPy solution with a concentration of 0.05mM.

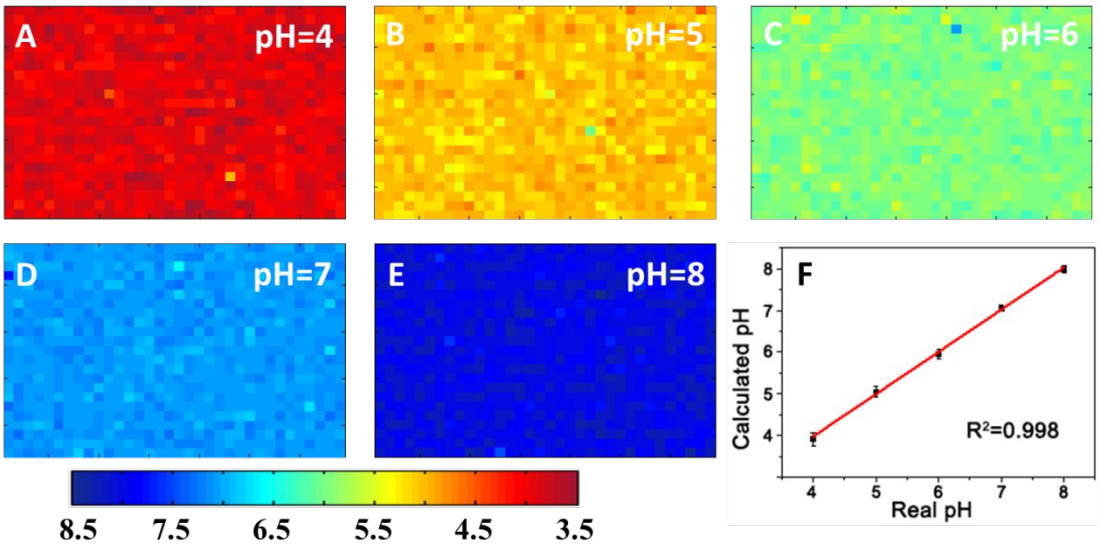

Figure S3. (A-E) pH images of the substrates using the intensity ratio of 1610 cm^{-1} to 1575 cm^{-1} under different pH values indicated in each image. (F) The calculated pH values from pH maps in A using the calibration curve in Figure 2C at different pH values.

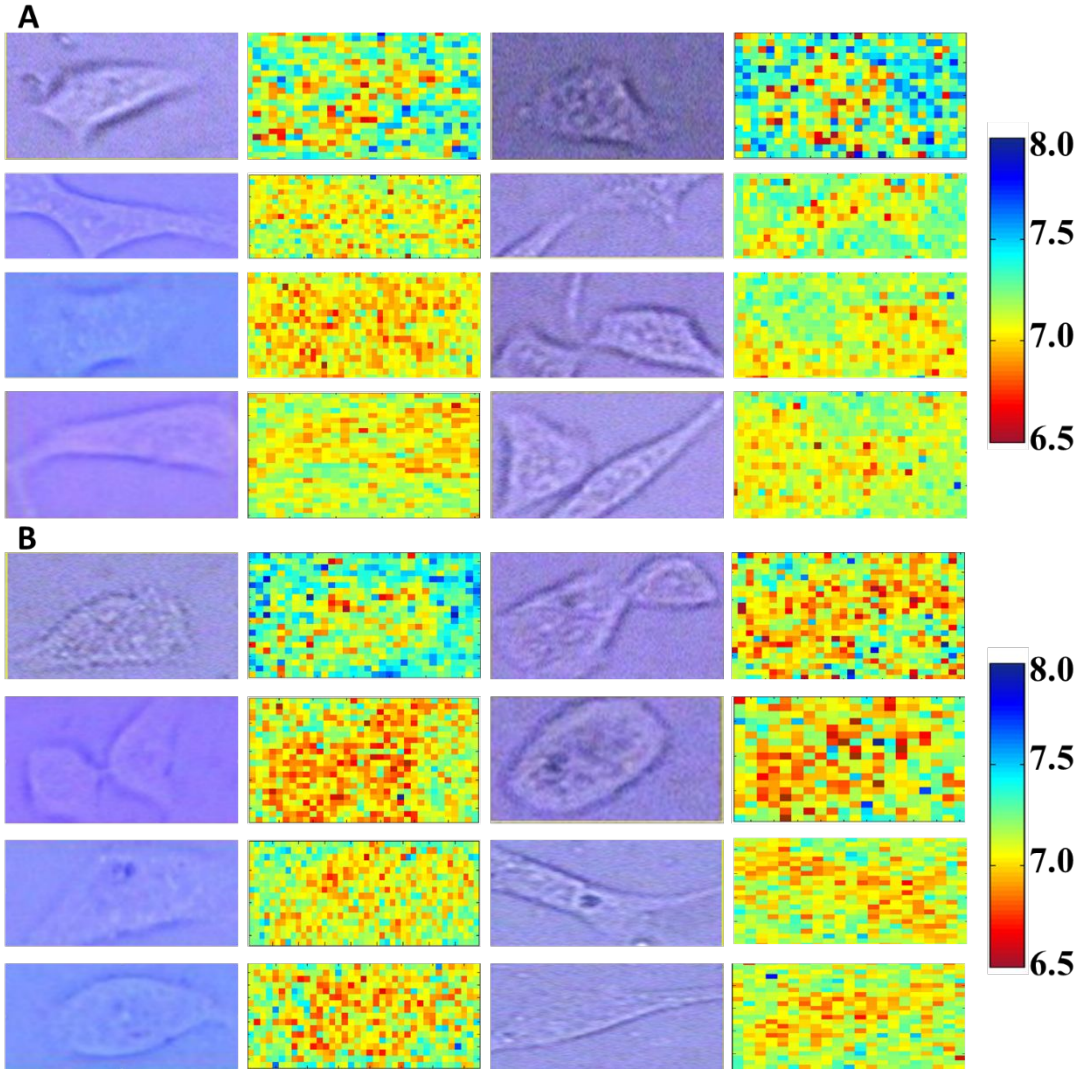

Figure S4. SERS-based live-cell pHe imaging of different cell lines, TCA-8113 cells (A) and SCC-4 cells (B) with 4-MPy modified gold substrates. Bright-field microscopic images and pHe images using the intensity ratio of 1610 cm^{-1} to 1575 cm^{-1} were taken for eight different cells. The measurements were performed under ex situ condition after incubation of cells with the substrates for 24 h.

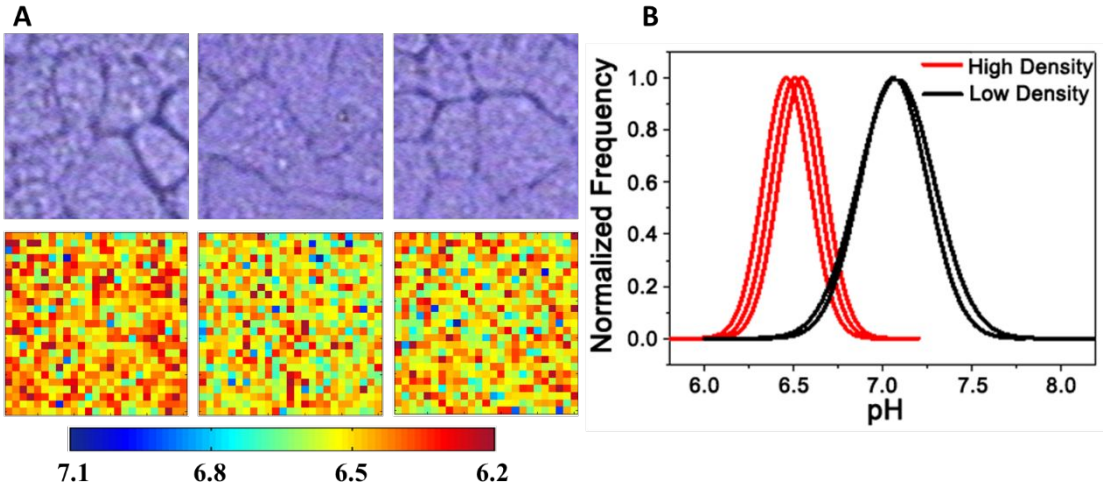

Figure S5. (A) Bright-field microscopic images (top panels) and pHe images using the intensity ratio of 1610 cm^{-1} to 1575 cm^{-1} (bottom panels) of TCA-8113 cells with a high density. The measurements were performed after incubation of cells with the substrates for 48 h. (B) The statistical profiles constructed using the pH distribution data obtained within the cell region of (A) for cells of high density (red curve) and Fig. 3B for cells of low density (black curve). Each curve was normalized by setting the highest pH occurrence as 1.

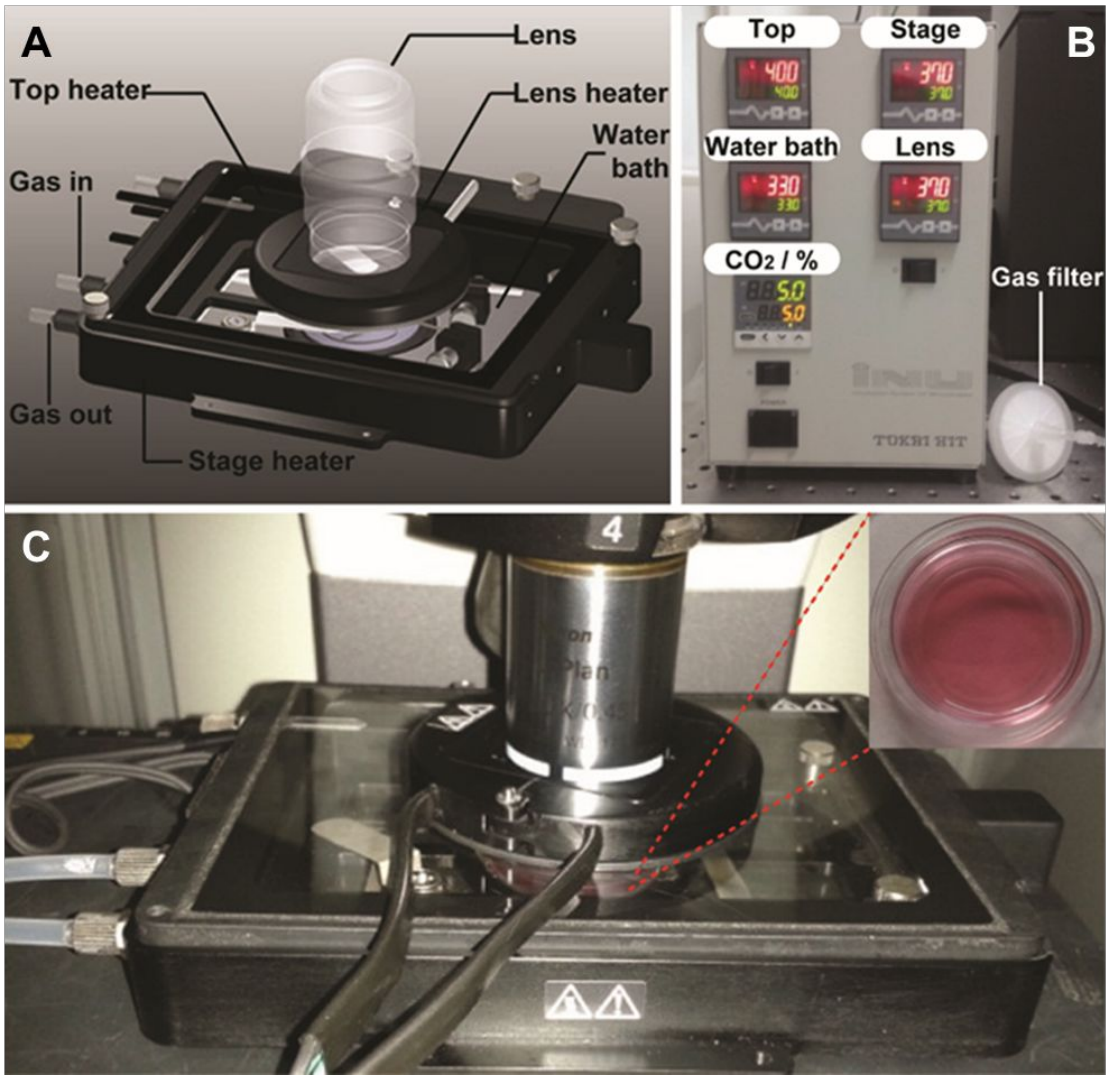

Figure S6. Illustration of the in situ cell culture and microscopic detection system. (A) The schematic diagram of the heating cell culture chamber (reproduced with permission from http://www.tokaihit.com). (B) The temperature-gas control unit for regulating the environment in the cell culture chamber in (A). (C) The photo of the combination of in situ cell culture chamber and Raman microscopic detection device used on the Raman-11 (Nanophoton) confocal Raman microscope. The inset shows the cell culture dish.

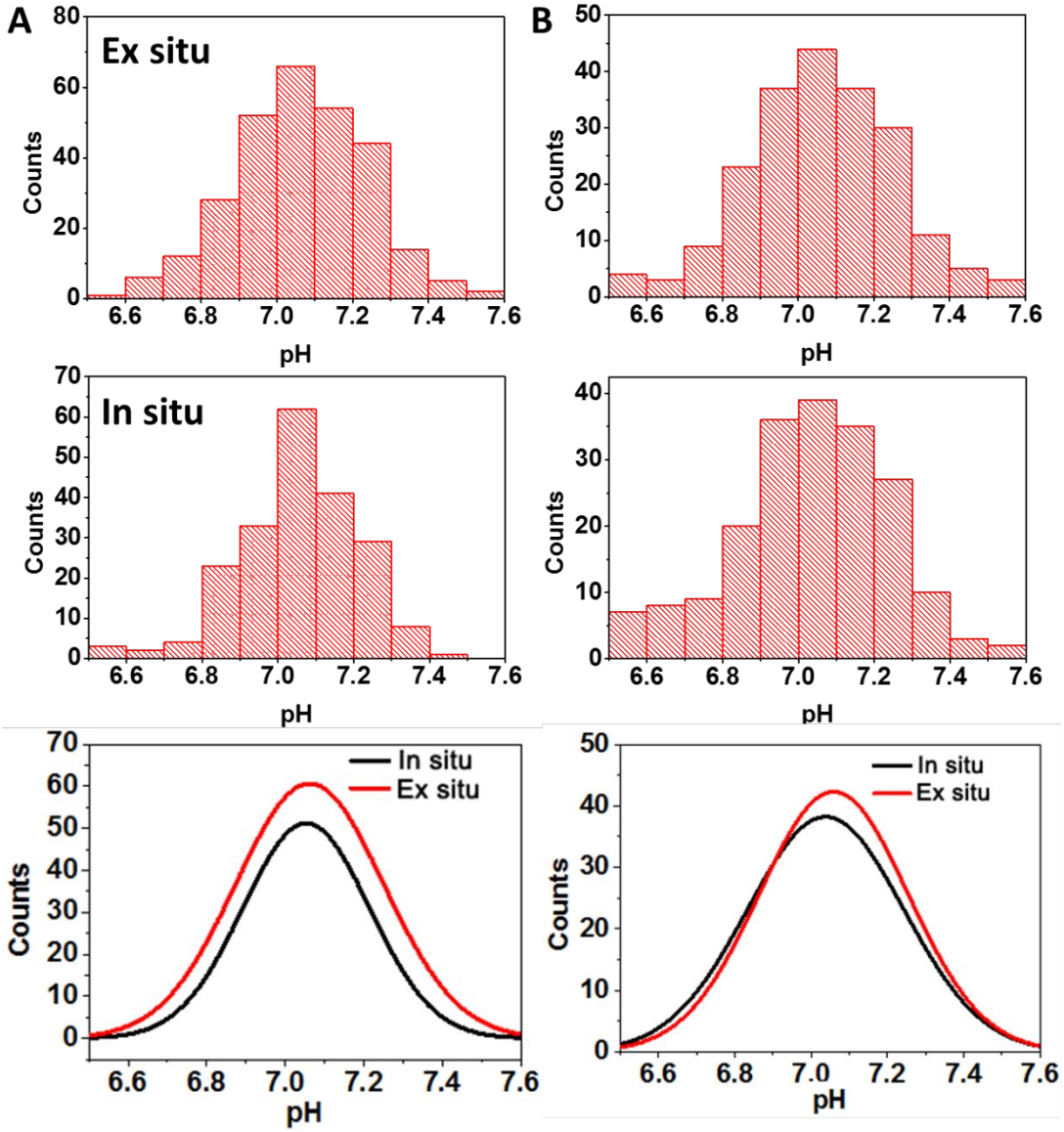

Figure S7. The comparison of pHe distribution within cell region of TCA-8113 cells (A) and SCC-4 cells (B) under ex situ experiment (top panel) and after 4 h in situ experiment (middle panel). The bottom panel is the statistical profiles constructed using the pH distribution data obtained from the upper images.

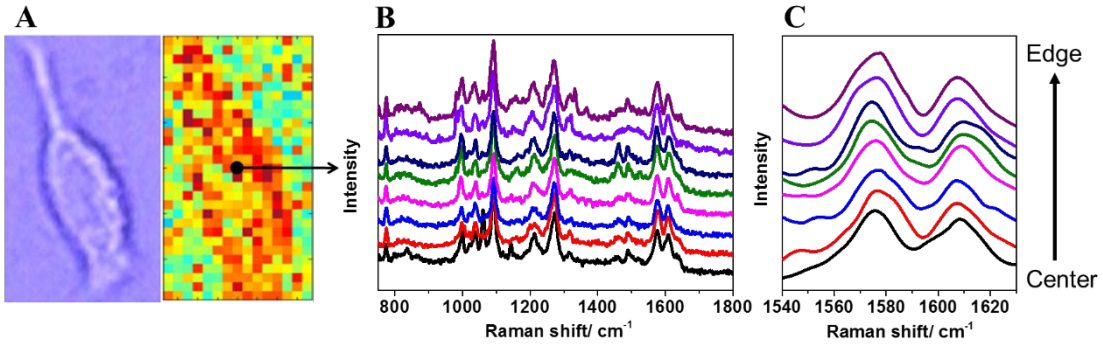

Figure S8. Typical SERS spectra obtained from the TCA-8113A cell after stimulation of TGF-β for 4 h during the in situ experiment. (A) Bright field image and corresponded pH image of the cell. The black arrow in the pH image indicates the data points we chose for spectra analysis. (B) Full spectra and (C) the zoom-in spectra in the spectral range of 1540 to 1630 cm^{-1} of the selected data points.

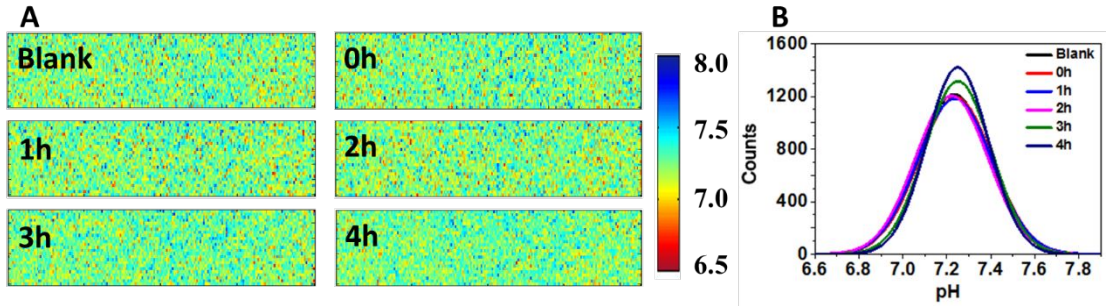

Figure S9. (A) pH images of the substrate in DMEM as a control and the following 4 h after the addition of DMEM with 20 ng/mL TGF-β. pH distribution images were produced by converting the experimentally obtained peak intensity ratio of 1610 to 1575 cm-1 to pH values using the work curve in Figure 2(C). (B) The statistical profiles constructed using the pH distribution data obtained at specific time points in (A).