

Electronic Supplementary information for

**Integrated Heart/Cancer on a chip to reproduce the side effects of
anti-cancer drugs *in vitro***

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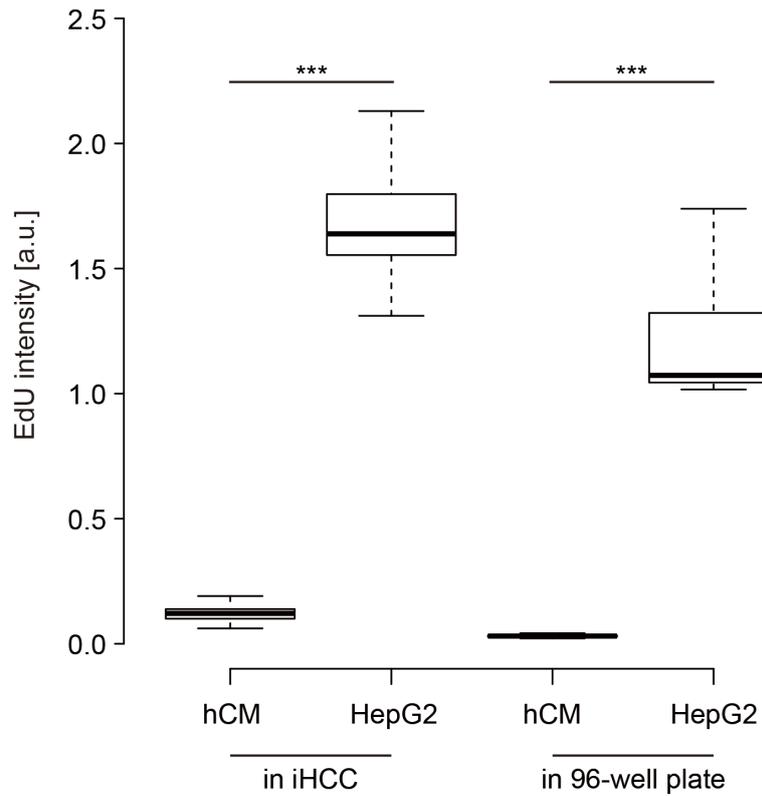


Fig S1. Quantitative single-cell profiling to reveal the difference of EdU intensity in human cardiomyocytes (hCM) and hepatocellular carcinoma (HepG2) cells cultured in iHCC or a 96-well plate. We used primary hCMs, which did not show high proliferation like other cancer cells, such as HepG2. Therefore, in both iHCC and 96-well plate, EdU uptake in hCM was significantly lower than that in HepG2, and was almost at the lower detection limit of EdU. Fluorescent EdU intensities in over 8000 individual cells were analyzed for each sample. P -values ($*** < 0.001$) were determined by Mann Whitney's U test. Center lines show the medians; box limits indicate 25% and 75% as determined by R software; whiskers extend 1.5 times the interquartile range from 25% and 75%.

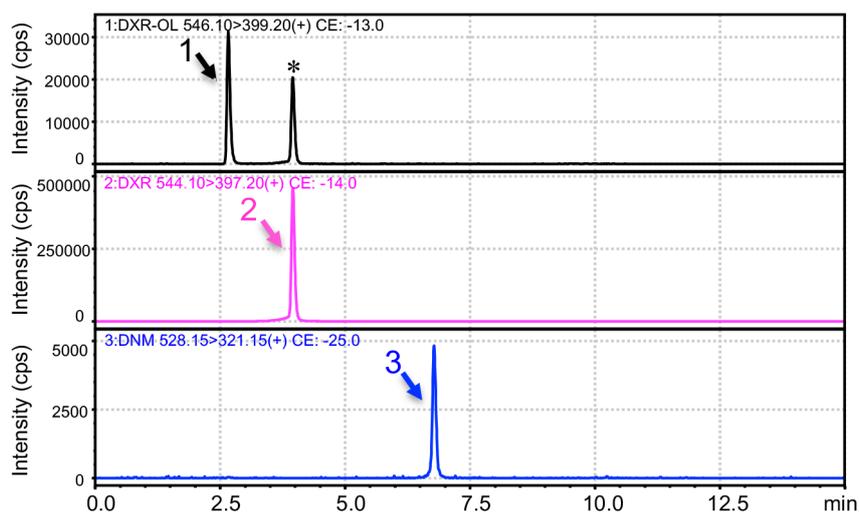


Fig. S2. Ultra-high performance liquid chromatography-tandem mass spectrometric analysis of DXR, DXRol and DNM. Representative MRM chromatograms for the extract of HepG2 cells treated with DXR are shown. MRM peaks corresponding to DXRol, DXR and DNM are indicated by *black* (1), *magenta* (2) and *blue* (3) arrows, respectively. X- and Y-axes indicate retention time (min) and intensity (count per second (cps)). As indicated by the asterisk in the top chromatogram, we detected non-specific peak in the MRM chromatogram for DXRol at the retention time of DXR. This was because the MRM transition for DXRol detected the mass isotopomer of DXR (m2).

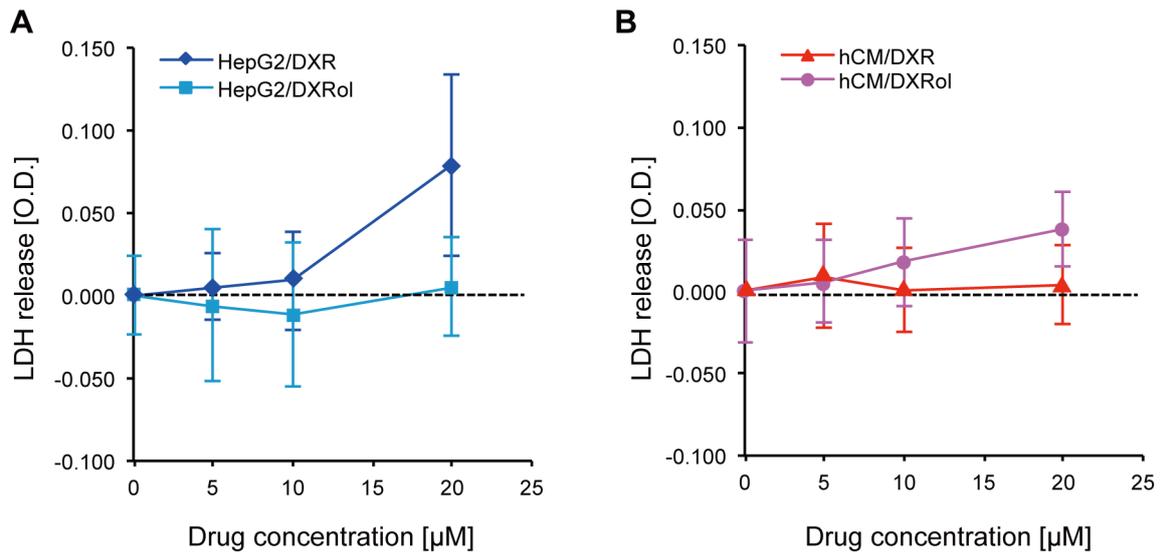


Fig. S3. DXR and DXRol showed inverse cytotoxic effects on HepG2 (A) and hCM (B) determined by lactate dehydrogenase (LDH) assay. (A) DXR caused cell damages of HepG2 cells, but DXRol did not. (B) The metabolite of DXR, DXRol caused cell damages of hCMs, but DXR did not. These results suggested that the metabolites of anti-cancer drug might cause the damage, leading to the side toxicity. Each data represents a mean \pm standard deviation ($n = 3$).

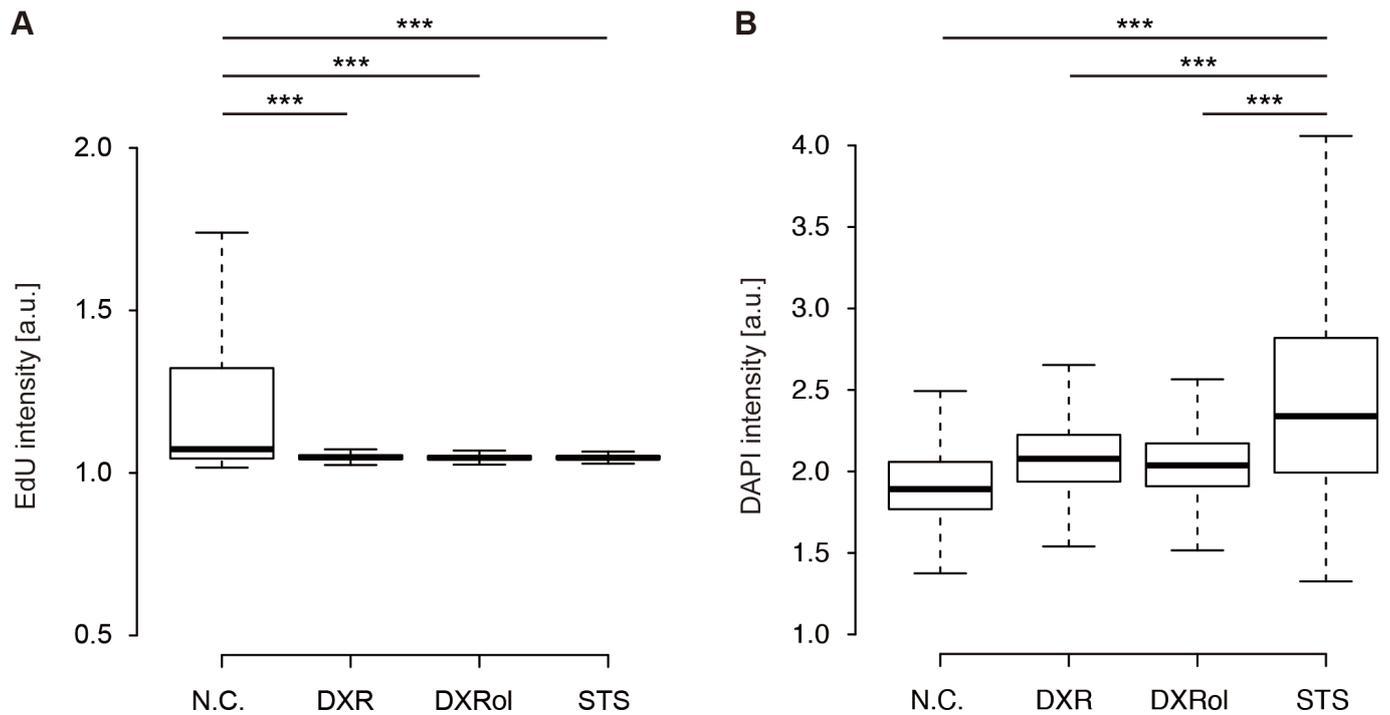


Fig. S4. Quantitative single-cell profiling to investigate the effects of doxorubicin (DXR) and its metabolite, doxorubicinol (DXRoi), on HepG2 cells. (A) DXR (20 μ M) and DXRoi (20 μ M) similarly reduced the number of proliferating cells. (B) Both DXR and DXRoi damaged HepG2 cells. Fluorescent EdU and DAPI intensities in over 8000 individual cells were analyzed for each sample. P -values (***) ($P < 0.001$) were determined by Steel-Dwass test. Center lines show the medians; box limits indicate 25% and 75% as determined by *R* software; whiskers extend 1.5 times the interquartile range from 25% and 75%.