# Dynamic Regulation of Glucose Transporter Expression in Colorectal Cell Lines: a Proof of Concept for Tumor Targeting Strategies via Nanoparticles Drug Delivery

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## BACKGROUND

Since GLUT2 can be overexpressed in some cancer cells, including colorectal and breast cancer, targeting GLUT receptors or glucose metabolism pathways represents a promising approach for cancer treatment. In this study, we altered the expression of glucose receptors in three distinct colon cell lines (Figure 1) to confirm the internalization of recently synthesized nanoparticles functionalized with glucose monomers. In particular, we were able to determine which cell lines, under which glucose conditions, could be targeted for abundant and specific internalization by varying the concentration of glucose in the cell culture medium and measuring the variation of the *SCL2A2* receptor (GLUT2).

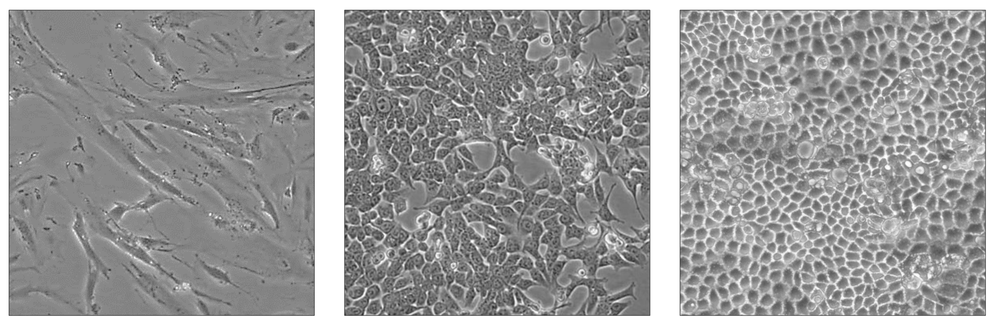

**Figure 1**. Cell Lines used in this work: Sane Cells CCD-841 (left), Carcinoma Cells HCT-116 (middle) and Adenocarcinoma Cells CaCo-2 (Right).

## MATERIALS

Three immortalized human colorectal cell lines were used for this work: CaCo-2 (adenocarcinoma), HCT-116 (carcinoma), and CCD-841 (normal). The biocompatibility of nanoparticles was assessed using an MTT assay. To differentially express the GLUT2 receptor, cells were grown under three different conditions: BASAL, with a glucose concentration equal to the elective medium; DEPRIVATION, with 0 g/L glucose; and PLUS, with 10 g/L glucose. The differential expression of the receptor was assessed using RT-qPCR. Then, under the same glucose conditions, cells were treated with nanoparticles (400 ng/µL) for 30 minutes. Internalization of nanoparticles was assessed using a Synergy Multiscanner, exciting at 350 nm and absorbing at 420 nm, normalizing absorbance values for PBS (solvent).

## RESULTS

At concentrations below 2 µg/µL, the nanoparticles exhibited a biocompatibility greater than 85%, indicating minimal cytotoxicity and high compatibility with the cell lines tested. The variations in GLUT2 receptor expression under different glucose conditions are illustrated in Figure 2A, which shows that HCT-116 cells undergo the most significant changes in GLUT2 expression in response to fluctuating glucose concentrations. This adaptation underscores the dynamic nature of GLUT2 regulation in cancer cells.Following this pattern, we observed that increased GLUT2 receptor levels indeed facilitated greater internalization of the glucose-functionalized nanoparticles, as shown in Figure 2B. This internalization process was notably efficient in the HCT-116 cell line, particularly under high glucose conditions, where GLUT2 expression was maximized. Furthermore, the internalized nanoparticle concentration was directly proportional to the GLUT2 receptor expression, confirming a coherent and statistically significant relationship between GLUT2 levels and nanoparticle uptake. These findings validate our hypothesis and highlight the potential for targeted nanoparticle delivery based on receptor expression.

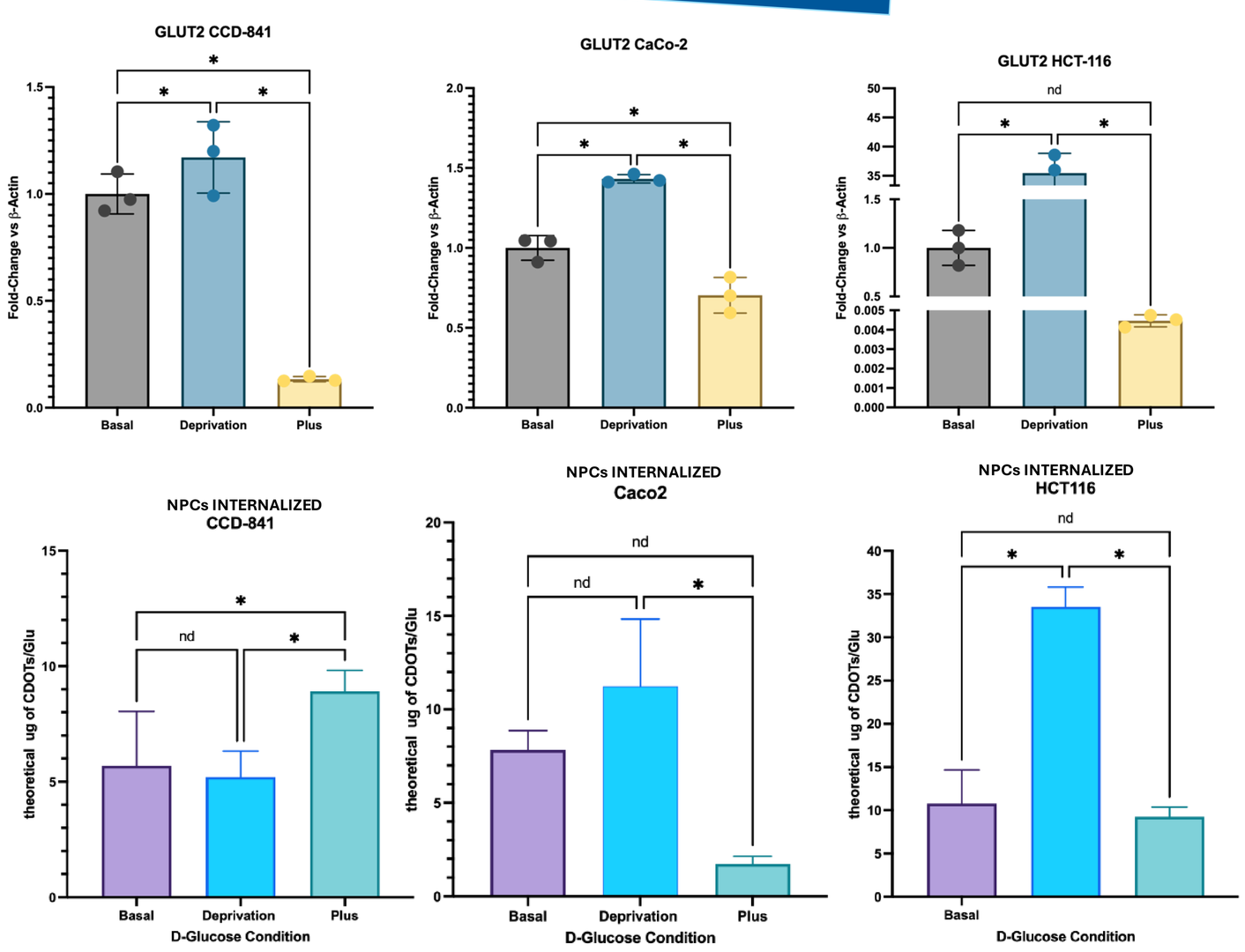


**Figure 2.** (A, above) different expression of GLUT2 receptor of the three cell lines compared to the basal condition. (B, below) theoretical micrograms of nanoparticles internalized measured with the fluorescence emitted and recorded at multiscanner.

## CONCLUSIONS

This study successfully demonstrates that targeting glucose receptors, specifically GLUT2, can be an effective strategy for the selective internalization of functionalized nanoparticles in colorectal cancer cells. We confirmed that the expression of the GLUT2 receptor can be differentially modulated by altering the glucose concentration in the culture medium. The nanoparticles used in this study showed high biocompatibility, with more than 85% cell viability at concentrations below 2 µg/µL, making them suitable candidates for further biomedical applications. Our data show a strong positive correlation between GLUT2 expression levels and the internalization efficiency of glucose-functionalized nanoparticles. The ability to enhance nanoparticle internalization through glucose concentration modulation highlights the potential for targeted cancer therapy. By adjusting glucose levels, we can selectively increase nanoparticle uptake in cancerous cells with overexpressed GLUT2 receptors, minimizing off-target effects on normal cells.

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