Nanoparticle-Mediated Delivery of Antioxidants for Improving the Survival of Beta Cell Implants for Treating Type 1 Diabetes

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Objective

The goal is this study is to design and deliver bilirubin nanoparticles and quercetin nanoparticles to beta cells in order to improve post-hypoxia survival outcomes for islet transplantation.

Introduction

The most direct curative therapy for type I diabetes involves transplanting islets from a healthy donor to restore normoglycemia in the afflicted patient. However, even with advancements in transplantation, 60% to 80% of the isolated islets frequently die upon exposure to a hypoxic environment outside the body.

Recent studies have demonstrated that two candidate antioxidants, bilirubin and quercetin, can significantly increase beta cell viability under hypoxic stress. Therefore, PLGA-PF-127 polymeric nanoparticles surface-coated with chitosan were encapsulated with bilirubin and quercetin for delivery to beta cells to increase drug uptake and cell viability post-hypoxia.

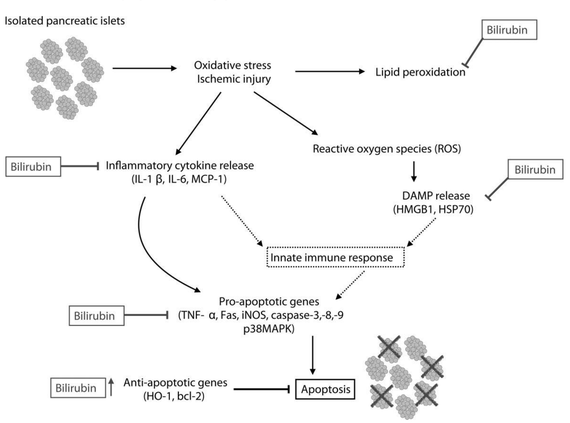

Figure 1. *Antioxidant effects of bilirubin*

Nanoparticle Characterization

The single emulsion nanoparticles demonstrated ~25% encapsulation efficiency and ~200 nm in size with a polydispersity index less than 0.1 for all three different nanoparticles.

Table 1. *Characteristics of bilirubin and quercetin nanoparticles*

Nanoparticle Type	Encapsulation Efficiency (%)	Loading Content (%)	Diameter (nm)	Zeta Potential (mv)
Bilirubin	26.7±0.24	1.27±0.01	190.5±54.74	8.94±6.89
Quercetin	24.9±0.65	4.98±0.13	202.0±64.79	6.98±6.85
Control Nanoparticles	N/A	N/A	187.7±45.38	4.22±5.22

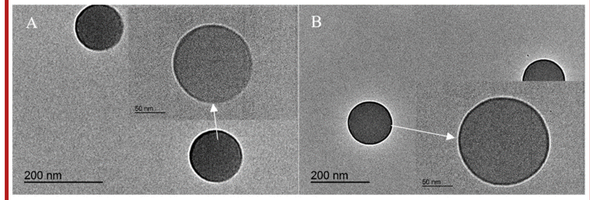

Figure 2. *TEM images of bilirubin (A) and quercetin (B) nanoparticles*

Cellular Uptake

For both MCF-7 and TC-6 cells, nanoparticle-encapsulated bilirubin exhibited increased uptake compared to free bilirubin in a dose-dependent manner.

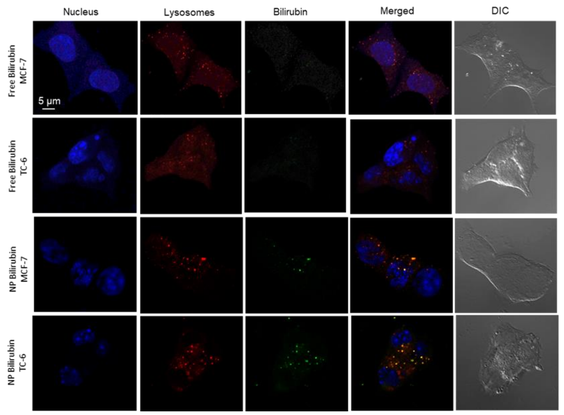

Figure 3. *Uptake of nanoparticle (NP)-encapsulated and free bilirubin (10 µM)*

Nanoparticle Effect on Cell Viability Post-Hypoxia

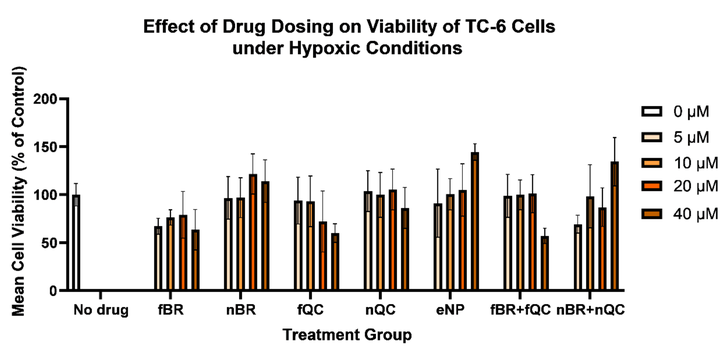

Figure 4. *Mean viability of TC-6 cells treated with different concentrations of nano-encapsulated or free bilirubin and quercetin and exposed to 24 hr hypoxia*

The group treated with 40 µM of nanoparticle-encapsulated bilirubin and nanoparticle-encapsulated quercetin witnessed significantly higher cell viability than the control group with no drug treatment ($p = 0.017$) as well as free bilirubin ($p = 0.0039$), free quercetin ($p = 0.0007$), nanoparticle quercetin ($p = 0.017$), and free bilirubin and quercetin ($p = 0.0008$) of the same concentration.

Conclusions

The results of the study demonstrate sufficient encapsulation efficiency, positive zeta potential, and polydispersity index of the nanoparticles, which were taken up much more readily into TC-6 cells than their free drug counterparts. Pretreatment of the TC-6 cells with nanoparticle-encapsulated bilirubin and quercetin, at 40 µM, before exposure to 24 hours of hypoxia resulted in significant increase in cell number and potentially increased viability compared to controls with no drug treatment. Future studies will corroborate the cytoprotective effects of this nanoparticle-mediated combination on murine pancreatic islets and confirm the preservation of glucose-stimulated insulin secretion. The discovery of this combinatory therapy of antioxidant nanoparticles could preserve islet mass more efficiently, reducing donors needed and improving therapeutic outcomes for patients with type 1 diabetes.

Conclusions

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References

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