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DEVELOPMENT OF AN INTESTINAL BARRIER SYSTEM FOR THE STUDY OF DRUG PERMEABILITY

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Development of an Intestinal Barrier System for the Study of Drug Permeability

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ABSTRACT

In order to bring promising new therapeutics into the clinic to benefit patients, the safety and bioavailability of drug candidates must be evaluated preclinically using model systems. Drugs need to be absorbed through the intestinal lining to be effective, and the standard in vitro system to test this is a monolayer of differentiated Caco-2 colon cancer cells grown on a permeable filter. The goal of the present study is to establish the Caco-2 barrier model and compare it with a novel intestinal organoid-based system. Caco-2 cells were grown on 0.4 µ filters and barrier function was assessed using trans-epithelial electrical resistance (TEER). Organoids were cultured in 3D using Matrigel and similarly seeded onto filters using proliferation-promoting medium and subsequently differentiated. The Caco-2 cells exhibited minimal barrier function measured by TEER during the first week on the filter but increased to form a functional barrier (TEER > 1000 Ω.cm2) by 2 weeks and was stable for at least another week. No differences in barrier were observed between filter size (12 and 24 well plates) or composition (polycarbonate or polyester). Barriers were confirmed by treating with calcium-deficient medium that resulted in TEER < 400 Ω.cm2. Changing medium to add drugs caused a transient decrease in TEER to approximately 700 Ω.cm2 that recovered in an hour at 37°C. Human ileal and descending colon organoids similarly generated stable barriers that differed between proliferating and differentiating tissue. Both systems produced similar apparent permeability values for lucifer yellow. Our results demonstrate that we have established in vitro permeability models in our laboratory, and that human organoid-based barriers might offer a superior alternative for drug testing.

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