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Heat-regulated human hepatoma culture system with enhanced hepatic function for drug response evaluation

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Introduction

In drug discovery,

Animal experiments



- Interspecies differences
- Ethical concerns

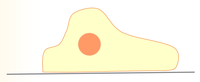
Human cell culture



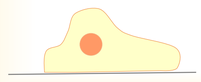
- Cell source
- Differences from *in vivo*

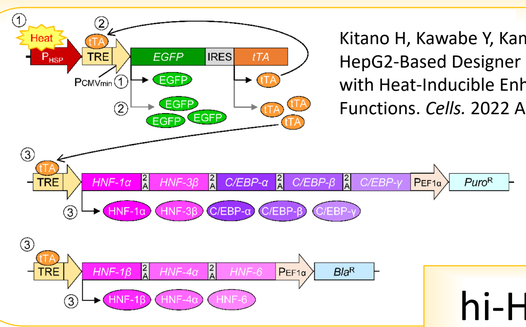
In our group,

HepG2 cells

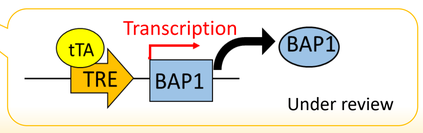


hi-Hep cells





Kitano H, Kawabe Y, Kamihira M. HepG2-Based Designer Cells with Heat-Inducible Enhanced Liver Functions. *Cells.* 2022 Apr 1;11(7):1194.



Under review

hi-Hep cells can be switched

Growth → Function

By heating treatment

Aim:

To develop a 3D hiHep-based culture system with enhanced hepatic function for drug screening applications.

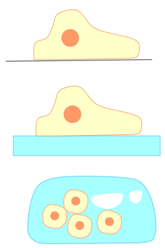
Topics

Liver ECM



In vivo

Which is best?



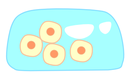
Collagen coat

On collagen gel

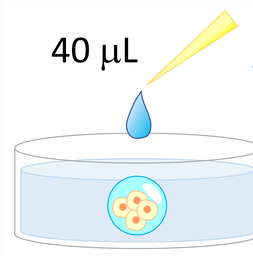
In collagen gel

Heating treatment

Order?



Encapcelation



Sodium alginate

✓ Rapid gelation

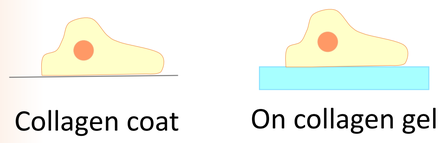
Type I collagen

✓ Main components of ECM

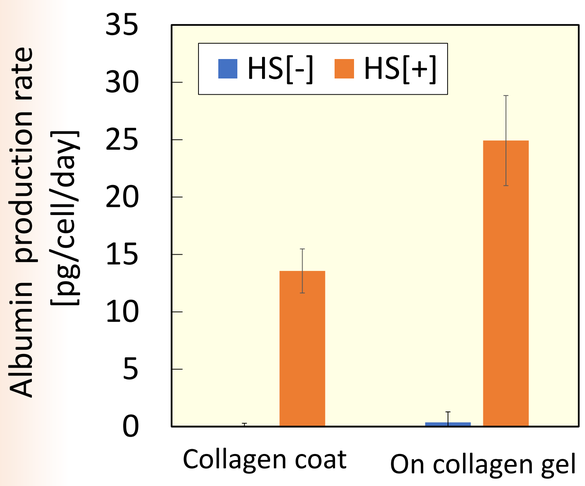
Mixture ratio? Cell density?

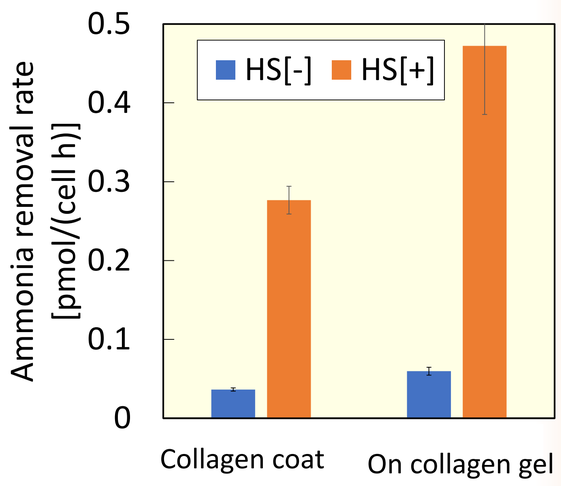
Results

Comparison of culture conditions



hi-Hep cells were seeded at 4.0 × 10^4 cells/mL the day after the heating treatment (HS).

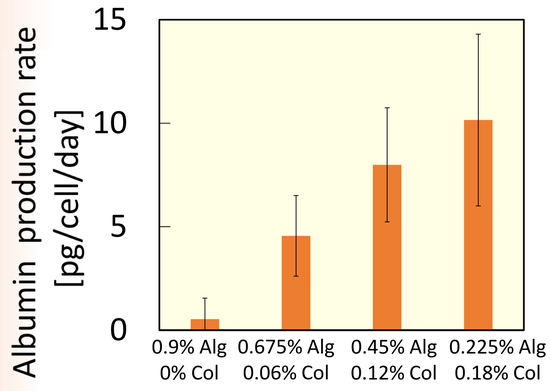


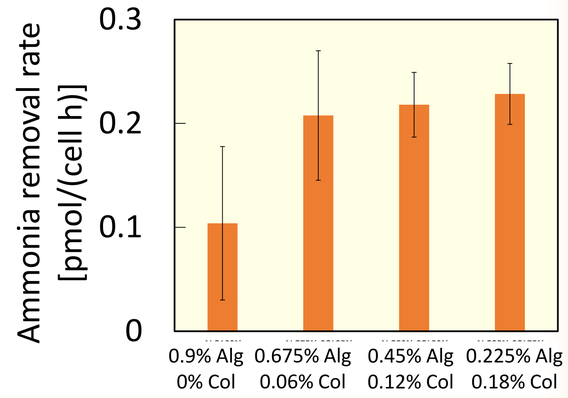


hi-Hep cells cultured on collagen gels showed higher albumin secretion than monolayer cultures.

The ratio of type I collagen to sodium alginate

Sodium alginate + Type I collagen + 10 × 10^4 cells/mL hi-Hep cells



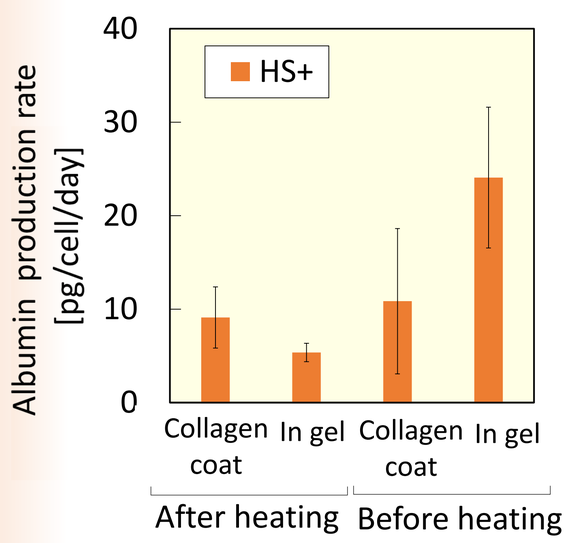


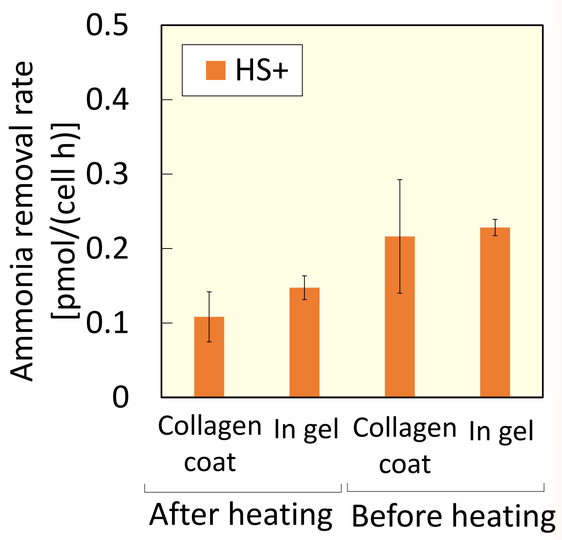
Hepatic function was increased with collagen concentration.

Effect of heat treatment timing

Heating treatment → Encapcelation : After heating

Encapcelation → Heating treatment : Before heating

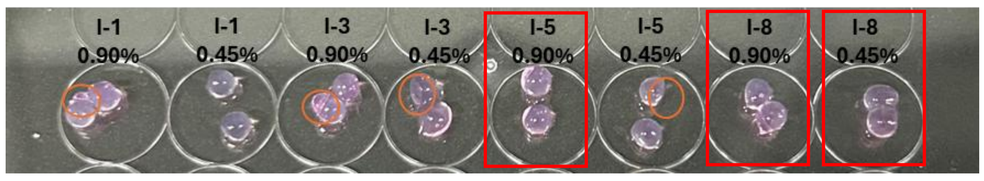




Hepatic functions were higher in cells heat-treated after embedding in collagen gels.

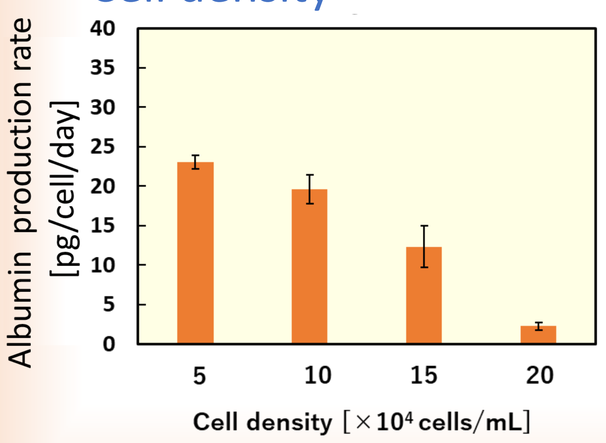
Sodium alginate condition

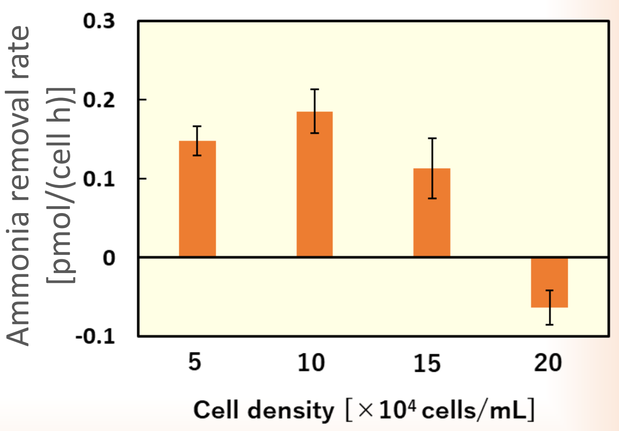
Name	Viscosity (1% solution)
I-1	80 ～ 200 mPa・s
I-3	300 ～ 400 mPa・s
I-5	500 ～ 600 mPa・s
I-8	800 ～ 900 mPa・s



Based on capsule controllability and ease of operation, I-5 0.90% was used with 0.12% collagen.

Cell density





10 × 10^4 cells/mL was good cell density.

Conclusion and Future work

Collagen-based three-dimensional culture enhanceed hepatic function in hi-Hep cells.

Optimization of alginate concentration and cell density will allow the development a simple and scalable platform for drug testing and bioartificial liver applications.

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