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3D Printed scaffolds as cancer microenvironment models for drug discovery

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, Göteborg, den 6 maj 2022, klockan 9.00

av Jennifer Rosendahl

Fakultetsopponent:

Professor/biträdande överläkare Johan Hartman, Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Landberg G, Fitzpatrick P, Isakson P, Jonasson E, Karlsson J, Larsson E, Svanström A, Rafnsdottir S, Persson E, Gustafsson A, Andersson D, **Rosendahl J**, Petronis S, Ranji P, Gregersson P, Magnusson Y, Håkansson J, Ståhlberg A. Patient-derived scaffolds uncover breast cancer promoting properties of the microenvironment, *Biomaterials. 2020 Mar;235:119705*

II. Svanström A*, **Rosendahl J***, Salerno S, Leiva MC, Gregersson P, Berglin M, Bogestål Y, Lausmaa J, Oko A, Chinga-Carrasco G, Petronis S, Standoft S, Ståhlberg A, Håkansson J, Landberg G. Optimized alginate-based 3D printed scaffolds as a model of patient derived breast cancer microenvironments in drug discovery, *Biomed Mater. 2021 Jun 25;16(4).*

III. **Rosendahl J***, Svanström A*, Berglin M, Petronis S, Bogestål Y, Stenlund P, Standoft S, Ståhlberg A, Landberg G, Chinga-Carrasco G, Håkansson J. 3D Printed Nanocellulose Scaffolds as a Cancer Cell Culture Model System, *Bioengineering (Basel). 2021 Jul 10;8(7):97.*

IV. Svanström A, **Rosendahl J**, Salerno S, Jonasson E, Håkansson J, Ståhlberg A, Landberg G. The Effect of Hypoxic and Normoxic Culturing Conditions in Different Breast Cancer 3D Model Systems, *Front Bioeng Biotechnol. 2021 Nov 4;9:711977.*

* = equal contribution

SAHLGRENSKA AKADEMIN
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3D Printed scaffolds as cancer microenvironment models for drug discovery

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Abstract

Cancer is one of the most common diseases in the modern world and major efforts are made globally to develop new diagnostics and treatments. It originates from a cell which, at some point, has begun to divide and grow uncontrollably. The most common type is breast cancer, and like all other cancers there is a need of more efficient drug therapies. Drug development is an expensive and time-consuming process and in conventional pre-clinical evaluation, drugs are tested on cells grown in 2D followed by experimental studies in animals. Only the drug candidates with best efficacy and safety profiles are allowed to proceed to clinical trials in humans. A major problem is that the pre-clinical test methods most often do not adequately represent the microenvironment in the human body and only a portion of the drugs that show good effect in pre-clinical studies pass the clinical trials and reaches market. Failures in late development mean large losses both financially and in time, and better pre-clinical test methods are needed that can predict more accurate results for safety and efficacy.

The behavior of cancer cells is strongly influenced by the surrounding microenvironment, but today's drug development focuses mainly on the cells themselves and does not sufficiently take this into account. This thesis combines 3D printing and cell biology to develop new and more representative test systems, with the ambition to mimic the tumor microenvironment in three dimensions. By using patient tumor tissue and removing the original cells, we produce a cell-free extracellular matrix scaffold to which standardized reporter breast cancer cell lines are reintroduced. The cell lines grown in the patient derived scaffolds developed more stem cell properties and formed a more heterogeneous cell population compared to 2D cultures. Moreover, the gene expression profile could be linked to clinical data, such as relapse. In an attempt to synthetically mimic the human tumor tissue, we used an alginate-based biomaterial to print 3D scaffolds. Breast cancer cells cultured in the 3D printed scaffolds showed a more similar growth- and gene expression pattern to cells cultured in patient derived scaffolds indicating that we were able to simulate the human tumor microenvironment. Further, we showed that the cells cultured in both patient derived scaffolds and 3D printed scaffolds had a similar response to hypoxic conditions – which is an important factor in tumors. Finally, we also showed that nanocellulose could be used to 3D print scaffolds and that cells cultured in these demonstrated comparable results to cells grown in alginate-based 3D printed scaffolds.

Keywords: 3D Printing, Breast cancer, Biomaterials, Drug development

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