Studying the correlation between EDCs and gynaecological malignancies

What do endocrine disrupting chemicals have to do with ovarian cancer, placental cells, and endometriosis? Plenty, says Dr Emmanouil Karteris, who has a long standing interest on the impact of EDCs on gynaecological malignancies.

Dr Emmanouil Karteris, Senior Lecturer and Head of the Cellular Endocrinology

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An environmental chemical called Bisphenol A has received a lot of publicity during the past few years. It is one of the best characterised EDCs (endocrine disrupting chemicals) that interfere with physiological systems. EDCs can adversely affect hormone balance, i.e. the body's endocrine system, and disrupt the normal function of organs that are heavily regulated by hormones.

EDCs are mostly man-made chemicals that are found in various materials such as pesticides, plastics, industrial chemicals, cosmetics and other personal care products. They are also found in additives or contaminants in food. EDCs have been associated with obesity, diabetes, breast cancer, and altered reproductive function in males and females.

Dr Emmanouil Karteris, the Senior Lecturer, Programme Lead for Biomedical Sciences and Head of Cellular Endocrinology Laboratory in Brunel University of London, is investigating the impact of Bisphenol A (BPA) on the female reproductive system.

The World Health Organisation (WHO) has raised major concerns about the global increasing trends of endocrine-related disorders in humans.

"EDCs are affecting the nature and wildlife as well, of course, and these affects have been studied a lot more. But in their report called 'State of the science of endocrine disrupting chemicals' from 2012, WHO emphasized that there are many gaps in the available chemical test methods for screening chemicals and their endocrine disrupting effects in female reproduction", Dr Karteris explains.

Hormonal interactions under the microscope

The Cellular Endocrinology Laboratory in Brunel University has two main interests of research. Firstly, they are studying the effects of endocrine disrupting chemicals in placental physiology as well as in gynaecological malignancies such as endometriosis and ovarian cancer. Secondly, they are looking for diagnostic or prognostic tests for ovarian cancer using liquid biopsies.

"There are thousands of EDCs in the world, and we can't study them all, so we have focused on studying the effects of Bisphenol A. It is a chemical used to make plastics, including materials that come into contact with food such as refillable drinks bottles and food storage containers", Dr Karteris says, quoting the Food Standards Agency in the UK.

When BPA comes to contact with the human body, it mimics the estrogen hormone by binding and activating estrogen receptors. Scientists have found that there is a positive correlation between EDCs and recurrent miscarriages. A link with the onset of pre-eclampsia has also been proposed. BPA accumulates in the amniotic fluid during pregnancy, which increases the risk of the foetus getting exposed to the chemical.

“In our research project, we are trying to find out what kind of effect BPA has on placental physiology. We are using GrowDex hydrogel as a means to establish a robust system where we could later do *in vitro* testing for a number of EDCs”, Dr Karteris says.

Problems with animal models

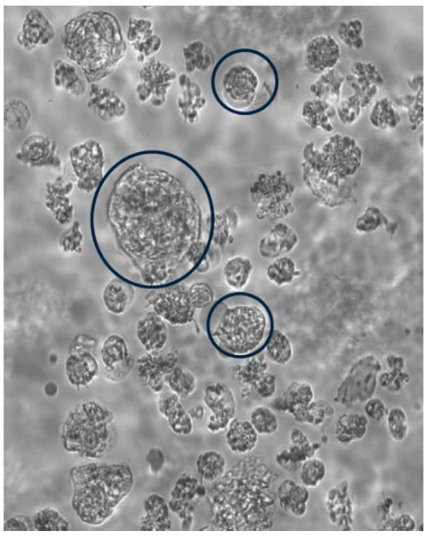
Dr Karteris and his team have always been keen to replace animal-based products in their work. Although mouse models have been used in placental work in a number of studies before, Dr Karteris notes that there are several problems when interpreting the data. This is due to the intrinsic differences between the human and the mouse placenta, for example in their morphogenesis and their endocrine functions.

“Animal models are not the best to study placentation. And I believe that this is where GrowDex can play a really big role”, Dr Karteris says.

His team had been trying to grow placental cells in 3D with limited success, when they heard about GrowDex.

“We decided to give it a try and we tested three different percentages of GrowDex according to recommendation. It worked very, very well. It was easy to use and portable, its shelf life is long, and the quality was consistent. There was zero batch variation, which was fantastic, and the cells appeared to grow a lot better in GrowDex than in other matrices we had tested previously.”

Dr Karteris and his team have been using GrowDex for almost a year now.



BeWo Cells growing in GrowDex. In circles images of cells forming structures resembling tertiary sysncytialised villi (image curtesy of Sophie Jahn, PhD student)

Placental cells grow better in GrowDex

BeWo cells are a placental cell line that has been widely used as an *in vitro* model for studying placental responses. According to Dr Karteris, 3D cell culture is definitely the way to go with BeWo cells or other placental cells, since 2D studies done so far have had their weaknesses.

“When you put BeWo cells in 2D and try to grow them, they must be chemically induced with a number of substances to become endocrine active in terms of secreting human chorionic gonadotrophin (hCG). The problem is that these chemicals can also kill the cells in prolonged exposures.”

GrowDex turned out to provide the right kind of physical scaffold for the cells to become endocrine active.

“The moment we started growing BeWo cells on GrowDex, we negated the necessity of chemical inducing. Somehow the scaffolding allows the cells to start syncytializing and becoming endocrine active. They secrete both human chorionic gonadotropin (hCG) as well as estradiol (E2)”, Dr Karteris says.

His group is currently studying this process.

One of the unique properties of GrowDex is the possibility to remove the matrix by enzymatic degradation. Using the GrowDase™ cellulase enzyme enables easy degradation of the matrix while retaining the 3D spheroid structure. The grown 3D structures can then be sub-cultured or collected for further analysis.

“The GrowDase enzyme has also worked very well for us. We have obtained a high yield and very pure RNA from cells after they have grown in GrowDex.”

These fascinating preliminary results still have to be validated. If they are, that would mean that the team would have created a 3D platform with endocrine active placental cells.

“The cells could then be treated with any EDC we like, and we could identify some good biomarkers of placenta and foetal toxicity using this 3D model”, Dr Karteris says.

There is a lot of challenging work to be done. Dr Karteris respects the fact that UPM has come forward to facilitate the work of scientists.

“Having a forum like The Annual 3D Cell Culture Seminar organized by UPM in Helsinki is really important to us. It allows scientists from all over the world to meet, exchange ideas and push the borders of science. This two-day brainstorming meeting was an unprecedented opportunity. Very few companies do that. As a scientist, I am really grateful.”