The organotypic culture of HPV-transformed keratinocytes: an effective in-vitro model of pre-neoplastic lesions of the uterine cervix

Fact Sheet

Project Information

Grant agreement ID: BIO4980097

Funded under
Specific research, technological development and demonstration programme in the field of biotechnology, 1994-1998

Start date
1 October 1998

End date
30 September 2000

Total cost
€ 0,00

EU contribution
€ 0,00

Coordinated by
UNIVERSITE DE LIEGE*ULG
Belgium

Objective

Cancers associated with potentially oncogenic viruses represent good models for research aimed at developing anti-tumoral vaccines because the viral proteins could be tumor antigens. The most actively investigated example of a tumor-virus is human papillomavirus (HPV), which is associated with more than 90% of squamous carcinoma of the uterine cervix. The generation of an effective protective response in
the cervical mucosa is, however, still poorly understood and may be influenced by factors produced by infected keratinocytes and infiltrating immune cells. Because different patterns of synergism or antagonism may be observed between these factors and immune effectors, preliminary studies of immunotherapeutic manipulations should be performed in models approximating the in vivo environment of the tissue of origin.

The purpose of this project is to develop a reliable in-vitro human model to test new immunotherapeutic approaches for squamous carcinoma developed on mucosal surfaces and particularly for cancer of the uterine cervix. The organotypic (raft) culture permits cells to proliferate and differentiate at an air-liquid interface on a dermal equivalent support. Normal keratinocytes stratify and fully differentiate in a manner similar to the normal squamous epithelial tissues, while HPV-immortalized and established squamous carcinoma cell lines exhibit dysplastic morphologies similar to (pre)neoplastic lesions seen in vivo. The ability of these organotypic cultures to be manipulated (for example, by integrating immunocompetent cells) may provide a useful tool to investigate the factors contributing to the presence and function of immunocompetent cells within a neoplastic epithelium developed on a mucosal surface.

The programme will be a shared activity of eight research units involved in HPV molecular and cellular virology, cutaneous or mucosal physiology and pathology by investigating reconstructed skin and mucosa models, cellular immunology, vaccine strategies or quantitative image analysis of immunohistochemical sections.

The project will be developed in seven partially overlapping tasks:
A: Validation of a reconstructed squamous mucosa model (organotypic culture) by using keratinocytes derived from monolayer cultures or cervical biopsies. B: Integration of in-vitro generated dendritic cells/Langerhans cells in organotypic cultures of HPV-transformed keratinocyte cell lines and biopsies.
C. Integration of HPV-sensitized lymphocytes generated with viral peptides-loaded dendritic cells/Langerhans cells in organotypic cultures of HPV-transformed keratinocyte biopsies.
D: Integration of macrophages in organotypic cultures of HPV-transformed keratinocyte biopsies.
E: Integration of lymphocytes retargeted by bispecific antibodies in organotypic cultures of HPV-transformed keratinocyte biopsies. F: Interactions between cytokines produced by HPV-transformed keratinocytes and immunocompetent cells.
G: Improvement of new anti-HPV vaccination strategies in a murine model by using the knowledge obtained from the in-vitro studies.

The benefits of the project are scientific, social and ethical by the European collaboration required to develop an in-vitro model of reconstructed mucosa as an alternative method for studying mucosal immunity in relation to vaccinology and testing new immunotherapeutic procedures for squamous (Pre)neoplastic lesions.

Fields of science
Programme(s)

**FP4-BIOTECH 2 - Specific research, technological development and demonstration programme in the field of biotechnology, 1994-1998**

Topic(s)

0502 - Transdisease vaccinology

Call for proposal

Data not available

Funding Scheme

**CON - Coordination of research actions**

Coordinator

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EU contribution

No data

Last update: 3 March 1999