رسالة الدكتوراه – العام 2005

الموضوع:

The Role Of E-Cadherin in Modulating the Behavioural Characteristics of Oral Squamous Carcinoma Cells

المشرف:

1. Prof. Ian Hart: Cancer Research United Kingdom (CR-UK) Tumour Biology Laboratory At Queen Mary, University Of London Centre For Tumour Biology
2. Dr. Gareth Thomas: Eastman Dental Institute, University College London

ملخص رسالة الدكتوراه (إنجليزي)

The incipient invasion of epithelial tumour cells, characterised by disruption of normal cell-cell adhesion, marks the point of transition to malignancy. Cadherins are a family of calcium-dependent, transmembrane, cell-cell adhesion molecules whose function requires association with the actin cytoskeleton of the cell through cytoplasmic proteins called catenins. Oral keratinocytes express E-cadherin, which is considered a regulator of the epithelial phenotype. Loss of E-cadherin commonly is seen in oral squamous cell carcinoma (OSCC), particularly in poorly differentiated tumours, allowing cells to detach from the tumour mass, invade and metastasise.

An E-cadherin negative OSCC cell line was identified where E-cadherin expression and function was restored through cDNA transfection resulting in functional cell surface expression of the protein and the formation of cell-cell attachments, with significant alteration in levels and distribution of catenins. Alteration of cell morphology, from a spindle to an epitheloid form, was observed. Additionally, restoration of E-cadherin showed a marked inhibition of the invasive potential of this OSCC cell line. These effects were not observed in the control cell line transfected with the expression vector containing antisense E-cadherin cDNA.

Most findings in cell and molecular biology, presented in the literature, are based, primarily, on *in vitro* studies obtained from the culture of cells growing in 2-dimensional (2-D) tissue culture dishes. In this study I have investigated if E-cadherin plays a role in modulating tumour cell growth in a 3-D, as opposed to a 2-D, environment. Results showed that the epitheloid-like morphology brought about by E-cadherin expression under 2-D conditions allows differences in density dependent inhibition to occur accompanied by enhancement in the apoptotic capacity of the cells. However, where

constraints of 3-D culture are imposed, these variations between E-cadherin expressing and non-expressing lines disappear. To explore the basis of these changes I have examined Western blot analysis of proteins known to play a role in mediating cell proliferation or regulation of apoptosis, such as Bcl-2, Akt-1, ILK and N-cadherin. I showed that changes in levels of expression of these proteins under 2-D conditions is markedly affected when cells were implanted in 3-D collagen I cultures.

I also investigated the possible molecular cross talk between E-cadherin and the β4-integrin subunit. Results obtained from β4-knock-down experiments showed that β4-integrin plays a role in the maturation of E-cadherin-dependent cell-cell contacts. I investigated the possible mechanisms of this apparent cadherin-integrin cross-talk and preliminary results showed that the function of β4-integrin was, potentially, executed through the Rac1 small Rho GTPase.