**CANCER 8**

**EXTERNAL FACTORS CONTROLLING CELL DIVISION**

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This lecture aims to outline the diverse factors in the extracellular environment that affect cell growth and proliferation.

**What external influences are detected by cells?**

* **Chemical**:- hormones, growth factors, ion concs, ECM, molecules on other cells, nutrient and dissolved gas (O2/CO2) concs.
* **Physical**:- mechanical stresses, the topography or “layout“ of the ECM and other cells

Although all external factors may potentially influence cell proliferation, the best understood, and the ones to be considered here are: Growth factors, cell-cell adhesion and cell-ECM adhesion.

**Anchorage dependence**

* in suspension, cells do not significantly synthesise protein or DNA
* cells require to be attached to ECM (and a degree of spreading is required) to begin protein synthesis and proliferation (DNA synthesis)
* attachment to ECM may be required for survival (e.g. epithelia, endothelia)

**Anchorage dependence**

Cell-ECM adhesion molecules

* Cells have receptors on their cell surface which bind specifically to ECM molecules
* these molecules are often linked, at their cytoplasmic domains, to the cytoskeleton
* this arrangement means that there is mechanical continuity between ECM and the cell interior

**Integrin structure**

**Integrins**

* are the most important ECM receptors
* αβ heterodimers (both sub-units span the plasma membraneare β known α and 8once), ~10
* α5β1recognise short, specific peptide sequences (e.g. fibronectin receptor binds asp-gly-arg (RGD)
* known α/β more than 20 combinations of
* each combination specifically binds a particular peptide sequence
* such peptide sequences found in more than one ECM molecule, e.g. RGD found in fibronectin, vitronectin, fibrinogen plus others
* linked, via actin-binding proteins, to the actin cytoskeleton (most integrins)
* α6β4 intergin complex found in epithelial hemidesmosomes,the linked to the cytokeratin (intermediate filament) network
* integrin complexes cluster to form focal adhesions (most) or )hemidesmosomes (α6β4
* these clusters are involved in signal transduction
* integrins also bind to specific adhesion molecules on some cells αvβ3 binds to PECAM-1(CD31) on endothelial cells in inflammation)(e.g.

**Signalling to and from ECM receptors**

* ECM receptors (e.g. integrins) can act to transduce signals
* e.g. ECM binding to an integrin complex can stimulate the complex to produce a signal inside the cell, i.e. “outside-in” signalling

**Signalling to and from ECM receptors (I)**

* a signal generated inside the cell (e.g. as the result of hormone binding to receptor) can act on an integrin complex to alter the affinity of an integrin (i.e. alter its affinity for its ECM binding)

this is “inside-out” signalling (e.g. in inflammation or blood-clotting, switching on adhesion of circulating leukocytes)

**“Outside-in” signalling**

* a cell can receive information about its surroundings from its adhesion to ECM
* e.g. the composition of the ECM will determine which integrin complexes bind and which signals it receives
* this can alter the phenotype of the cell

**Control of proliferation**

When cells in culture form a confluent monolayer, they cease proliferating and slow down many other metabolic activities. This used to be known as contact inhibition of cell division. Another set of experiments suggest that it is competition for external growth factors and not cell-cell contact responsible:- density dependence of cell division.

**Mechanism of anchorage dependence?**

* growth factor receptors and integrin signalling complexes can activate identical signalling pathways (e.g. MAPK)
* individually, this activation is weak and/or transient
* together, activation is strong and sustained
* the separate signalling pathways act synergistically

**Interactions between cells**

* long term, stable interactions resulting in formation of cell-cell junctions
* short-term transient interactions between cells which do not form cell-cell junctions

**Cell-cell contact between non-epithelial cells**

When non-epithelial cells “collide”, they do not form stable cell-cell contacts. They actually “repel” one another by paralysing motility at the contact site, promoting the formation of a motile front at another site on the cell, and moving off in the opposite direction.

This is contact inhibition of locomotion and is partly responsible for preventing the multilayering of cells in culture and in vivo.

**Long-term cell-cell contacts**

Upon contact, some cell types strongly adhere and form specific cell-cell junctions (adherens junctions, desmosomes, tight junctions, gap junctions) (see 1st year MCD lecture).

This is true of epithelial cells and endothelial cells, which form layers, and neurones forming synapses.

**β-catenin dynamics in cells: a mechanism for contact inhibition of proliferation?**

* when bound to cadherin at the membrane, **β-**catenin not available for LEF-1 binding and nuclear effects
* βnormally, cytoplasmic**-**catenin rapidly degraded
* β-catenin cytoplasmic levels rise as a result ofif inhibition of degradation or loss of cadherin-mediated adhesion, β-catenin/LEF-1 complex enters nucleus and influences gene expression, leading to proliferation.

**Cells can lose their social skills**

Under certain conditions, cells lose their behavioural restraints. As a result, they will

* proliferate uncontrollably (lose density dependence of proliferation)
* are less adherant and will multilayer (lose contact inhibition of locomotion and anchorage dependence)
* epithelia breakdown cell-cell contacts
* not Hayflick-limited, express telomerase i.e. cancer

**Many components of signal transduction pathways are proto-oncogenes**

* if the gene coding for a component of a signalling pathway is mutated so that the protein is constitutively active, that pathway will be permanently ‘on’
* receptors, signalling intermediates and signalling targets (e.g. transcription factors) are proto-oncogenes
* this is the mechanism of short-circuiting leading to uncontrolled proliferation as a result of loss of growth factor dependence etc.

**Metastasis**

* in addition to deregulated proliferation, a major feature of cancerous tumours is their ability to spread
* most human cancers are carcinomas (i.e. of epithelial origin)
* in order to spread to other sites (metastasis), cells must break away from the primary tumour, travel to a blood or lymph vessel, enter the vessel, lodge at a distant site, leave the vessel, and ultimately establish a secondary tumour

**How does a primary carcinoma cell metastasise?**

* cell-cell adhesion must be down-regulated (e.g. cadherin levels reduced)
* the cells must be motile
* degradation of ECM must take place; (matrix metalloproteinase (MMP) levels increased in order to migrate through basal lamina and interstitial ECM
* the degree of carcinoma cell-cell adhesion is an indicator of how differentiated the primary tumour is, and indicates its invasiveness and the prognosis for the patient.