**Cancer 6**

**Signaling mechanisms in growth and division**

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Intracellular signaling involves transmitting signals through the cell to control global cellular responses such as survival, division, differentiation and death. This frequently involves reception of an extracellular ligand by a cell surface receptor followed by production of a second messenger and signal transmission via:

• Regulation of protein function by reversible phosphorylation

• Signaling cascades

• G proteins (GTPases)

• Adapter proteins

This results in signal integration and amplification and regulation of divergent responses, and is modulated by other pathways.

Protein kinase cascades are characterised by the sequential phosphorylation of a series of kinases (at serine, threonine or tyrosine residues) ultimately resulting in the phosphorylation and activation or deactivation of target proteins. These cascades are regulated by the opposing action of specific protein phosphatases.

GTP-binding (G) proteins can be activated by certain cell surface receptors and exchange bound GDP for GTP, thus changing conformation and allowing them to interact with downstream effector molecules. This is reversed by intrinsic or stimulated GTPase activity.

Nucleotide exchange is frequently stimulated by exchange factors that are brought to

activated receptors by so-called adaptor proteins (e.g. Grb2) that have no catalytic function but serve to couple receptor to downstream pathways, and also provide an additional point of regulation.

Examples of peptides involved in cell growth regulation are EGF and PDGF. These bind as dimers to their transmembrane tyrosine kinase receptors causing receptor dimerisation and transphosphorylation on tyrosine. The resulting phosphorylated tyrosines are docking sites for adaptors and downstream signaling molecules such as the Grb2/Sos exchange factor for the small G protein Ras, a key player in the regulation of normal cell growth and differentiation that is often mutationally activated in cancer cells.

Ras then brings the kinase Raf to the membrane, Raf is activated and triggers a kinase (MAPK or ERK) cascade involving several downstream kinases ultimately leading to phosphorylation of targets involved in regulation of gene transcription, protein synthesis and the cell cycle.

Cell cycle control is based on cyclically activated protein kinases, the cyclin-dependent kinases (Cdks), which are present in proliferating cells throughout the cell cycle and are regulated by interaction with cyclins and by complex phosphorylation. Cyclins are proteins whose expression is regulated transiently at specific points in the cell cycle by cyclical synthesis and degradation.

Different cyclin-Cdk complexes trigger different events in the cell cycle such as S phase (Cdk2/Cyclin A), mitosis (Cdc2/Cyclin B) and G1 progression (Cdk2/Cyclin E). Genes activated by the Ras-ERK pathway include the “immediate early” genes c*-jun*, c*-fos*, and c*myc* encoding transcription factors which in turn activate other genes (e.g. cyclin D). Cyclin D then activates Cdk4 and Cdk6 to stimulate synthesis of cyclin E.

Cdks phosphorylate proteins (on serine or threonine) to effect cell cycle progression,

including nuclear lamins (causes breakdown of nuclear envelope) and Retinoblastoma protein (Rb; activates gene transcription required for cell growth and division).

Thus, the cell cycle is controlled by a complex network of interacting proteins providing multiple checks and balances.

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