Cancer And The Role Of Cell Cycle Checkpoints

Cell division and cell proliferation as well as cell death are the two major physiological processes that are used to regulate tissue homeostasis in the adult organism. Genome integrity, cell proliferation and survival are controlled by a network of pathways that include cell cycle checkpoints, DNA repair, DNA recombination and programmed cell death. Tissue homeostasis involves the regulated organisation of these processes within cell populations as well as the to the ability to either enhance proliferation or diminish cell population depending on the cell type and condition (Cooper & Youle, 2012). The loss of both genomic integrity and cell death regulation can potentially lead to uncontrolled cell growth and disease development (Zhivotovsky & Orrenius, 2010) and hinders cell viability.

Proto-oncogenes regulate normal cell behaviour and growth by encoding for proteins that are necessary for cell division. Examples of proto-oncogenes include growth factors, transcription factors and intracellular transducers. They are usually conditionally expressed, only through the stimulation of the cell by its specific growth factor, however in certain conditions they can transform to an overactive state. This dysregulated state is primarily present within cancer and leads to tumour formation.

At least three mechanisms can suffice the conversion of a proto-oncogene to oncogene. Point mutations, localized gene amplification of a DNA segment that includes a proto-oncogene or chromosomal translocation that brings a growth-regulatory gene under the regulation of a dissimilar promoter (Alberts, 2000).

An example of proto-oncogene that behaves as a growth factor is epidermal growth factor receptor (EGFR), which is a tyrosine kinase receptor. EGF is a common mitogenic growth factor that stimulates the proliferation of multiple cell types, in particular fibroblasts and epithelial cells (Guillaud & Wong). EGF is activated upon ligand binding via the EGF receptor (EGFR/ErbB), which in turn initiates intracellular signalling. Moreover, the EGFR family is expressed in neurons within regions of the central nervous system, such as the hippocampus, cerebellum, and cerebral cortex in addition to other regions of the central nervous system (CNS). EGF stimulates the differentiation, maturation and survival of a multiple neurons (Guillaud &Wong). The overexpression and amplification of the EGFR gene are predominantly expressed within many cancers leading to abnormal EGFR signalling. e.g. avian erythroblastic leukaemia. In some tumours, EGFR is activated by autocrine or paracrine growth factor loops, whereas in others activating mutations encourage EGFR signalling. Furthermore, the inability to reduce receptor signalling via receptor downregulation can result in cellular transformation; heterodimerization of EGFR with ErbB2 prevents downregulation of EGFR and hence, further enhances growth factor signalling (Zandi et al, 2007).

Cell death also allows for effective regulation of tissue homeostasis as mentioned above and is classified three main subtypes: apoptosis, necrosis and autophagy. Necrosis can be described as passive, accidental process resulting from trauma or toxicity, whereas autophagy is a regulated form of cell degradation via lysosomes. Apoptosis is a form of active and programmed cell death (PCD) that occurs in response to certain stimuli. PCD occurs in health, during development and ageing and aids with cell population maintenance. Additionally, it is used as a

defence mechanism within the immune system to prevent self-immunity or when cells are injured by diseased/harmful agents (e.g. chemical toxins, ROS and radiation).

Apoptosis is a very complicated process that involves multiple components and it can be initiated through the action of 2 molecular pathways; intrinsic and extrinsic pathway, both of which lead to caspase activation. The Extrinsic pathway specifies cellular death activated through extracellular signals which result in ligand binding via trans-membrane receptors, also known as death receptors. The intrinsic pathway is activated in response to several stress-promoting cellular conditions including DNA damage and oxidative stress. Excessive cell death can be regulated through pathway inhibition via growth factors and cell survival signal expression; enhancing cell viability.

A family of Bcl-2 proteins act as key regulators of the intracellular apoptotic pathway (figure 1) and all components are predominately characterized by the presence of at least one Bcl-2 Homology (BH) domain. They can be classified as anti-apoptotic members containing three or four BH domains (such as Bcl-2, Bcl-xl) and pro-apoptotic members with two or three BH domains (Bax, Bak,) or with just one (Bad, Bik, Bid,Puma) (Favaloro, 2012). The pro-apoptotic members facilitate apoptosis by disrupting mitochondrial membrane integrity through pore formation, whereas, the anti-apoptotic proteins would halt apoptosis by interfering with pro-apoptotic protein accumulation.

Tumour suppressor genes (TSGs) also play a key role in cell proliferation and cell viability regulation. They are involved in DNA damage repair, inhibition of cell division, imitating apoptosis and metastasis suppression. P53 is one of the most significant tumour suppressor genes and is located on chromosome 17 and encodes a 393 amino acid protein. In normal cells, p53 has a short half-life and is maintained at low levels by MDM2. MDM2 is an E3 ubiquitin ligase that promotes the ubiquitination and proteasomal degradation of p53. Cellular stress induces post-translational modification of p53 via phosphorylation and hence allows for its activation (illustrated in figure 1). Upon p53 binding to DNA it can induce cell cycle checkpoint activation, cellular senescence, apoptosis, or autophagy. For example, Polo-like kinase 1 is a key p53 target for G2-M cell cycle checkpoint activation (Lee & Muller, 2010). The Inactivation of p53 is apparent within many cancers and results in incorrect cell cycle functioning; inactivation through homozygous deletion, point mutations and methylation has been detected in human cancers (Wang, 2018).

Despite the beneficial role apoptosis has within healthy cellular responses, the dysregulation of cell death pathways is detected in cancer. For example, Bcl-2 has been found to be overexpressed in Hodgkin’s lymphoma, small cell lung and renal cell carcinoma. A polymorphism within the Bcl-2 promoter is associated with aggressiveness and worsened diagnosis in glioblastoma and chronic lymphocytic leukaemia. Furthermore, Apaf-1 inactivation is found to be frequently silenced or inactivated in human cancers; downregulation of Apaf-1 via epigenetic changes is present in melanomas, glioblastomas, leukaemia’s and cervical carcinomas (Favaloro, 2012).

Within neurodegenerative diseases we further observe cell death dysfunction. Caspases 1 and 3 In involvement has been shown in Parkinson’s disease (PD) has been shown using animal models. PD has been associated to mutations within the PTEN-induced kinase 1 (PINK1) gene. This gene is associated with the inhibition of mitochondria-dependant apoptosis and hence a loss of PINK1 can elevate caspase levels (Favaloro, 2012).

Aside from the diseases mentioned, cell death and proliferation impact numerous other disease pathways and hinder the cell viability. This disruptive ability demonstrates the significance behind functioning cell homeostatic mechanisms and the need for regulatory measures.