Summary & Conclusion

Apoptosis

Apoptosis is a form of programmed cell death in multicellular organisms. It involves a series of biochemical events leading to a characteristic cell morphology and death .the morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation . Processes of disposal of cellular debris by phagocytosis do not damage the organism differentiate apoptosis from necrosis.

Apoptosis can be triggered by various stimuli from outside or inside the cell, e.g. by ligation of cell surface receptors, by DNA damage as a cause of defects in DNA repair mechanisms, treatment with cytotoxic drugs or irradiation, by a lack of survival signals, contradictory cell cycle signalling or by developmental death signals. Death signals of such diverse origin nevertheless appear to eventually activate a common cell death machinery leading to the characteristic features of apoptotic cell death.

Extrinsic apoptosis pathway

In extrinsic apoptosis pathways, e.g. procaspase-8 is recruited by its DEDs to the death inducing signalling complex (DISC), a membrane receptor complex formed following to the ligation of a member of the tumor necrosis factor receptor (TNFR) family. When bound to the DISC, several procaspase-8 molecules are in close proximity to each other and therefore are assumed to activate each other by autoproteolysis.

Intrinsic apoptosis pathway

Intrinsic apoptosis pathways involve procaspase-9 which is activated downstream of mitochondrial proapoptotic events at the so called apoptosome, a cytosolic death signalling protein complex that is formed upon release of

cytochrome c from the mitochondria. In this case it is the dimerization of procaspase-9 molecules at the Apaf-1 scaffold that is responsible for caspase-9 activation. Once the initiator caspasce have been activated, they can proteolytically activate the effector procaspases-3, -6, and -7 which subsequently cleave a specific set of protein substrates,including procaspases themselves, resulting in the mediation and amplification of the death signal and eventually in the execution of cell death with all the morphological and biochemical features usually observed.

Mitochondrial regulation

Apoptotic proteins that target mitochondria affect them in different ways; they may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out. There is also a growing body of evidence that indicates that nitric oxide (NO) is able to induce apoptosis by helping to dissipate the membrane potential of mitochondria and therefore make it more permeable.

Mitochondrial proteins are released into the cytosol following an increase in permeability, binds to inhibitor of apoptosis proteins (IAPs) and deactivates them, preventing the IAPs from arresting the apoptotic process and therefore allowing apoptosis to proceed. IAP also normally suppresses the activity of a group of cysteine proteases called caspases, which carry out the degradation of the cell, therefore the actual degradation enzymes can be seen to be indirectly regulated by mitochondrial permeability.

Cytochrome c is also released from mitochondria due to formation of a channel, in the outer mitochondrial membrane, and serves a regulatory function as it precedes morphological change associated with apoptosis. Once

cytochrome c is released it binds with Apaf-1 and ATP, which then bind to pro-caspase-9 to create a protein complex known as an apoptosome.

The channel is itself subject to regulation by various proteins, such as those encoded by the mammalian Bcl-2 family of anti-apoptopic genes Bcl-2 proteins are able to promote or inhibit apoptosis either by direct action on The channel or indirectly through other proteins. It is important to note that the actions of some Bcl-2 proteins are able to halt apoptosis even if cytochrome c has been released by the mitochondria.

Apotosis in health

The development and maintenance of multicellular biological systems depends on a sophisticated interplay between the cells forming the organism, it sometimes even seems to involve an altruistic behaviour of individual cells in favour of the organism as a whole. During development many cells are produced in excess which eventually undergo programmed cell death and thereby contribute to sculpturing many organs and tissues .

A particularly instructive example for the implication of programmed cell death in animal development is the formation of free and independent digits by massive cell death in the interdigital mesenchymal tissue. Other examples are the development of the brain, during which half of the neurons that are initially created will die in later stages when the adult brain is formed and the development of the reproductive organs. Also cells of an adult organism constantly undergo physiological cell death which must be balanced with proliferation in order to maintain homeostasis in terms of constant cell numbers. The majority of the developing lymphocytes die either during genetic rearrangement events in the formation of the antigen receptor, during negative selection or in the periphery, thereby tightly controlling the pool of highly

efficient and functional but not self-reactive immune cells and at the same time keeping lymphocyte numbers relatively constant.

Taken together, apoptotic processes are of widespread biological significance, being involved in e.g. development, differentiation, proliferation/homoeostasis, regulation and function of the immune system and in the removal of defect and therefore harmful cells.

Disease as a consequence of dysregulated apoptosis

Dysregulation of apoptotic signalling can play a primary or secondary role in various diseases with insufficient apoptosis leading to e.g. cancer (cell acumulation, resistance to therapy,), autoimmunity (failure to eliminate autoreactive lymphocytes), persistent infections (failure to eradicate infected cells), whereas excessive apoptosis contributes to e.g. neurodegeneration (Alzheimers' disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis), autoimmunity (uncontrolled apoptosis induction in specific organs), AIDS (depletion of T lymphocytes), and ischaemia (stroke, myocardial infarction). Malfunction of the death machinery results from the mutation of genes that code for factors directly or indirectly involved in the initiation, mediation, or execution of apoptosis, and several mutations in apoptosis genes have been identified as a causing or contributing factor in human diseases as cardiovascular disease, endocrine disease, gastrointestinal disease, liver disease ,renal diseases and lung diseases.

Therapeutic Strategies For Regulation of The Apoptotic Process

The role of apoptosis in the pathogenesis of various diseases implicates immense potential for the manipulation of apoptosis to treat these diseases.

Apoptosis as target for novel drugs

Targeting apoptotic cell death pathways provides wideranging opportunities for the discovery and development of novel drugs. Some targeted therapies that selectively induce apoptosis in cancer cells are already marketed, and numerous pro-apoptotic drugs for treating cancer are currently being developed. The antiapoptotic drugs that are most advanced in development are targeting acute disease indications such as stroke, myocardial infarction and sepsis, in which the role of apoptosis has been best defined and inhibitors of the apoptotic pathway have shown activity in various animal models.

Apoptosis is a critical endpoint that coincides with the goal of successful treatment of human malignancies . In cancer treatment , the therapeutic goal is to trigger tumor-selective cell death. Activation of the apoptotic pathway in tumor cells offers attractive and potentially effective therapeutic targets.

Cell cycle regulators (cyclin-depandent kinases , p21 gene) and modulators of apoptosis (Bcl-2 oncoprotein , p53 tumor suppressor gene , surviving protein , etc) have attracted renewed interast as potential targets for anti-cancer therapy).