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Chapter 1

Introductory Chapter: Cytotoxicity

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77244

1. Introduction

Cell cytotoxicity refers to the ability of certain chemicals or mediator cells to destroy living cells. The cytotoxicity is a very important aspect, as destruction of healthy living cells around the wound will have a negative impact on the healing process. Cytotoxicity is the general quality of being toxic to cells, and can be caused by chemical stimuli, exposure to other cells (NK or T cells for example), or physical/environmental conditions (radiation exposure, temperature or pressure extremes, etc.) [1]. Chemical toxicity can occur in many ways, but we hypothesize that it can be broadly classified into two major categories: disruption of specific biomolecular targets or pathways (e.g., receptor agonist/antagonist effects and enzyme activation/inhibition), or generalized disruption of cellular machinery that can lead to cell stress and cytotoxicity [2]. Chemical toxicity can arise from disruption of specific biomolecular functions or through more generalized cell stress and cytotoxicity-mediated processes. Chemical toxicity can occur in disruption of specific biomolecular targets or pathways (e.g., receptor agonist/antagonist effects and enzyme activation/inhibition), or generalized disruption of cellular machinery that can lead to cell stress and cytotoxicity. Cell-disruptive processes include protein, DNA, or lipid reactivity; physicochemical disruption of proteins or membranes (e.g., by surfactants); or processes such as apoptosis, oxidative stress response, mitochondrial disruption, endoplasmic reticulum (ER) stress, microtubule disruption, or heat shock response [2]. Treating cells with a cytotoxic compound can result in a variety of cell fates. By using a cytotoxic compound, healthy living cells can either be induced to undergo necrosis (accidental cell death) or apoptosis (programmed cell death). Whereas apoptotic cell death is slower, more orderly, and is genetically controlled, the cells may undergo necrosis, in which they rapidly loss membrane integrity and die rapidly as a result of cell lysis. The cells can stop actively growing and dividing (a decrease in cell viability). Cytostasis is a special category of cytotoxicity, wherein cells remain alive but fail to grow and divide [1]. Cell death/cytotoxicity cannot be the sole causal driver of this phenomenon. Some cytotoxicity may be driven by physicochemical factors, such

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as protein denaturation or reactivity, which would affect both the cell-free and cell-based assays. Another possibility is very low-affinity non-covalent binding to receptors, enzymes, etc. that only occurs at very high concentrations [2].

1.1. Cytotoxicity

Cytotoxicity is one of the most important methods for biological evaluation as it has a series of advantages, along with the preferred and mandatory items. Given this information, the ability to accurately measure cytotoxicity can prove to be a very valuable tool in identifying compounds that might pose certain health risks in humans [3]. The cytotoxicity test is one of the most important indicators of the biological evaluation system *in vitro* to observe the cell growth, reproduction and morphological effects by chemicals, and with the progress of modern cell biology; experimental methods to evaluate cytotoxicity are also continuously being developed and improved [3].

1.2. Cytotoxicity studies

Cytotoxicity studies are a useful initial step in determining the potential toxicity of a test substance, including plant extracts or biologically active compounds isolated from plants. Minimal to no toxicity is essential for the successful development of a pharmaceutical or cosmetic preparation and in this regard, cellular toxicity studies play a crucial role. The concept of basal cytotoxicity, where deleterious effects are noted on structures and functions common to all human cells, is relevant when considering the relationship between acute toxicity and cytotoxicity. The selectivity index is an important measure to identify substances with promising biological activity and negligible cytotoxicity. Various bioassays and a number of different cell lines have been used to assess cytotoxicity of chemicals. Regulations of cytotoxicity *in vitro*, countries have to make the relevant provisions of the corresponding cytotoxicity tests according to their actual situation [4]. With the continuous development of cytotoxicity tests, methods, such as detection of cell damage by morphological changes, determination of cell damage, measuring cell growth and metabolic properties, have appeared and have gradually been developed from qualitative evaluation to quantitative [5–8]. The ability to measure early indicators of toxicity is an essential part of drug discovery. *In vitro* cytotoxicity assays involving tissue specific cell cultures are considered as valuable predictors of human drug toxicity. However, there are no uniform cytotoxicity test methods and all these existing methods have particular problems. Measuring cell cytotoxicity also proves to be quite indispensable in the process of developing therapeutic anti-cancer drugs. By determining the cytotoxicity levels of cancer cells, anti-cancer medications can hinder the proliferation of target cells either by messing with their genetic material or by blocking the nutrients that the cells needs to survive. Additionally, understanding the mechanisms involved in cytotoxicity can likewise give researchers a more in-depth knowledge on the biological processes (both normal and abnormal) governing cell growth, cell proliferation, and death.

Identification of cytotoxic chemicals may be crucial in helping to explain target cells, and organ toxicity and species differences. Understanding the consequences of the induced natural

or chemical substances should be helpful in creating proper different models for extrapolation to low doses. In addition, biomarkers of exposure are gaining importance as tolls in the cytotoxicity research. The detection of the cytotoxic chemicals in humans may be useful in assessing human exposure or cellular injury. Also, understanding specific mechanisms may be useful in identifying the potential target tissues *in vivo* because cell types have different capacities to handle different types of chemicals.

Today, we need to understand the cytotoxicity that particular cells, organs, and organism are facing and identifying specific treatment interventions to address their unique needs both at macro- and micro-levels. The scope of this book goes precisely toward this direction. Each chapter offers the ways of intervention to address some of the most pressing cytotoxic chemicals of our time.

Cytotoxicity book is a web based resource, encompassing some of the cytotoxicity natural and different chemical substance, such as natural coumarins, colchicine alkaloids, titania nanosheets, asbestos fiber, nanomaterials, nanocrystals, and composites, and curcumin loaded copolymer encapsulated ZnO nanocomposites.

"Cytotoxicity" is an essential reading to all medical students, biologist, biochemist, and professionals involved in the field of toxicology. The book is an useful and ideal guide for novice researchers interested in learning research methods to study cytotoxic bioactive compounds.

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