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Title: **Manipulation of Programmed Cell Death in Cell Culture**

Apoptosis is a highly coordinated form of programmed cell death characterized by distinct morphological and biochemical changes and is crucial for the development, maintenance and disease control of multicellular organisms. Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled, regulated fashion. This makes apoptosis distinct from another form of cell death called necrosis in which uncontrolled cell death leads to lysis of cells, inflammatory responses and potentially to serious health problems. Apoptosis, by contrast, is a process in which cells play an active role in their own death, so often referred to as cell suicide.

There is increasing evidence that apoptotic-like cell death pathways also exist in unicellular organisms such as yeast. These studies have successfully validated yeasts as a powerful genetic tool with which to investigate mechanisms of apoptosis. *Candida albicans* is one of the most commonly encountered human pathogens, causing a wide variety of infections ranging from mucosal infections in generally healthy persons to life-threatening systemic infections in individuals with impaired immunity. Exploring the occurrence of apoptosis in *Candida* can be used as a tool for understanding and characterization of the molecular mechanisms that regulate the active cell death process. This could facilitate the development of novel antifungal agents that work by activating the endogenous cell suicide mechanisms in this important pathogen.

In our study, various concentrations of test agents (Nitric oxide, Hydrogen peroxide, acetic acid & garlic extract) were investigated for their effect on growth and cell death parameters of *Candida*. It was observed that the agents have cytotoxic effects which was dose dependant and triggered apoptotic cell death. The mode of programmed cell death was characterized by examination of cell death markers that are typical of apoptosis. An early marker of apoptosis, translocation of the phospholipids to the outer leaflet of plasma membrane was observed. Breakage of double-stranded DNA based on labeling the free 3'-OH termini by biotinylated nucleotide was seen, but the endonuclease cleavage of DNA into nucleosomal fragments visible as DNA "ladder' was absent. In order to bring about an organized form of cell death, certain cysteine proteases, designated as caspases in metazoans break down specific substrates and its activation is a key process in apoptosis in mammalian cells. The activity of caspases was not observed in our studies, which suggests the cell death pathway in *Candida* to be caspase independent. Mitochondria represent key organelles for survival of the cells and their role in programmed cell death is known. Interference in the electron-transport chain within the mitochondria by the stimuli was observed and it was dependent on the duration of exposure to the stress agents.

All the test agents used in our study, have the potential as pro-apoptotic agents. This capability can be exploited as tool for development of useful compounds, such as fungicides and antifungal therapeutics and suggests a new approach for drug design against fungal infections. The field of apoptosis has grown rapidly and the increased understanding will be the key, both in terms of increasing our knowledge of the apoptotic mechanisms and as a tool to develop therapeutics.