


Chapter 9

Apoptotic Pathway: A Propitious Therapeutic Target for Cancer Treatment


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ABSTRACT

Cancer is a major killer disease caused by uncontrolled growth and invasion of cells. Apoptosis is the cell's natural mechanism of death, which maintains tissue homeostasis. Any mutation that disturbs the apoptotic pathway leads to deregulated proliferation, resistance, and evasion of apoptosis. This evasion is one of the hallmarks of malignant developments. Apoptosis takes place via two distinct pathways i.e. the intrinsic and the extrinsic pathways. These pathways use cleaved caspases to execute apoptosis which in turn cleave many downstream proteins to kill the cells. They can also be inhibited through various means that include up-regulation of anti-apoptotic and down-regulation of pro-apoptotic factors. The authors here aim to impart a comprehensive understanding of the biochemical characteristics of these pathways that render scientists target these pathways and assess apoptosis restoring abilities of the novel drugs and natural products for cancer treatment.

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INTRODUCTION

To carry out essential biological functions, the structural and functional organization of all the cells in our body and the macromolecules (DNA, RNA, proteins etc.) within should be perfectly balanced and carefully regulated. Typically, a cell grows and divides to increase its number according to the requirement of the body and keeps the individual healthy. Any alteration in the expression or functions of the factors responsible for cell cycle progression and normal cell division, can either lead to abnormally high or poor growth and division of cells. The abnormal proliferation can lead to highly abnormal cell growth turning them cancerous. A cancerous cell performs abnormal functions and colonizes territories which are reserved for normal cells. From these aberrantly growing cells, a tumour- the neoplasm (reliantly growing mass of abnormal cells) may arise. It is estimated that 20% of males and 17% of females get cancer at some point in their lifetime and about 13% of males and 9% of female die from it (Jemal et al., 2011). Roughly 55% of cancer death occurs in less developed regions of the world that are the countries with a low or medium level of the Human Development Index (Bray et al., 2012). According to recent reports, cancer is a major killer disease of humans (Priestly et al., 2019). It is expected that approximately 1.8 million new cancer cases with about 0.6 million death will occur in 2020 in the United States itself (Siegal et al., 2020). In short, cancer is one of the most aggressive kind of diseases and proper treatment of which would be a boon to mankind. Unfortunately, cancer is mostly associated with poor treatment efficacy which makes the researchers constantly search for the novel and effective treatment strategies to target cancer cells efficiently and specifically.

As discussed above, the development and progression of cancer are caused by the alteration of various cellular pathways. In 2011, Hanahan and Weinberg proposed eight hallmarks of cancer and the two enabling characteristics of it (Figure 1) that still continue to provide a solid foundation for understanding the biology of cancer. Understanding of these hallmarks may help in the development of the unique and efficient treatment modalities against cancer by targeting one or more of these pathways. One such pathway is the apoptotic pathway that is well established to serve as a blockade to cancer progression (Adam and Corry, 2007). There are various pro-apoptotic and anti-apoptotic proteins that promote and down-regulate apoptosis respectively. A Cancer cell manages to suppress pro-apoptotic proteins and up-regulate anti-apoptotic proteins, thereby resisting cell death via apoptosis, which in turn favours cell proliferation. In this chapter, apoptosis and all its modulators and players are being discussed in detail.

APOPTOSIS AND OTHER TYPES OF CELL DEATHS

The word “apoptosis” comes from the Greek words “απο” (apo) and “πτωσις” (ptosis) that means “dropping off” in context to the falling of leaves from trees during autumn. It is a type of programmed cell death. In a biological perspective, it is used to describe cell death upon receiving some stimuli. It was first described by Kerr, Wyllie, and Currie in 1972.

It is a part of normal developmental and ageing phenomena that maintains the homeostasis of cell populations in tissues. It also occurs as a defence mechanism in the immune system or when cells are attacked by a certain disease or harmful agent (Norbury and Hickson, 2001).

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