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# Review on Cell Death Based Therapy

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**Abstract :**

Apoptosis means programme cell death. This is a body mechanism by which its help us to remove the mature cell and developed our body. In present days this Apoptosis became a most interesting and hottest topic in Medical ground. In 1972, Kerr et al, Wyllie,and Currie coined the term “apoptosis” to describe a basic biological phenomenon with wide ranging implication in tissue kinetics.They postulated that apoptosis can occure spontaneously in untreated malignant neoplasm, and is involved in therapeutically induced tumor regression. Similarly, apoptosis has a big role from survival from many diseases. Mainly CD95 and some other inhibitors of apoptosis has a big role in the survival of many disease. The targeted induction of necroptosis represents a promising strategy to overcome apoptosis resistance in cancer.To the present days,more than ten different cell death modalities have been recognised by the Nomenclature committee on cell death. The disturbance in cell death pathways are not only linked with cancer but also other diseases of enormous social importance,such as HIV,

Atherosclerosis, Ischemia, Reperfusion injury, Infection, Inflammation, Autoimmune and neurological disorder also.

KEY WORDS : programmed cell death, Tumor, Autoimmune disease

## 1. INTRODUCTION

After being familier with the term apoptosis Anna Kane Laired suggested that the retardation of tumor growth observed by researchers and clinicians might be due to an active decrease in tumor growth rate or to cell death. She postulated that "stimulation of natural growth-retarding factors might be of practical importance in reducing the incidence of clinical cancer, i.e., the systemic illness and death of the host, if tumor growth could be retarded enough to bring it to an upper limit that is within the physiological tolerance of the host"[1].In case of cancer the tumor cell growth can be easily reduced by anti apoptotic agents like Bcl2.

A retrospective look at the basis of human disease pathogenesis almost always reveals an apoptotic component that either contributes to disease progression or accounts for it. What makes this field particularly exciting is the breadth of therapeutic opportunities that are on offer. The pace of apoptosis research has raised expectations that therapeutics will follow soon. But many of the organizations that are best placed to take advantage of these discoveries consider the ability to modulate the life or death of a cell for the purpose of disease treatment as perhaps being 'too good to be true'. Nevertheless, practical therapeutics that modulate apoptosis will no doubt appear in the clinic or on the shelf in the next few years.

An accumulation of all the data says that suppression or activation of one type of cell death can influence the activity of another and that the balance between them can affect the response of cells to treatment.many types of apoptosis help to remove the disease from the body like necroptosis or ferroptosis (associated with kidney-associated disease).Now a days,cancer is the most important topic to research and scientist have found many apoptotic inhibitors which can give relief mankind from cancer.Not only cancer but other diseases too.

The U.S. Food and Drug Administration (FDA) recently approved pembrolizumab, an anti-programmed cell death protein 1 cancer immunotherapeutic, for use in advanced solid tumors in patients with the microsatellite-high/DNA mismatch repair-deficient biomarker. [2]

In this review paper our key agenda is to know how the disease are cure by cell death base treatment (apoptosis and necrosis).

## 2. MECHANISM OF CELL DEATH BASE TREATMENT IN CANCER

From the various research it is proved that tissue specific and organ specific cell death influence how various disease respond to treatment.Researchers are also seen that suppression or activation of one type of cell death can results the activity of another and the balance between them can affect the response of cells to treatment.

There are several factors that can lead to drug resistance, such as disrupted apoptobsis machinery, overactive pro-survival signaling pathways, increased expression of the therapeutic target, activation of alternative compensatory pathways, a high degree of molecular heterogeneity, and upregulation of drug transporters [3]. Drug resistance has frequently been associated with genetic mutations and/or with abnormal expression of apoptosis-related molecules, such as FLIP, Bcl-2, Bcl-XL, MCL-1, p53, APAF-1, Bax, Fas, FADD, and caspases .[4]

Until a few years ago, it was believed that efficient anticancer regimens would either kill tumor cells, by engaging the apoptotic machinery, or permanently arrest them in the G1 phase of the cell cycle. More recently, it was observed that some anticancer agents can induce other forms of cell death, such as programmed necrosis or mitotic catastrophe-engaged apoptosis [5]. This aspect may be particularly interesting since: (i) necrosis could prove helpful in removing those cancer cells that have developed resistance to apoptosis, and (ii) cancer cells are particularly susceptible to the induction of mitotic catastrophe thanks to their genomic instability [6]. In fact, an entire class of anticancer agents, such as taxanes and vinca alkaloids, triggers mitotic catastrophe by binding to tubulin and disrupting the mitotic spindle.[7]

Nonetheless, since most, if not all, cancer cells exhibit or acquire increased resistance against pro-apoptotic agents, the future of anticancer therapy also relies on the exploitation of non- and pre-apoptotic signaling cascades. For instance, as mentioned above, another intensively studied programmed cell death pathway of interest in the field of oncology is called necroptosis, a process regulated via the RIPK1/RIPK3/MLKL activation pathway [8,9]. Of notice, this pathway is often deregulated in tumor cells, including melanoma cells in which RIPK3 expression is lacking [10,11]. Conventional pro-apoptotic agents, including TNF-related apoptosis-inducing ligand (TRAIL), the inhibitors of apoptosis protein inhibitors (IAP), Bcl-2 and several anticancer drugs can induce necroptosis, when apoptosis is blocked. For example 5-Fluorouracil (5-FU) induces RIP1/MLKL-dependent necroptosis in caspase-3-deficient cancer cells [12], whereas cisplatin (CDDP) caused RIP3-dependent necroptosis in apoptosis-resistant cancer cells through necrosome formation and autocrine TNF-α signaling [13]. Interestingly, necroptosis is often accompanied by autophagy, which may be responsible for suppression of apoptosis and bias toward necroptosis.

## 3. CELL DEATH BASE TREATMENT

In present we can prevent many diseases by the effect of apoptotic agents or apoptotic inhibitors.

### 3.1. Crohn's disease

The combination of a novel caspase inhibitor IDN-7314 with 5-fluorouracil synergistically blocked tumor growth compared with 5-fluorouracil alone, via induction of necroptosis[14]. However, activation of necroptosis does not always imply successful therapy. Necroptosis is involved in the regulation of pathogenesis of inflammatory diseases, suggesting that triggering necroptosis in cases of Crohn's disease or inflammatory skin disease might have off-target effects, leading to pathological inflammation of normal tissues. These concerns should be taken into consideration during the planning of treatment. With these concerns in mind, Infliximab (Remicade) was successfully tested as a potential treatment for Crohn's disease, which is associated with inflammasome dysfunction.

### 3.2. Autoimmune and inflammatory disease

The role of necroptosis in neutrophil cell death is discussed by Wang and colleagues [15]. The authors highlight the key inducers of necroptosis in neutrophils. Thus, inhibition of caspase-8 activates apoptosis in response to the presence of the TNF ligand and RIPK3-dependent necroptosis can be triggered by phagocytosis of S. aureus. However, under some conditions, TNFR1 stimulation via TNF triggers other cellular pathways, such as activation of NF-kB signaling or apoptotic cell death. Since neutrophils are involved in various types of tissue inflammation and disease, it is important to understand the different mechanisms regulating neutrophil necroptosis in order to uncover novel drug targets for treatments of autoimmune and inflammatory diseases.

### 3.3. Urinary tract cancer

Martin-Sanchez and colleagues[16] describe the role of different cell death modalities in the pathogenesis and therapy of urinary tract-associated diseases. In cancer of urinary tract there are several key processes that lead to escape from apoptosis, including autophagy, downregulation of Fas and caspase-3 as well as upregulation of Bcl-2. A deficiency of VHL in renal cell carcinoma makes it resistant to NK cells and hypoxia-induced cell death, whilst inflammatory signaling induced by NF-kB promotes necroptosis. Tumors of the urinary tract develop resistance to cell death, but infection of urothelial cells with uropathogenic E. coli may,

depending on the bacterial strain, prevent host cell death or promote cell death by apoptosis, necrosis or an iron-dependent mechanism.

### 3.4. Embryonic development

Apoptosis, or programmed cell death, is a mechanism in embryonic development that occurs naturally in organisms. Apoptosis is a different process from cell necrosis, which is uncontrolled cell death usually after infection or specific trauma. As cells rapidly proliferate during development, some of them undergo apoptosis, which is necessary for many stages, including neural development, reduction in egg cells (oocytes) at birth, as well as the shaping of fingers and vestigial organs in humans and other animals. Sydney Brenner, H. Robert Horvitz, and John E. Sulston received the Nobel Prize in Physiology or Medicine in 2002 for their work on the genetic regulation of organ development and programmed cell death. Research on cell lineages before and after embryonic development may lead to new ways to reduce or promote cell death, which can be important in preventing diseases such as Alzheimer's or cancer.

### 3.5. Immunotherapy

The role of the tumor vasculature in anti-tumor immunity and immunotherapy is a hot topic in cancer biology and is summarized by Schaaf and colleagues [17]. Activated CD8+ T cells can recognize tumor-associated antigens at the surface of tumor cells and promote tumor cell death via the perforin-granzyme and/or FasL/TRAIL systems. However, the tumor vasculature creates physical and functional barriers to infiltration of immune cells. The authors describe the mechanisms by which tumor-associated blood vasculature promotes an immunoresistant tumor microenvironment. At present, several methods of stimulating anti-tumor immunity with IL-2, TNF-α, and IFN-γ are subject to intensive investigation.

### 3.6. Neuroblastoma :

Amplification of MYCN and mutations in anaplastic lymphoma kinase (ALK) are considered the main drivers of neuroblastoma (NB). Valter and colleagues discuss various pathways that allow NB cells to escape death [18]. It has been suggested that MYCN plays a role in regulation and expression of p53 and Tap73 and their relation to apoptosis in NBs. Hypoxia promotes activation of several factors, including HIF-1 that can block apoptosis by inhibiting p53 or promote tumor growth by stimulation of glycolysis and angiogenesis. Hence, it has been proposed that inhibitors of HIF-1 could promote apoptosis in NB cells. Since many NB cells do not express caspase-8, treatments that increase expression of necroptotic proteins are amongst the promising strategies for triggering necroptosis in NBs.

### 3.7. Gleoblastoma

Simone Fulda[19]discusses potential routes to reactivation of pathways triggering cell death in glioblastomas. Current treatment regimens for glioblastoma include radiation and chemotherapy with the alkylating agent temozolomide (TMZ). It has been suggested that SMAC mimetics operate synergistically with TMZ by promoting apoptotic cell death. This mechanism would engage NF-κB-dependent upregulation of interferon-β, which promotes apoptosis by upregulating Bax and Puma. Other treatments for glioblastoma include targeting TRAIL death receptors in combination with kinase or HDAC inhibitors as well as BH3 mimetics. Thus, reactivation of apoptosis is one of the main aims of glioblastoma treatments.

### 3.8. Development of cell death in drosophilla

During the development of metazoans, programmed cell death (PCD) is essential for tissue patterning, removal of unwanted cells and maintaining homeostasis. In the past 20 years Drosophila melanogaster has been one of the systems of choice for studies involving developmental cell death, providing an ideal genetically tractable model of intermediary complexity between Caenorhabditis elegans and mammals. The lessons learned from studies using Drosophila indicate both the conserved nature of the many cell death pathways as well as novel and unexpected mechanisms. In this article we review the understanding of PCD during Drosophiladevelopment, highlighting the key mechanisms that are evolutionarily conserved as well as apparently unusual pathways, which indicate divergence, but provide evidence of complexity acquired during organismic evolution.

### 3.9. Chilhood cancer

Cell death-based therapies of childhood cancer are discussed by Westhoff and colleagues [20]. These authors describe the ways in which malignant cells escape pharmacological inhibition of kinase, such as mutation or upregulation of tyrosine kinase receptors. Several kinase inhibitors have been suggested as potential treatments for pediatric tumors. These tumors often exhibit resistance to death-receptor targeted therapy due to downregulation of caspase-8. BH3-mimetics have been shown to be potent treatments in high-risk groups of patients with ALL and NBs, whereas Smac mimetics are to “sensitize” pediatric tumors to apoptosis. Thus, cell death-based treatments are one of the main forms of precision therapy for childhood cancers.

### 3.10. Alzeihmer’s disease :

Some scientist starts their research and they found that cell suicide may have some role in Alzheimer’s disease,that is not proven yet.mainly the alzheimer’s disease happens

due to the deposition of β-amilode plaque .Scientist are observed that the neuron gets died for the deposition of β-amilode plaque but some of the neuron died due to apoptosis. If we control the apoptosis then we can stop the death of neuron. Researchers have found that the brains of alzheimer's patient contain dying neurons that display certain characteristics science of apoptosis,such as DNA breaks.Three proteins which is responsible for alzheimer's disease such as β-amilode and two presenilins proteins drives into the apoptosis in normal case.If Apoptosis does turn out to play a role in the nerve cell loss then alzheimer's disease will be cured-a goal that keeps researchers interested despite the uncertainities.

## 4. Conclusion

Cell death based therapy is under research from last 50 years after observation of apoptosis.This long research give us many new way in disease recovery. They mainly research on cell death process and how can we prevent necrosis and sometime apoptosis by anti apoptotic agent and anti necrotic agent and also some inhibitors.Caspase cascade system is the main invention of this disease recovery system.After this review we have concluded some points that are : (1)This cell death apoptosis can fully remove by caspase cascade pathway and and Bcl-2 inhibitors.

(2)neurodegenerative disease can be also cure to some extent.

(3)As it is a cell death process if we can inhibit this process by anti apoptotic inhibitor then we can can get a anti-aging property too.

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