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Review Article

ROLE OF APOPTOSIS IN HUMAN DISEASES

MAHESH CHAVAN[1*], RAHUL PATIL[1], DHEERAJ BAVISKAR[1], DINESH JAIN[2]

[1]Institute of Pharmaceutical Education, Boradi, Tal-Shirpur, Dhule, 425428 (M.S.) India, [2]College of Pharmacy, I.P.S. Academy, Rajendra Nagar, Indore, 452 012 (M.P.) India. Email: maheshpharma11@gmail.com

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ABSTRACT

An apoptosis play a significant role in tissue homeostasis and in removal of damaged cells from tissue both improved and inadequate cell death can lead to human disease. The ability to modulate the life or death of a cell is recognized for its immense therapeutic potential. There is growing facts that the processes of neoplastic alteration, sequence involve change in the normal apoptotic pathways. The large of chemotherapeutic agents as well as radiation utilize the apoptotic pathway to induce cancer cell death. Resistance to standard chemotherapies also seems to be determined by change in the apoptotic pathways of cancer cells. The function of apoptosis in cardiac is progress of and evolution of cardiac disease merits for further investigation. Reactive oxygen species which implicated in cardiac pathophysiology can trigger myocyte apoptosis by up-regulating pro-apoptotic proteins, such as Bax and caspases, and the mitochondria-dependent pathway. In HIV infection indirectly induces start-dependent apoptosis in bystander immune $CD4^+$T-cells, a hallmark of AIDS pathogenesis. It is better identified that this pathogenetic event is considerably linked with an elevated virus load. Active viral replication occurs in HIV-1 asymptomatic carriers throughout all stages of clinical disease. Resveratrol is a capable natural compound for control and treatment of a variety of human cancers.

Keywords: Apoptosis, Homeostasis, Cancer, Cardiac disease, HIV.

INTRODUCTION

In 1972 the word apoptosis (a-po-toe-sis) was first used by Kerr, Wyllie, and Curriei to designate a morphologically different form of cell death [1]. Apoptosis is of greek source, having the meaning "tumbling off or dropping off". This analogy underscores that the death of live matter is a vital and essential part of the life cycle of organisms. Upon physiological and pathological disorders the apoptotic type of cell death is an active and definite process which plays a vital part in the progress of multicellular organisms and in the directive and care of the cell inhabitants in tissues. It should be tense that apoptosis is a distinct and probably the most common form of planned cell death, but those other non-apoptotic kinds of cell death also might be of natural importance [2].

The significance of apoptosis

The development and protection of multicellular biological systems depends on a refined relationship between the cells developing the organism, it occasionally even appears to implicate a noble behaviour of singular cells supportive of the organism as an entire. Much of cells are developed in excess which finally undergo automated cell death and thereby contribute to sculpturing several body parts and tissue during growth [3].

Morphology of apoptosis

Many morphological an alteration that arise throughout apoptosis recognised by light and electron microscopy [4]. By light microscopy throughout the early progression of apoptosis, cell contraction and pyknosis are observable [1]. The cells are lesser in size, the cytoplasm is thick and the organelles are more closely packed with cell contraction. Pyknosis is the outcome of chromatin compression and this is the most distinctive feature of apoptosis. Apoptosis involves single cells or small bunches of cells on histological inspection with hematoxylin and eosin dye. An elliptical mass with gloomy eosinophilic cytoplasm with broad purple nuclear chromatin fragments appear by apoptotic cell (Fig.1).

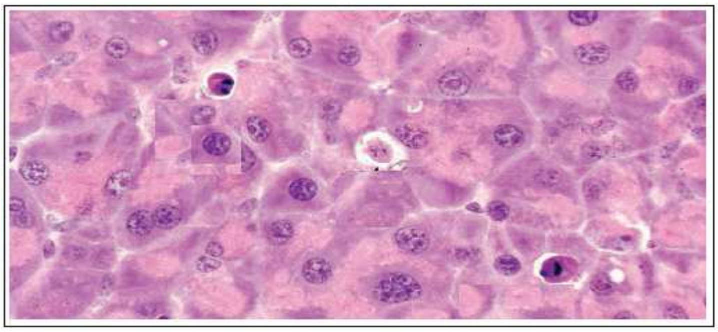

Fig. 1: A photomicrograph of a section of exocrine pancreas from a B6C3F1 mouse (4)

By electron microscopy the subcellular changes can superior define. The electron-solid nuclear material naturally aggregates peripherally below the nuclear membrane while there can also be uniformly opaque nuclei (Fig.2a, 2b) Early during the chromatin condensation phase. "Budding" termed as general plasma membrane blebbing occurs followed via karyorrhexis and parting of cell fragments into apoptotic bodies through a process. Apoptotic bodies consist of cytoplasm with strongly packed organelles with or without a nuclear portion. The organelle integrity is enclosed within an intact plasma membrane and is still maintained. These bodies are afterward phagocytosed by macrophages, parenchymal cells, or neoplastic cells and despoiled within phagolysosomes. Macrophages that swallow up with digest apoptotic cells are called "tingible body macrophages" along with are often found within the reactive germinal centres of lymphoid follicles or infrequently within the thymic cortex. The tingible bodies are the bits of nuclear waste from the apoptotic cells. There is essentially no inflammatory reaction coupled with the process of apoptosis not with the elimination of apoptotic cells because: (1) in the close interstitial tissues apoptotic cells do not release their cellular parts. (2) Likely preventing secondary necrosis with rapidly phagocytosed by adjacent cells. (3) The engulfing cells do not produce anti-inflammatory cytokines [5, 6].

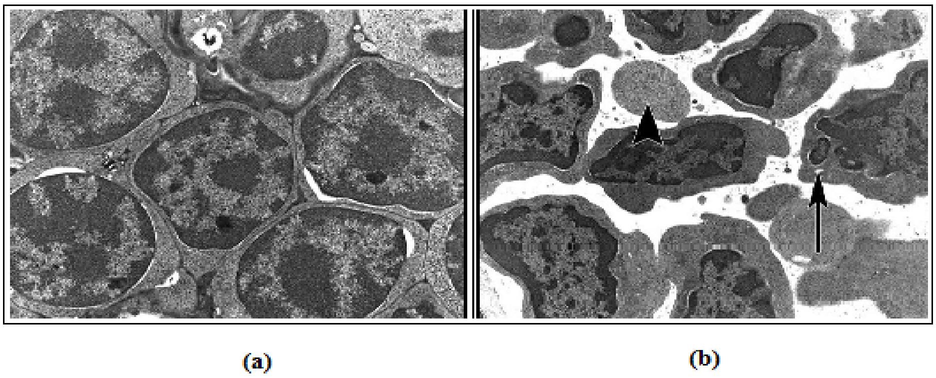

Fig. 2: Transmission electron micrograph (TEM)

(a) The normal thymus tissue depicted (5) (b) Apoptotic thymic lymphocytes in an early phase with Condensed and peripheralized chromatin (6)

DISTINGUISHING APOPTOSIS FROM NECROSIS

Necrosis is different to apoptotic cell death, which is considered to be a poisonous method where the cell is a passive victim and follows an energy-independent type of death. But since necrosis refers to the degradative processes to facilitate happen once cell death, it is considered by some to be an unsuitable word to describe a mechanism of cell death. Apoptosis leads to cell death with cell shrinkage, pyknosis and karyorrhexi whereas oncosis is used to explain a procedure that leads to necrosis with karyolysis and cell swelling. The word "oncotic cell death" and "oncotic necrosis" have been projected as alternatives to explain cell death that is accompanied via cell swelling, except these word are not broadly used at this time even though the mechanisms and morphologies of apoptosis and necrosis vary, there is overlap between these two processes. Data indicates that necrosis and apoptosis characterize morphologic expressions of a shared biochemical system described as the "apoptosis-necrosis continuum" [7]. Such as, two factors that will change an ongoing apoptotic method into a necrotic process include reduce within the availability of caspases and intracellular ATP [8, 9]. Whether, a cell dies by necrosis or apoptosis depends in component on the nature of the cell loss signal the tissue type the developmental step of the tissue and the physiologic milieu using conventional histology, it is not always simple to differentiate apoptosis from necrosis, and they can happen simultaneously based on factors as the intensity and period of the stimulus, the amount of ATP depletion and the accessibility of caspases. Apoptosis is controlled and energy-dependent and can change individual or clusters of cells whereas necrosis is an uncontrolled and passive procedure that generally affects large fields of cells. Necrotic cell injury is facilitated by two main mechanisms; interference with the power supply of the cell and straight injure to cell membranes [7].

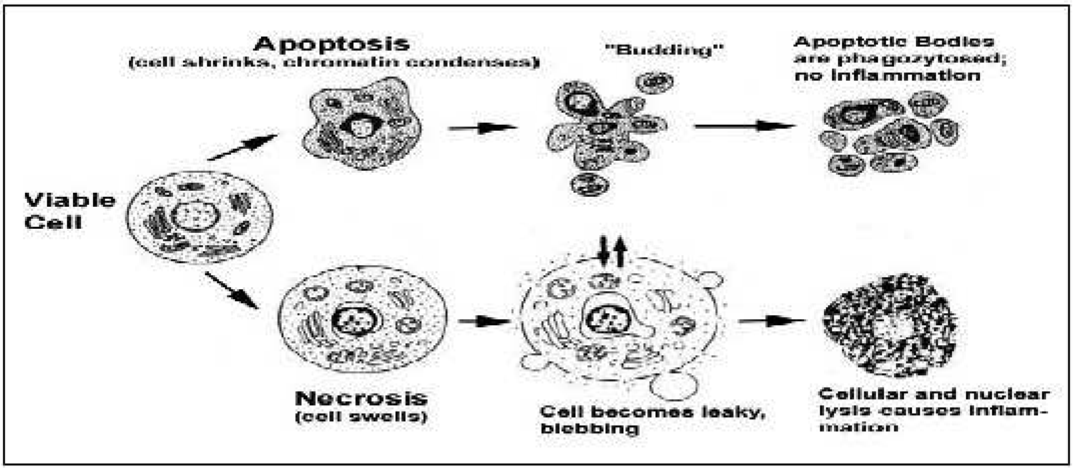

Fig. 3: Distinguishing apoptosis from necrosis (8)

Mechanisms of apoptosis

The mechanism of apoptosis is very complex and difficult involving an energy dependent cascade of molecular procedures (Fig.4). There are two major apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial path. There is an extra path that involves T-cell mediated cytotoxicity and perforin-granzyme dependent killing of the cell. The perforin/granzyme pathway can make apoptosis by either granzyme B or granzyme A. This path is initiated by the cleavage of caspase-3 and results into DNA destruction, conditions of cytoskeletal and nuclear proteins, cross linking of proteins, formation of apoptotic bodies and appearance of ligands intended for phagocytic cell receptors and finally uptake by phagocytic cells. The granzyme A path activates an equivalent caspase-independent cell death way via single stranded DNA injure [10].

Extrinsic Pathway

Transmembrane receptor-mediated relations engage the extrinsic signaling pathways that begin apoptosis. These occupy loss of receptors that are members of the tumor necrosis feature (TNF) receptor gene super family [11]. Members of the TNF receptor family split like cyteine-rich extracellular domains and have a cytoplasmic domain of in relation to 80 amino acids termed as "death domain" [12]. The chains of events that explain the extrinsic phase of apoptosis are excellent categorized with the FasL/FasR and TNF-α/TNFR1 models. A death-suggest signalling complex (DISC) is produced resultant in the auto-catalytic start of procaspase-8 [13]. Once caspase-8 is activated, the completing phase of apoptosis is triggered. The serine proteases granzyme A and granzyme B are the most main component inside the granules. Granzyme B will cleave proteins at aspartate residues and will thus activate procaspase-10 and can cleave factors like ICAD (Inhibitor of Caspase Activated DNAse) [14]. Granzyme A is also significant in cytotoxic T cell induced apoptosis and activates caspase independent pathways. Once in the cell, granzyme A activates DNA nicking via DNAse NM23-H1, a tumour suppressor gene product [15].

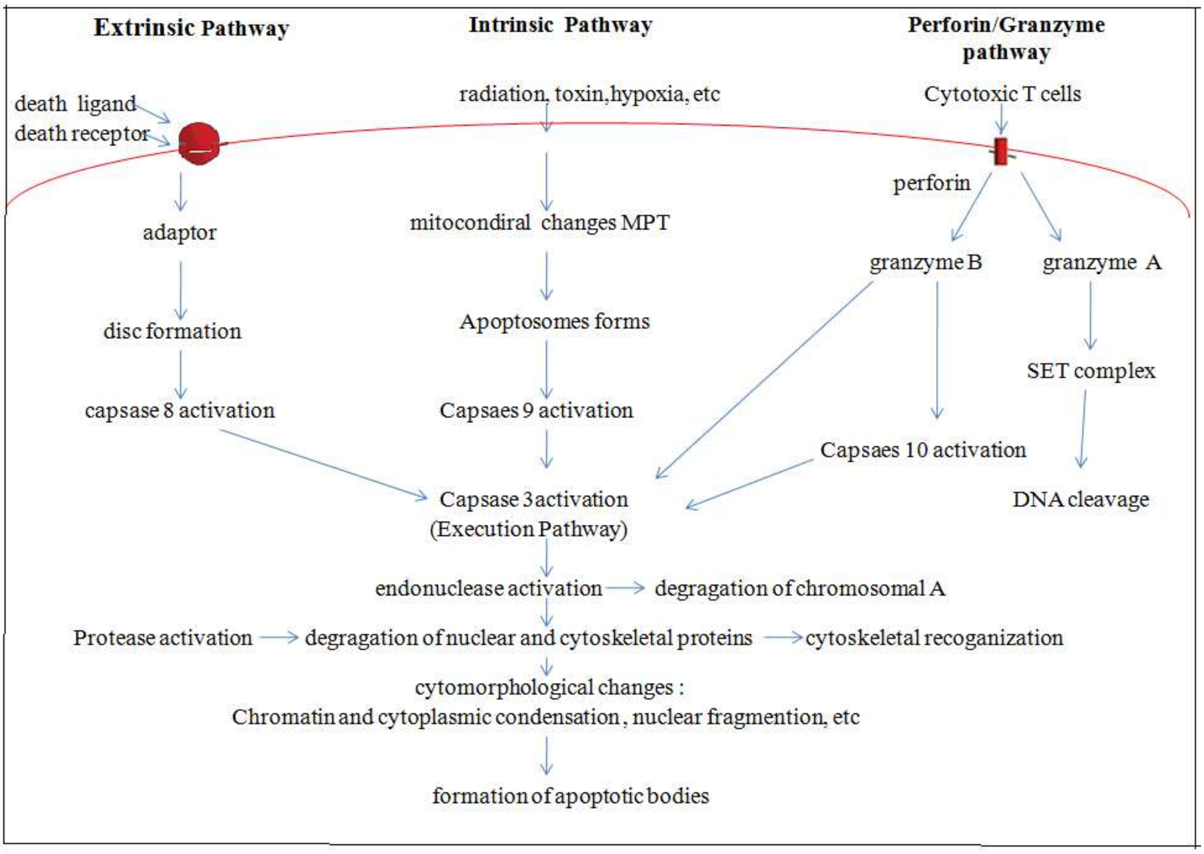

Fig. 4: Schematic representation of apoptotic events (10)

Intrinsic pathway

The intrinsic signalling paths that start apoptosis occupy a diverse collection of non-receptor-mediated stimuli that create intracellular signals that act directly on targets in the cell and are mitochondrial-initiated actions. The stimuli that initiate the intrinsic pathway make intracellular signals that may proceed in either a positive or negative manner. Negative signals involve the lack of definite growth factors, hormones and cytokines that can direct near failure of suppression of death events, there by triggering apoptosis. All of these stimuli lead to changes in the internal mitochondrial membrane that marks in an opening of the mitochondrial permeability transition (MPT) hole, loss of the mitochondrial transmembrane potential and release of two major groups of normally sequestered pro-apoptotic proteins from the intermembrane gap into the cytosol [16]. The first group consists of cytochrome c, Smac/DIABLO, and the serine protease HtrA2/Omi [17, 18]. These proteins start the caspase dependent mitochondrial pathway. Cytochrome *c* joins and activates Apaf-1 and procaspase-9, forming an "apoptosome" [19]. The clustering of procaspase-9 in this way leads to caspase-9 begins. Smac/DIABLO and HtrA2/Omi are reported to encourage apoptosis by inhibiting IAP (inhibitors of apoptosis proteins) activity [20, 21]. Endonuclease G and CAD are free from the mitochondria throughout apoptosis, but this is a delayed event that occurs following the cell has committed to expire. AIF translocates to the nucleus and causes DNA destruction into ~50–300 kb parts and compression of peripheral nuclear chromatin [22]. This early on form of nuclear condensation is referred to as "stage I" condensation [23]. Endonuclease G also translocates to the nucleus where it breaks nuclear chromatin to produce oligonucleosomal DNA fragments [24]. AIF and endonuclease G together function in a caspase-independent manner. CAD is next free from the mitochondria and translocates to the nucleus where, after cleavage by caspase-3, it leads to oligonucleosomal DNA fragmentation and an extra pronounced and advanced chromatin condensation [25]. This later on and other pronounced chromatin condensation is referred to as "stage II" condensation [23].

Execution pathway

The extrinsic and intrinsic paths together end at the point of the execution phase, considered the final path of apoptosis. It is the start of the execution caspases that start this phase of apoptosis. Execution caspases activate cytoplasmic endonuclease, which degrades nuclear material, and proteases that degrade the nuclear and cytoskeletal proteins. Caspase-3, caspase-6, and caspase-7 function as effector or "executioner" caspases, cleaving many substrates contain cytokeratins, PARP, the plasma membrane cytoskeletal protein alpha fodrin, the nuclear protein NuMA and others, that eventually cause the morphological and biochemical changes seen in apoptotic cells [26]. Caspase-3 is considered to be the mainly significant of the executioner caspases and is activated by any of the initiator caspases (caspase-8, caspase-9, or caspase-10). Caspase-3 specifically activates the endonuclease CAD. In proliferating cells CAD is complexes with its inhibitor ICAD. In apoptotic cells, activated caspase-3 cleaves ICAD to free CAD [27].

APOPTOSIS IN CHEMOTHERAPY

Chemotherapy has become an essential component of treatment of most, if not all, solid-organ cancers. Chemotherapy is used to target presumed micro metastatic disease in an adjuvant setting as well as for documented macro metastases, although in the latter setting, complete elimination of the disease and hence, long term survival is uncommon. The list of chemotherapeutic agents that have been tested on a variety of tumor types is lengthy, as are the respective biochemical mechanisms of action. It has become clear that most, chemotherapeutic agents ultimately induce cell death through the triggering of the apoptotic pathway. Disruption of cellular homeostasis through the alteration of essential processes are direct results of most chemotherapeutic agents, yet the details of the progression leading ultimately to cell death have only recently been elucidated. The cytotoxic process following exposure to a chemotherapeutic agent can be broken down into four separate stages; alterations of each have a significant impact on the efficacy of each a specific interaction with intracellular target, such as RNA, DNA or micro-tubules. This interaction results in dysfunction of the target structure. The second stage is the recognition by the cell of the disruption of homeostasis, which, in the case of DNA damage, involves p53 and presumably other proteins. In the third stage, the cell deciphers the severity of the injury and somehow makes a decision to attempt repair of the injury or proceed to apoptotic cell death. Finally, the fourth stage is the initiation of apoptosis with the sequential activation of the cellular machinery leading to cell death. Resistance to chemotherapy may stem from deficiencies in the dysfunction of the tumor cell to complete each of the above referenced steps. Mutations in p53 disrupt the detection of DNA damage and subsequent induction of apoptosis [28].

Therapy directed at apoptosis

The role of apoptosis in the progression of cancer and in both chemo- and radio-therapy of malignancy will influence the development of future treatment regimens. We would anticipate that therapy will be influenced in two distinct areas:

(1) Therapy based upon the molecular apoptotic characteristics of a specific tumor dictate further therapy and

(2) Gene therapy techniques directed at members of the apoptotic pathway will be used. There is already sufficient preclinical information to foresee these changes in the treatment of cancer.

Gene therapy

Diseases like tumor are difficult to cure and they require newer better approaches as treatment tools .Gene therapy has become an attractive method of cancer treatment brought about by the information gathered regarding the molecular events involved in the neoplastic process. Much of the early work focused on introducing genes into cancer cells that had been deleted or mutated in the process of neoplastic transformation, or attempting to heighten the immune system or make tumors more immunogenic. With the increasing information about the involvement of the apoptotic genes in cancer, it would seem logical to begin to target the apoptotic pathway for manipulation by gene therapy. It has become clear that p53-mediated gene therapy simultaneously alters the reintroduction of wild-type ~53 in lung tumors results in substantial increases in the apoptotic index, which may be further augmented by chemo- or radiotherapy [29].

APOPTOSIS AND OXIDANTS IN THE HEART

Oxidative stress as an apoptotic stimulus

Apoptosis occurs in cardiovascular diseases and may play a significant role in the development of heart failure [30, 31, 32]. Despite intensive investigation of apoptosis in cardiovascular diseases, the exact stimulus of apoptosis remains controversial. The balance between endogenous apoptotic stimuli and inhibitors decide the fate of the cell (i.e. death vs survival). Many apoptotic stimuli in the heart have been recognized, including oxidative stress, serum withdrawal, angiotensin II, hyperglycemia, pressure overload, mitochondrial dysfunction, proapoptotic factors such as TNF-α, and loss of Caradiomyocyte (CM) survival factors [32, 33]. Oxidative stress refers to the cytopathologic cost of an imbalance involving the production of free radicals and the defense system, the antioxidants the heart suggest that oxidative stress plays an important role in CM cell death by way of apoptosis or necrosis. Exposure to UV radiation and ionization, which generate such ROS as H_2O_2 and OH^-, are known to cause apoptosis [34].

Oxidative stress and apoptosis in the heart:

An oxidative stress was shown to trigger CM apoptosis in myocardial infarction, ischemia/reperfusion injury, cardiomyopathy, atherosclerosis, and heart failure[30, 31]. In the heart, apoptosis is a dominant form of CM death in ischemia/reperfusion, [35] which is fit recognized to be associated with the production of ROS that exert harmful effects in this disorder. In reperfused ischemic hearts, increase in oxidative stress and decrease in antioxidant defense have been reported to lead to cardiac dysfunction [36, 37]. Excessive ROS may derive from intracellular source such as mitochondrial dysfunction or may be secreted by infiltrating neutrophils during the inflammatory response to the ischemic insult [38].

Nitric Oxide and Apoptosis in the Heart

The free-radical gas NO is generated from L-arginine by way of an enzymatic reaction of a family of enzymes, including neuronal NO synthase and endothelial NO synthase, that are known as constitutively active isoforms, as well as a third isoform known as inducible nitric oxide synthase (iNOS). NO plays a physiologic as well as a pathologic role in vascular and cardiac diseases [39]. The exact role of NO and under what conditions NO shows its dual action, cytoprotective and toxic, is not clear. The toxicity of NO is significantly increased when $ONOO^-$ is yielded as a result of chemical reaction between NO and superoxide (O_2^-) in the cell. It has been reported that NO is proapoptotic in many cell types, including CMs. Recently It is reported that NO produced by iNOS induces apoptotic cell death in neonatal and adult CMs. CM apoptosis induced by NO alone has been shown to be significantly less than that induced by $ONOO^-$ [40]. NO alone or $ONOO^-$ have also been reported to cause a decrease in myocardial function [41] and to induce CM apoptosis [42].

Inhibition of apoptosis by antioxidants

Free radicals generated by aerobic mechanisms in normal life are counterbalanced by endogenous enzymatic SOD, catalase, glutathione peroxidase, and nonenzymatic antioxidants such as vitamins A, E, and C. Apoptosis induced by TNF-alpha is mediated by oxidative stress and inhibited by antioxidants such as thioredoxin and *N*-acetylcysteine [34].

APOPTOSIS-INDUCING HIV-1 PARTICLES

Particle-mediated apoptosis:

Several reports have focused on the possible function of HIV-1-related proteins such as soluble gp120 and/or *Tat* to prime signals for induction of apoptosis in bystander cells [43, 44, 45, 46]. Even if these reports have discovered the ability of these proteins to induce apoptosis by with the Fas : Fas L system in $CD4^+$ T-cells, they frequently examined the effect on T-cell lines after contact to large amounts of recombinant HIV-1 proteins. Thus, soluble gp120 was shown to major apoptosis only in T-cell lines or activated PBMCs, but not in freshly arranged resting PBMCs [47, 48, 49]. A subclone (named L-2), which produces noninfectious HIV-1 particles was established by limiting dilution of survivor cells obtained after MT-4 cells had been infected with the HIV-1 LAI strain [50, 51]. This subclone was found to carry a provirus with a one-base insertion in the *pol* protease, leading to the appearance of a stop codon in the protease gene [52]. Thus, the doughnut-shaped, immature HIV-1 particles in the L-2 cell culture fluid are reverse transcriptase-negative and noninfectious. Surprisingly, these L-2 particles exhibit a higher fusion activity for $CD4^+$ T-cells, as shown by their syncytia formation in virus-to-cell fusion, than the parental wild-type HIV-1 LAI particles [53].

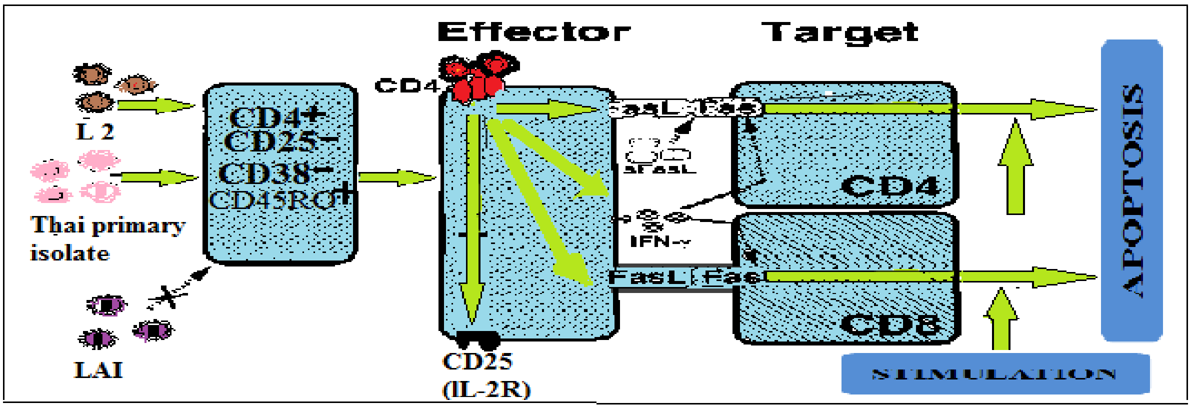

Fig. 5: Proposed model for HIV-1 particle-mediated apoptosis induction in bystander CD4+ and CD8+ T-cells (54).

Model for the potential role of p7 *Nef* molecules on apoptosis

Model, as shown in describes the assembly of three different types of HIV-1 particles as they occur under three different conditions: cleavage of *Gag-Pol* (PR, RT and IN) and *Nef* (p7 and p20) in wild-type HIV-1; no such cleavage in wild-type HIV-1 generated in the presence of protease; and immature *Gag* and truncated *Gag- Pol* and *Nef* (p7) in L-2 particles. It is based upon a previous model for murine leukemia virus assembly, where 60-70 myristylated *Gag-Pol* precursor molecules:virion were postulated to be located at what would eventually become icosahedral vertices of mature, infectious virion nucleocapsids [54], since there are also about 70 *Nef* molecules:virion [55].

RESVERATROL MODULATION OF SIGNAL TRANSDUCTION IN APOPTOSIS

Resveratrol

Resveratrol (3, 4`, 5-trihydroxystilbene) is a polyphenolic natural product, synthesized by a extensive variety of plant species counting grapes, and is present in red wine. Its stilbene structure is related to the synthetic estrogen diethylstilbestrol. Resveratrol has gained considerable notice because of its possible cancer chemopreventive or anticancer properties [56]. In addition, resveratrol may be beneficial in the control of atherosclerosis, heart disease, arthritis or autoimmune disorders. Numerous biological activities have been ascribed to resveratrol, which may explain its anti-inflammatory, anticarcinogenic or anticancer properties [57]. Among its various actions, resveratrol has been demonstrated to inhibit cellular survival signaling. For example, resveratrol may interfere with apoptosis pathways both by directly triggering apoptosis-promoting signaling cascades and by blocking antiapoptotic mechanisms. By blocking survival and antiapoptotic pathways, resveratrol can sensitize cancer cells, which may result in synergistic antitumor activities when resveratrol is combined with conventional chemotherapeutic agents or cytotoxic compounds [58].

Resveratrol as inhibitor of cell survival signaling

Antiapoptotic mechanisms regulating cell death have also been implicated in promoting tumorigenesis and cancer resistance by allowing cancer cells to evade the cell's intrinsic death program [59]. Thus, signaling to cell death is often impaired in cancer cells, especially in resistant forms of cancer. Primarily, tumor cells may acquire resistance through upregulation of key antiapoptotic components or by down regulation of proapoptotic signaling molecules. Inhibitor of apoptosis proteins (IAPs) such as survivin are expressed at high levels in many tumors and have been associated with refractory disease and poor prognosis [60,61]. Survivin is a member of the IAPs, which may supply to resistance of tumors by facilitating both evasion from apoptosis and aberrant mitotic progression [61]. Since IAPs block apoptosis at the core of the apoptotic machinery by inhibiting caspases [60].

Inhibition of NF-kappaB pathway

Resveratrol was found to block activation of NF-kappaB in response to the pro-inflammatory cytokine TNF-alpha. This antiinflammatory property of resveratrol was mediated by suppressing TNFalpha-induced IkappaB kinase activity, phosphorylation and nuclear translocation of the RelA/p65 subunit of NF-kappaB, as well as NF-kappaB-dependent reporter gene transcription [62, 63]. Resveratrol also blocked NF-kappa B activation induced by other inducers of NFkappaB including PMA, LPS, H_2O_2, okadaic acid and ceramide resveratrol suppressed proliferation and invasion and induced apoptosis through negative regulation of NF-kappaB activity in multiple myeloma cells [64]. These findings indicate that resveratrol may eliminate leukemic cells and become a potential agent in the treatment of AML or multiple myeloma. The chemo preventive activities of resveratrol have also been attributed to activation [65].

CONCLUSION

As we study more about apoptosis, its function in the development, progression and treatment of cancer becomes clearer. At present, there are still many components of the apoptotic pathway that remain unknown; CM apoptosis has been recommended as an active performer in the development of cardiac dysfunction and remodeling. Based on the results reported above for apoptosis of 'bystander' immune cells by different types of HIV-1 particles in tissue culture, we propose a suggestion to account for the apoptosis of T cells seen in vivo for patients infected with HIV-1, particularly at late stages of disease. Resveratrol has been shown to promote apoptosis by blocking expression of antiapoptotic proteins or by inhibiting signal transduction.

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