ISSN No:-2456-2165

Recurring Patterns of Apoptosis & Subsequent Health Issues and Management

Abhishek Bharti[1], Dinesh Kumar[2], Rutika[3], Kalpna Kashyap[4], Kundan Singh Bora[5*]
[1*]University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali, Punjab, India-140413
[2] School of Pharmacy, Career Point University, Hamirpur, Himachal Pradesh, India-176041
[4] Govt. pharmacy College, Nagrota Bagwan, Kangra, Himachal Pradesh, India, 176047

Abstract:- The pattern of altered cell end or apoptosis, is all things considered depicted by specific morphological characteristics and energy-subordinate biochemical parts. Apoptosis is seen as a basic fragment of various cycles including standard cell turnover, real new development and working of the safe structure, synthetic ward rot, beginning phase improvement and substance affected cell death. Uncalled-for apoptosis (either exorbitantly little or to a limit) is a factor in numerous human conditions including neurological contaminations, ischemia damage, invulnerable framework concerns and various sorts of unsafe development. It is seen that a cell has the power to change the cell's urgent therapeutic potential. Research continues, as is necessary, to explain and evaluate the telephone cycle system and its routes that control cell cycle capture and apoptosis. Given this, apoptosis research has been advancing at an alarmingly quick rate. Although innumerable important apoptotic proteins have been identified, the nuclear action or inaction parts of these proteins need to be explained. The purpose of this review is to provide an overview of the recurrent pattern data on apoptosis, including morphology, normal science, prosperity and ailment apoptosis work, and field procedures, as well as a discussion of feasible elective kinds of apoptosis.

Keywords:- *Apoptosis, Altered Cell Passing, Trademark/Outward, Perforin, Autophagy.*

I. INTRODUCTION

Cell injury can be characterized as different changes happening in a cell because of any outside just as inner ecological improvements. These improvements incorporate synthetic, physical, microbial, immunological or nourishing variables like ischemia, hypoxia or any dietary inadequacy. After cell injury, a progression of responses happens in the body which is a base of the multitude of sicknesses. These responses might be totally unlethal or deadly to the cell. Accordingly, cell injury can be named – "Reversible cell injury" and "Irreversible cell injury".[1] Reversible cell injury occurs if ischemia or hypoxia is of brief length. Hence their effects may be reversible on recovery of spread. Irreversible cell injury happens when ischemia and hypoxia proceed for a sweeping time interval achieving irreversible damage to the new development and limit of the telephone. Along these lines, cell passing occurs. Cycles including in cell demise might be central or nearby passing for example autolysis, rot and apoptosis or the progressions that follow it for example obsessive calcification, gangrene, or end of life for example cell death.[2]

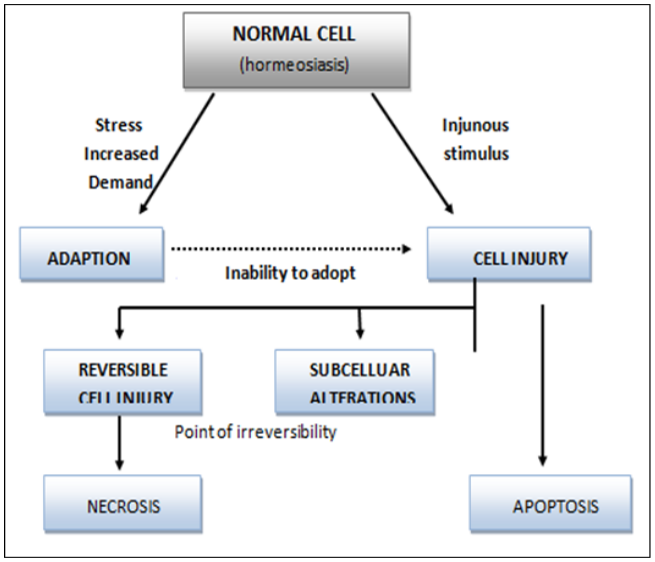

Fig 1 Adaptations to cell injury when stress applied, stress removed homeostasis maintained; but if unable to adapt cell injury occurs whether reversible or irreversible cell injury or sub cellular alterations- Necrosis/ Apoptosis.

II. APOPTOSIS

Apoptosis is acquired from a Greek word implies falling/dropping off. It is characterized as a modified cell passing which is a significant cycle vital for typical turn of events and upkeep of homeostasis of tissue. Despite what is generally expected, it is additionally engaged with different neurotic conditions like neurodegenerative wounds, cardiovascular infections, neurological wounds, AIDS, malignant growth and immunological diseases.[3] Apoptosis idea was first found by Kerr, Wyllie and Currie4 in mid-1970. It is characterized as morphological changes in kicking the bucket cell which includes blebbing of cell, buildup of chromatin, discontinuity of nucleases, loss of bond and cell shrinkage.[3] Due to these biochemical changes additionally happen, for example, high sub-atomic weight deoxyribonucleotide corrosive (DNA) fracture into an oligonucleosomal stepping stool, externalization of phosphatidyl serine[4] and proteolytic cleavage of different intracellular substrates.[5] Because of every one of these changes, apoptotic cells quickly go through phagocytosis. Besides, no provocative response is needed for apoptosis.

ISSN No:-2456-2165

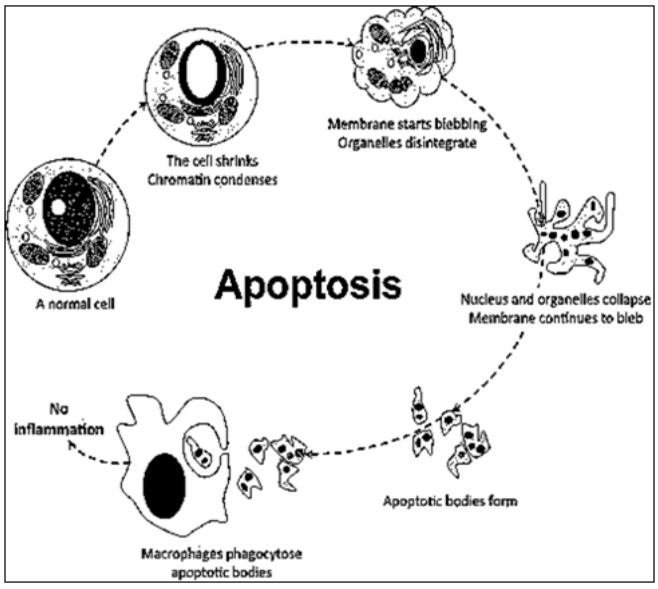

Fig 2 Morphological changes like buildup of chromatin, film blebbing, crumbling of organelles, Formation of apoptotic changes and phagocytosis happening during a cycle of modified cell passing.

III. REGULATORS OF APOPTOSIS

➢ *Caspases:*

The term caspase is gotten from c for cysteine protease; asp for aspartic corrosive and ase is utilized for naming enzyme[2]. These are arrangement of proteolytic compound which sever protein present at aspartic corrosive deposits. When they get enacted, the response can't be switched and hence followed by cell death.[8] These are profoundly communicated in cells and present in cytosol in dormant form.[6] Till date, around 10 significant caspases have been found and are grouped in three kinds initiators caspases for example (caspases-2,- 8,- 9,- 10;) effectors/killers for example (caspases-3,- 6,- 78 and provocative caspases for example caspases-1,- 4,- 5.[6] Initiator caspases have the significant part in setting off apoptosis as they enact killers. Killers caspases have the job in co-planning the passing of cell.[7] Some other caspase will be caspase -11, which are appeared to control cytokine and apoptosis development during caspase -12 or septic stun which direct endoplasmic explicit apoptosis.[8] Some different caspases like caspase - 13 is discovered to be ox-like gene11 and caspase-14,- 16 is found in mouse and people.

➢ *Adaptor proteins:*

These are known to outline joins between the cell passing effectors, caspases, and the cell end regulators, passing receptors and Bcl-2 family members. The homotypic associations between the spaces like the passing region {DD}, the end effector space (DED) & the caspase enlistment space {CARD} intervene the connection between connector proteins and caspases or TNF-R family members.[3,9] After the alliance, cross-interfacing and homotypic collaborations, assortment and establishment of caspases happens.[10] This is also coordinated by another space DED.

- *Tumor Necrosis Factor – Receptor Family:*

TNF receptors gets enacted by a gathering of fundamentally comparative ligands which has a place with TNF ligand family.[11] These receptors animate multiplication, endurance, separation or passing relying upon cell type or signals cells receives.[12] {TRAIL/APO-2L (TNF-related apoptosis – instigated ligand)} initiates apoptosis in changed cells. FADD (Fas related demise area) isn't just needed for death receptor-incited apoptosis yet additionally have a job in mitogen actuated expansion of T-lymphocytes.[13] Cells likewise contain regular inhibitors of caspases known as blocker of apoptosis proteins (IAPs). It was before found to be accessible in baculovirus yet then it was additionally present in human cells like XIAP, c-IAP1 and c-IAP2.[1415] These IAPs straightforwardly restrain two demise effector caspases caspase-3 and - 7. They likewise smother the actuation of two inhibitor caspases-8,- 9.[1617]

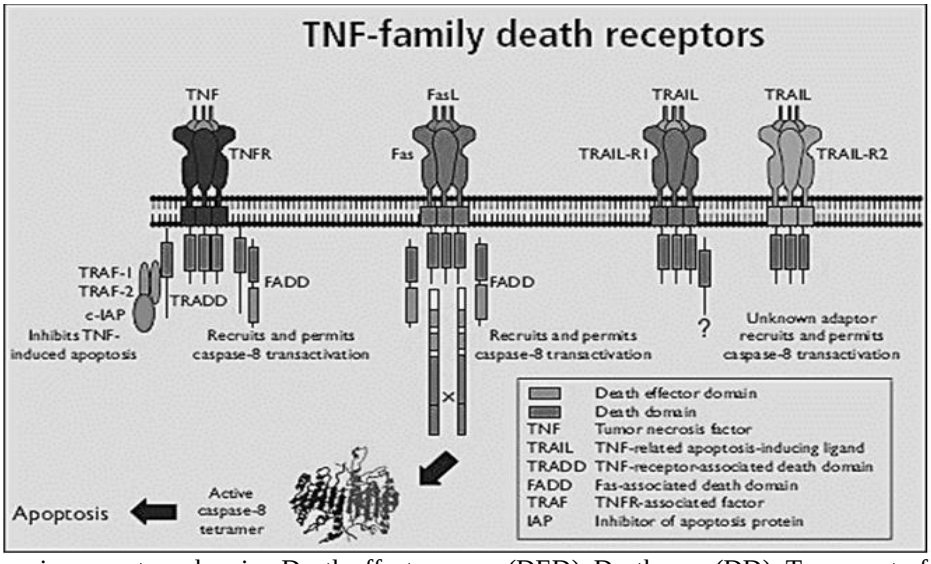

Fig 3 TNF-family passing receptors showing Death effector space (DED), Death area (DD), Tumor putrefaction factor (TNF), TNF-related apoptosis-inciting ligand (TRAIL), TNF-receptor related demise area (TRADD), Fas-related demise area (FADD), TNFR related factor (TRAF), Inhibitor of apoptosis protein (IAP).

ISSN No:-2456-2165

➢ *Bcl-2 Family:*

Bcl-2 was first founded as a proto-oncogene in follicular B-cell lymphoma. Later, it was known as a mammalian homolog to the apoptosis repressor ced-9 in *Caenorhabitidis elegans*. Till now, 19 bcl-2 family members have been identified in mammalian cells which have 1 to 4 conserved motifs known as Bcl-2 homology domains i.e. BH1 to BH4. There are basically three categories of Bcl-2 family according to their function and structure. pro apoptotic or anti apoptotic proteins and the BH3- only proteins. The pro- apoptotic group of proteins possesses a BH3 region and no similarity to Bcl-2 family and thus induces cell death such as Bax, Bak, and Bok. Whereas the anti-apoptotic group of proteins resemble the Bcl-2 family such as Bcl-2, Bcl-Xl, Mc1-1, A1, Bf1-1, and Bcl-w and therefore inhibit apoptosis or cell death. Bid, Bad, Bim are the BH3- is the only proteins as that contain third homology region BH3.[3]

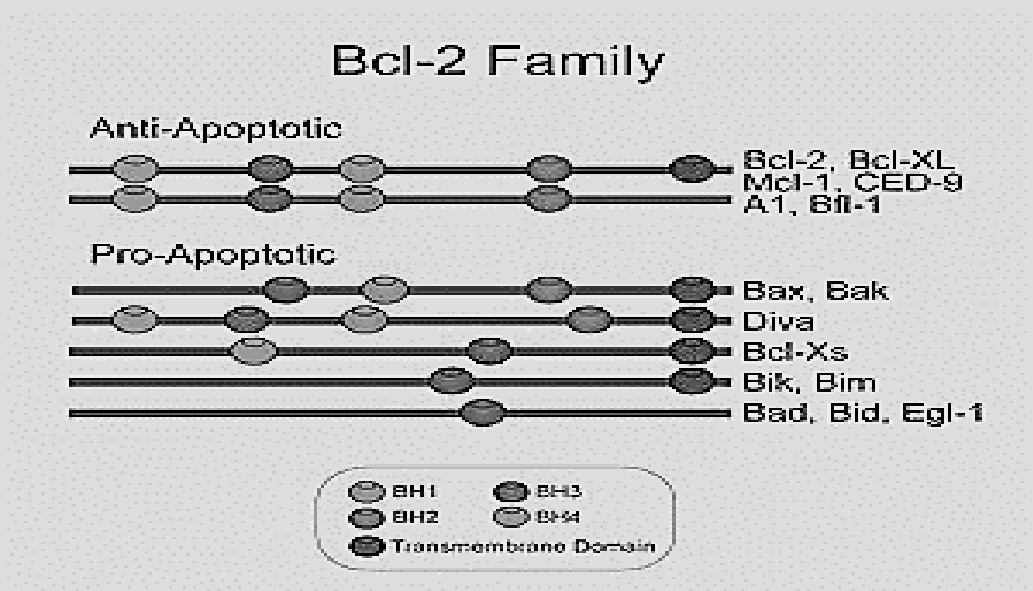

Fig 4 Bcl-2 Family showing against apoptotic proteins {Bax, Bak, Diva, Bcl-Xs, Bik, Bim, Bad, Egl-1} and Pro-apoptotic proteins (Bcl-2, Bcl-xl, Mcl-1, CED-9, A1, Bfl-1)

IV. MECHANISM OF APOPTOSIS

Component / flagging pathway of apoptosis is exceptionally unpredictable. It is an energy subordinate course of sub-atomic occasions. There are principally two sorts of flagging pathways till now, what begins with setting off occasions to an actuation for initiator of caspase and prompts apoptotic cell death. Main pathway incorporates demise receptor, for example, TNF receptor-1 and Fas molecule3 in this way known as extraneous or passing receptor pathway.[7] The subsequent one is subject to the support of mitochondria[3] accordingly known as mitochondrial or natural pathway. Extra pathway also known as {perforin/granzyme pathway}. It includes (T-cell) interceded perforin-granzyme and cytotoxicity subordinate slaughtering of cell. This cycle also executes apoptosis either by (granzyme an) or (granzyme B). Every one of the three pathways meet and execution pathway is started. It includes cleavage of caspase-3 which prompts discontinuity of DNA, atomic proteins and cytoskeletal debasement followed by cross connecting of proteins. This prompts the advancement of apoptotic bodies, enunciation of ligands for phagocytic cell in conclusion take-up by phagocytic cells.[7]

➢ *Extrinsic Pathway (Death Receptor Pathway):*

The outward flagging pathway includes trans-membrane receptor intervened collaborations and start apoptosis. It includes passing receptors which have a place with tumor festering receptor (TNFR) factor family like TNFR1, Fas (CD95), DR3/WSL, and the Path/Apo-2L receptors (TRAIL-R1/DR4, TRAIL-R2/DR5).[3] All these receptors tie with the ligands to instigate apoptosis. A portion of the ligand – receptor cooperation is {FASL/FASR, TNF-α/TNFR1, APO3L/DR3, APO2L/DR4 and APO2L/DR5}. [12, 21, 22, 23, 24] Individuals from the receptor family-TNF have comparative {cysteine-rich extracellular area and cytoplasmic space of 80 amino acids} inside carboxy end of receptor known as "Death domain".The succession of occasions of this pathway can be best clarified by FAS-FASL connection. It begins with the limiting of receptors with the homologous trimeric ligand. This ligation causes enrollment of cytoplasmic connector proteins which have comparing passing spaces. On restricting of FAS ligand to FAS prompts restricting of connector protein FADD. FADD likewise contains "passing effector space" which thusly selects procaspase-8. Therefore, a demise flagging complex (Disk) is framed which prompts autocatalytic enactment of procaspase-8.[18] The {caspase-8} once is actuated, the execution period of apoptosis/apoptosis caspase course set off.

➢ *Intrinsic Pathway (Mitochondrial Pathway):*

This pathway happens be course of action of non – receptor mediated lifts that produce intracellular signs that clearly circle back to targets present inside the cell. These are mitochondrial-begun events. The non-receptor figured upgrades may act either in certain or negative way. The negative signs incite apoptosis as there may be frustration of

camouflage of death programs due to nonattendance of various advancement components, synthetic substances or cytokines.[7] Every one of these signs start changes in the internal mitochondrial film which prompts opening of mitochondrial porousness progress (MPT) pore. Because of the kickoff of this pore, there is tremendous loss of mitochondrial transmembrane potential and two primary gatherings of proapoptotic proteins are delivered from intermembrane space to cytosol.[19] The principal gathering of proteins incorporates [cytochrome-c, Smac/DIABLO and serine protease] Htr A2/Omi. [2021] These types of proteins act through caspase-subordinate mitochondrial pathway. Cytochrome is encoded by a quality (atomic quality), yet when it goes into the mitochondria it ties with heme gathering and structure holo-cytochrome c. This type of cytochrome c starts caspase activation.[22] Cytochrome c ties with "Apaf-1 and procaspase-9 and enacts them to shape apoptosome". [235]

Procaspase-9 bunching enacts caspase-9. Smac/DIABLO and HtrA2/Omi restrains IAPs and prompt apoptosis.[2425] The second gathering of supportive of apoptotic proteins incorporates "AIF, endonuclease G and CAD". Both AIF and endonuclease G act by caspase-free way however CAD act through caspase-subordinate way. They are delivered from mitochondria during apoptosis yet in later stage when cell is going to bite the dust. AIF move from mitochondrion to core and cause fracture of DNA in between the range of ~50-300 kb pieces and buildup of fringe atomic chromatin.[26] This phase of early buildup is known as "Stage-1" condensation.[27] Endonuclease G additionally move from mitochondria to core. It separates atomic chromatin and produce oligonucleosomal DNA fragments.[28] CAD move to core where it gets cut by caspase-3. It prompts discontinuity of DNA to oligonucleosomal DNA sections and buildup of chromatin.[29] This high-level phase of buildup is known as "Stage-2" condensation.[27] The guideline of the occasions of this pathway is controlled by Bcl-2 family.[30] It is additionally directed by p-53 protein, however the specific instrument isn't known.[31] It is upto the individuals from Bcl-2 family to choose whether the cycle of apoptosis may proceed or stop.

V. EXECUTION PATHWAY

Both inherent and outward pathways end up with the last period of apoptosis known as execution pathway. It is started with the initiation of execution caspases (caspase-3, -6, - 7). This enactment prompts actuate the cytoplasmic endonucleases which debase atomic material. It additionally actuates proteases which debases atomic and cytoplasmic proteins. Among the effector caspases, caspase-3 is the rule which can be set up by any of the initiator caspases (caspase-8,-9,-10). Caspase-3 authorizes the endonuclease PC supported plan which is complexed with its inhibitor ICAD in expanding cells. In any case, in apoptotic cells, caspase-3 cuts off the ICAD and movement PC helped plan' CAD.[29]This CAD corrupts chromosomal DNA inside the cores and causes buildup of chromatin. Caspase-3 additionally assumes part in instigating cytoskeletal revamping and crumbling of cell into apoptotic bodies. Phagocytic cells follow up on these apoptotic bodies. It is the last segment of this stage. This segment is communicated by deviation of phospholipid and externalization of phosphatidylserine on the outside of apoptotic cells. Albeit, the specific system behind externalization isn't surely known. The presence of phosphatidyl serine on external surface of bodies brings about the non-provocative phagocytic acknowledgment and permits early take-up and removal of apoptotic bodies.[32] All this shows that no incendiary reaction is needed for apoptosis.

VI. APOPTOSIS-BENEFICIAL OR HARMFUL

Apoptosis - a modified cell demise is exceptionally controlled and very much saved instrument. Apoptosis manages different body cycles like evacuation of superfluous, excess, matured or harmed cells. It likewise wipes out self-responding resistant cells, sexual organ improvement and gamete arrangement. Along these lines, it is valuable for us. Then again, dysregulation of apoptosis may prompt deformities, different immune system sicknesses and disease. Expulsion of solid cells may likewise happen. It might prompts different neurodegenerative sicknesses or ischemic injury.[33]

VII. NEUROTROPHIC FACTORS AS ANTI-APOPTOSIS

Neurotropic components are the development factors which are associated with the neuronal endurance and recovery of neurons. It is finished by forestalling the modified cell passing apoptosis.[34]

- *Neurotrophic Factors*

Development factors are the gathering of proteins which animate the development of explicit tissues. They are communicated in different living beings including people. These development factors bestow a significant job by controlling assortment of cell cycles like expansion, separation and maturation.[35] Different development factors incorporate insulin-like development factors, epidermal development factors (EGFs), platelet-determined development factors, and nerve development factors (NGFs). Cytokines are likewise sort of development factors which are delivered by cell in order to control the capacity of another cell.[36] Neurotrophic factors are the development factors which can advance the endurance promotion recovery of neurons. They are otherwise called neurotrophies (NTs).[37] They are viewed as the basic ligands for neuronal cells. They are useful in multiplying, separate, and development during formative stages. The other significant capacities are looking after endurance, network availability a neuronal versatility in grown-up brains.[38] They likewise improve neuronal recovery in neurodegenerative illnesses, for example, Alzheimer's,[39] Parkinson's[40] and Huntington's disease.[41] Recent explores additionally show confirmations of tissue recovery outside of the sensory system.

ISSN No:-2456-2165

VIII. GLIAL DERIVED NEUROTROPHIC FACTORS (GDNF):

This family incorporates different development factors like "GDNF, nurturing (NRTN), persephin (PSPN), and artemin (ARTN)". These tight spot to various GFR receptors for example GDNF ties to GFRα1, NRTN ties to GFRα2, ARTN ties to GFRα3 and PSPN ties to GFRα4[42] [43]This family apply their capacity by initiating the transmembrane RET tyrosine kinase.

GDNF is the most examined individual from this family. It was first refined as a strong neurotrophic factor in 1993. It is considered to assume a significant part in advancing the endurance of numerous sorts of neurons particularly dopaminergic, engine and enteric neurons with their multiplication and regeneration.[44] They are likewise answerable for forestalling apoptosis of engine neurons.[45] Neurturin, a second individual from GDNF family was considered to advance the endurance of sensorimotor, thoughtful, parasympathetic, and enteric neurons.[46] They likewise advance the endurance of dopaminergic neurons.[46]

- *Neuropoietic Cytokines*

These are the little proteins that assume a significant part in safe reaction. This gathering incorporates "ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF)".[37] These demonstration through enactment of Janus-initiated kinase-signal transducer and activator of record (JAK-STAT) and the mitogen-actuated protein kinase (MAPK) pathways. CNTF is the first neurotrophic factor that can uphold the endurance of engine and parasympathetic neurons from the chick ciliary ganglion.[47] LIF is known for expanding totipotent undeveloped foundational microorganism (ESC) self-restoration.

- *Nerve Growth Factors*

Nerve development factors are the first neurotrophic factor. It is discovered predominantly in the cerebrum, most significant level in the hippocampus.[32] It is found to build the development of tactile and thoughtful neurons in the chicken embryo.[48] Its activity is intervened by means of "NGF receptor p75 and tyrosine kinase A receptor (TrkA)".[49] Its downstream system is engaged with the hindrance of apoptosis by down directing the Bcl-2 pathway. [62,63]

- *NT-3 and NT-4*

NT-3 and NT-4 are the other neurotrophic factors recognized after NGF AND BDNF.[5051]They are fundamental for endurance of tangible neurons and furthermore for their multiplication. NT-3 ties fundamentally to TrkC and furthermore enacts TrkA and TrkB though NT-4 ties ideally to TrkB. [5251]

- *Brain Derived Neurotrophic Factors (BDNF)*

BDNF was first separated from the pig mind in 1989 by Yves – Alain Barde and Hans Thomen[5354]Later, its biochemical design was likewise presented. It is one of the neurotrophic factors which is engaged with endurance, separation, and development of neurons in the sensory system. It additionally shows neuroprotective activity under different unfavorable conditions like hypoglycemia, cerebral ischemia, neurotoxicity and so forth It likewise assumes a significant part in energy homeostasis.[55]

IX. ORIGIN OF BDNF

BDNF is an individual from neurotrophin group of development factors which likewise incorporates nerve development factor, "neurotrophins-3, 4/5 and 6 [NT-3, NT-4/5, NT-6]". Its blend happens in the endoplasmic reticulum as expert BDNF (32-35kDa). At that point it travels through Golgi contraption and trans-Golgi organization (TGN). Favorable to BDNF is then arranged by vesicles within the sight of lipid pontoon related arranging receptor carboxy peptidase E (CPE). In this manner, it is additionally moved into action subordinate emission by post synaptic dendrites. Further, the terminal space of supportive of BDNF is cut to shape a 13kDa organically dynamic develop BDNF (m BDNF) with the assistance of an unmistakable protein convertase enzyme.[55]

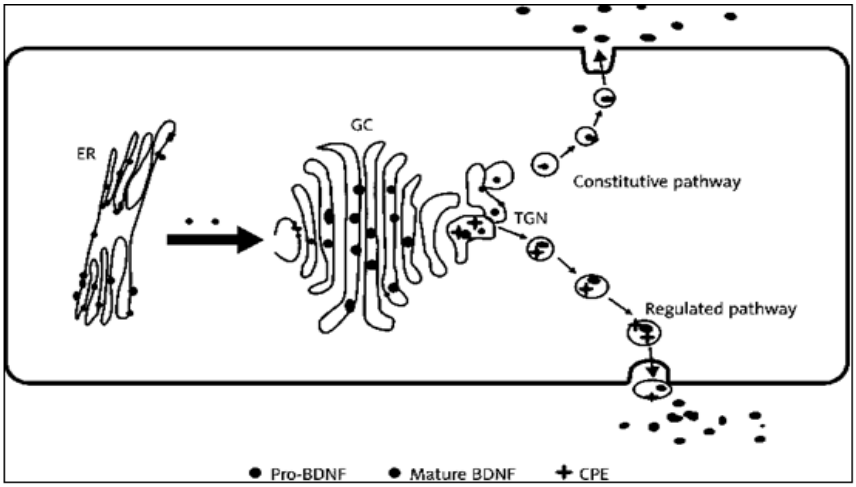

Fig 5 Above figure shows the origin of pro-BDNF in endoplasmic reticulum (ER), which is transported to Golgi complex (GC), and then to trans-Golgi network (TGN). Thus, in a regulated pathway, 13kDa mature BDNF is formed with the help of CPE and convertase and released outside the plasma membrane.

X. ROLE OF BDNF IN ANTI-APOPTOSIS AND CELL SURVIVAL

➢ *The receptor through which activity of BDNF is interceded is tyrosine receptor kinase B (TrkB). TrkB exists in two isoforms:*

- gp 145TrkB - A full length receptor glycoprotein having mol. wt. 145kDa.
- gp ¬95TrkB – A shortened structure which needs tyrosine kinase space and LNGFR (low liking development factor receptor otherwise called p75 NTR) having mol. wt. 95 kDa.[56]

BDNF is one of the huge advancement factors which gives helpful neuroprotective effect on neuronal limit like cell increase, cell perseverance, etc under carious upsetting conditions.[57]

➢ *Enactment oF TrkB:*

TrkB comprises of an extracellular area having different destinations of glycosylation, a novel transmembrane portion and intercellular space having TrkB activity.[58] When BDNF ties to TrkB, it triggers dimerization and autophosphorylation of tyrosine deposits in the receptor. This further selects connector proteins and transduction atoms. This eventually prompts enact three fundamental downstream phosphorylation falls. Every one of these pathways lead to antiapoptosis.[57]

XI. SIGNALING PATHWAYS INVOLVED IN ANTI-APOPTOSIS

BDNF flagging pathways may enact at least one record factors CREB and CREB – restricting protein (CBP). It directs articulation of qualities encoding such proteins which are associated with neuronal pliancy, cell endurance and stress resistance.[58]

➢ *Ras/MAPK/ERK PATHWAY:*

When ligand for example BDNF ties to TrkB, it prompts dimerization and autophosphorylation of tyrosine deposits. This outcome to shape a docking site for src homology-2 – space containing connector protein (Shc) and phospholipase c (PLC). Along these lines when Shc is docked with the receptor and tie to the connector protein Grb2 with the assistance of guanine nucleotide delivering factor SOS. Ras enacts following pathways: Ras/MAPK-ERK; PI3-K OR PLC pathway.

MAPK-ERK is significant for neurogenesis and advances endurance twoly:

- By enlistment of master endurance qualities
- Inhibition of proapoptotic proteins (Bad) [5960]

The supportive of endurance proteins, for example, “Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and Bfl-1 have BH1-4 areas”. These proteins hinder cell passing by restricting both of the two classes of favorable to apoptotic proteins-the Bax/Bak proteins and the BH3-just proteins. Subsequently, apoptosis is inhibited.[61]

➢ *IRS-1/PI3K/AKT pathway:*

It includes enactment of insulin receptor substrate-1 IRS-1/2), PI3K and protein kinase B (Akt). Thus, apoptosis is stifled through P13K; where PI3K initiates Akt. It prompts sequestering of supportive of apoptotic proteins in the cytoplasm away from their transcriptional targets.[55] Thus, P13K pathway assumes a significant part in actuation of favorable to endurance qualities answerable for cell survival.[62]

➢ *PLC/DAG/IP3 PATHWAY:*

After docking of BDNF with Trk receptor, connector protein PLC-γ is phosphorylated. It causes depletion of layer lipids to inositol 1, 4, 5 -triphosphates (IP3). This will advance an expansion in intracellular calcium focus and diacylglycerol (DAG). [636465] Further, DAG directs protein kinase C, which is needed for the MAPK/ERK signal embroiled in neurite outgrowth.

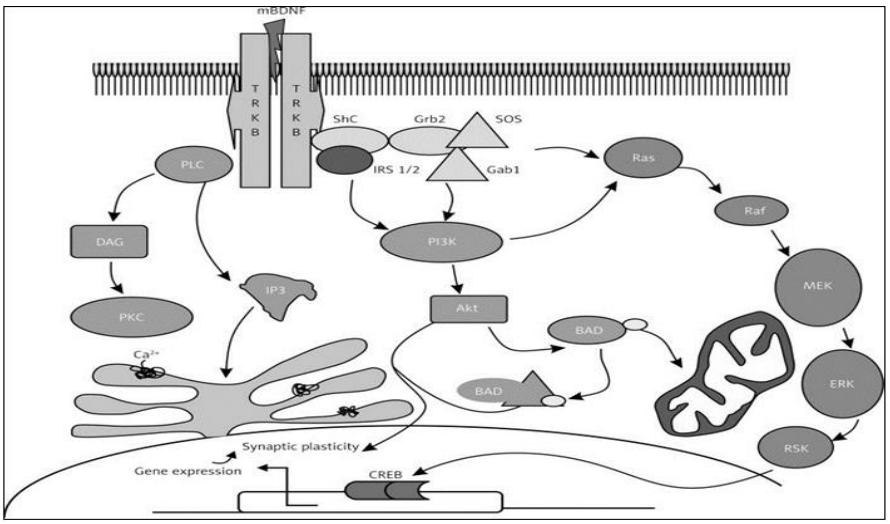

Fig 6 Above figure shows the signaling pathways of neurotrophic factors involved in anti-apoptosis: Ras/MAPK/ERK PATHWAY, IRS-1/ PI3K/ AKT pathway, PLC/DAG/IP3 PATHWY

➢ *Management*

Cancer can be seen as one of the major alterations in the cell causing this malignant transformation as a result of successive genetic changes during which the normal cell becomes malignant and cell death escape is one. In the 1970s, Kerri et al had already associated ap[66] Apoptosis, hyperplasia and growth of the tumor with the removal of potentially malignant cells (Kerr JF, Wyllie AH, Currie AR. Apoptosis: a fundamental biological event with broad implications in dynamic tissue. Cancer Br J.[4]

A malignant cell can reduce apoptosis or resistance to apoptosis in several possible ways. In general, the techniques by which apoptosis evasion takes place can be widely divided into: 1) altered pro-apoptotic and anti-apoptotic protein balance, 2) decreased caspase function, 3) defective signaling to the death receptors.

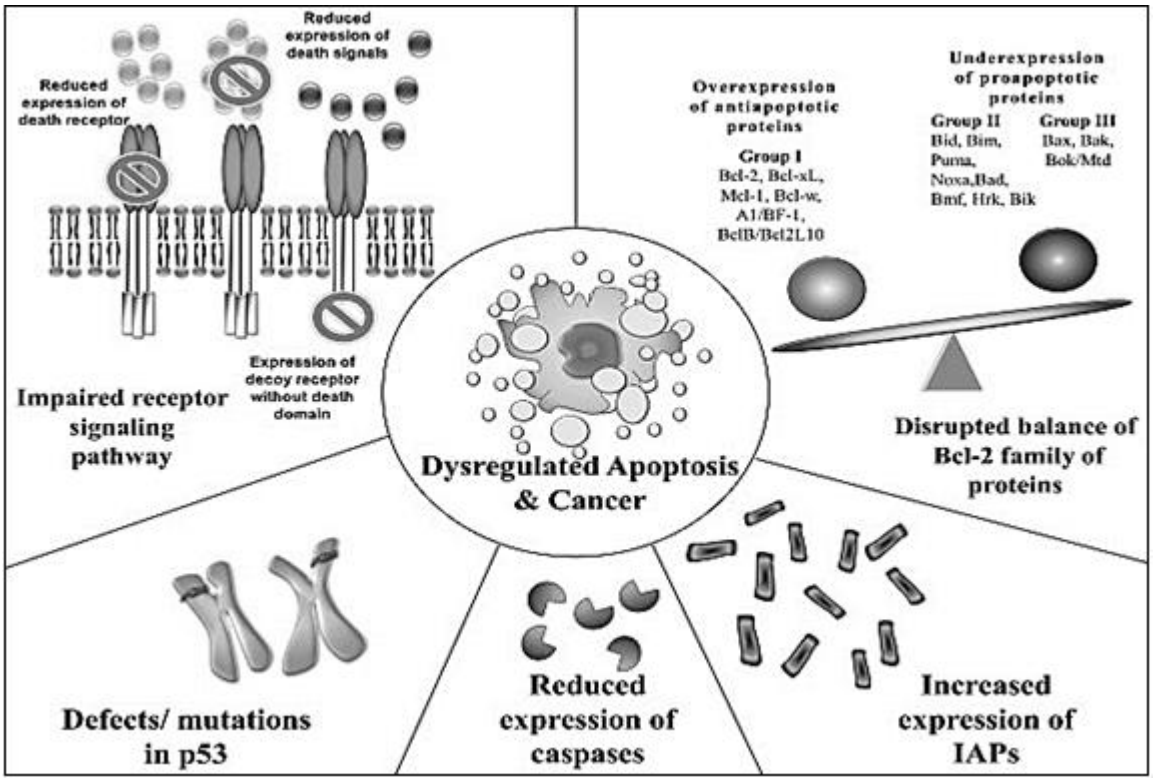

Fig 7 Mechanisms that help to prevent apoptosis and carcinogenesis are discussed

Table 1 A Summary of Apoptosis-Targeted Current Therapies

Treatment Strategy	Observations	Author& Reference
Bcl-2 Protein Family Target		
Agents which target proteins in the Bcl-2 family	*Oblimersen sodium*	
	This is reported in combination with conventional anticancer treatments in patients with chronic myeloid leukemia for chemical sensitization and improvements in their survival. *Bcl-2 class of protein small molecule inhibitors*	Rai *et al*., 2008[67], Abou-Nassar and Brown, 2010 [68]
	The molecules found to affect gene or protein expression are sodium butyrate, depsipetide, fenretinide and flavipirodo. The protein itself has proven to be active in Gossypol, ABT-737, ABT-263, GX15-070 and HA14-1.	Kang and Reynold, 2009 [69]
	BH3 mimetics Anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Bcl-W have inhibited ABT-737 and had lymphoma cytotoxicity, small lungs of a cell and primary cells obtained from patients ATF4, ATF3 and NOXA have been reported as binding and inhibiting Mcl-1.	Oltersdorf *et al*., 2005 [69] Albershardt *et al*., 2011 [70]
BCL BCL FAMILY PROTEINS/GENES Silencing	Specific siRNA for Bcl-2 is reported to inhibit in particular in in vitro and in vivo expression of the target gene in pancreatic cancer cell. Silent Bmi-1 in MCF cells apparently reduces expression of pAkt and Bcl-2 and enhances doxorubicin sensitivity by increased apoptotic cells in both vitro and in vivo.	Ocker *et al*., 2005 [71] Wu *et al*., 2011 [72]

Targeting p53		
Gene therapy based on p53	First study on the usage in tumor cells of non-small cell lung cancer obtained from patients of the wild type p53 retroviral vector gene. It has been stated that the use of p53 based gene therapy is feasible.	Roth *et al*., 1996[73]
	The wild p53 gene for sensitizing cells, colorectal, prostate and glioma ionizing of the head and neck. Identifying ionizers.	Chène, 2001 [74]
	ONYX-015 has been observed to multiply selectively in and lyse the p53-deficient tumor cells.	Nemunaitis *et al*., 2009 [75]
Drug therapy based on p53	***Small molecules***	
	Phikan083 reported that it binds to mutant p53 and restores it.	oeckler *et al*., 2008[76]
	CP-31398 reported that the complex of the DNA-p53 core domain is intercalated with DNA and altered and destroyed, hence restoring unstable p53 mutants.	Rippin *et al*., 2002 [76]
	Other agents	
	Nutlins have been shown to block interaction with MSM2-p53, stabilize p53 and preferentially cause cancer cell senescence.	Shangery and Wang, 2008 [77]
	MI-219 has demonstrated interference with the MDM2-p53 connection, resulting in cell proliferation suppression, selective apoptosis and full control of tumor growth.	Shangery *et al*., 2008 [78]
	Tenovins reported a diminution in vivo tumor growth	Lain *et al*., 2008 [79]
p53-based immunotherapy	Patients with advanced stage cancer reported stable disease in vaccines using a human-type wild-type replicate adenoviral vector p53.	Kuball *et al*., 2002 [80]
	Patients in the p53 peptide pulsed dendritic cells in a phase I study were given clinical and p53-selected responses to T cells	Svane *et al*., 2004 [80]
Treatment strategy ***Targeting XIAP***	*Antisense approach*	
	This has led to better in vivo radiation tumor control.	Cao *et al*., 2004 [81]
	Continuous use in vitro and in vivo lung cancer cells have been reported for increased chemotherapy and chemotherapy.	Hu *et al*., 2003 [81]
	siRNA approach	
	SiRNA XIAP targeting demonstrated an increase in human cancer cell radiation sensitivity independently of TP53 condition	
	XIAP or SRNA targeting sensitized hepatoma cells to death receptor and cell death triggered by chemotherapeutic drug	Ohnishi *et al*., 2006 [82] Yamaguchi *et al*., [83]
Targeting Survivin	*Antisense approach*	
	Survivor transfection to YUSAC-2 and LOX malignant melanoma cells found to lead to spontaneous apoptosis	Grossman *et al*., 1999 [84]
	Apoptosis and sensitize are reported to lead to the development of chemotherapy of spinal cells in the head and neck	Sharma *et al*., 2005 [85]
	Human lung cancer cells SPCA1 and SH77 have been reported to decrease proliferation and induce death.	Liu *et al*., 2011 [86]
	Responding to survival suppressions in SKOV3/DDP ovary cancer cells, decrease cell proliferation and improve apoptosis.	Zhang *et al*., 2009 [87]
	Radio senses of human non-small cell lung cancer cells are reported to increase	Yang *et al*., 2010 [87]

XII. CONCLUSION

The verse explains that studies of apoptotic processes in neurodegenerative disorders new light on pathogenesis is anticipated to shed in AD, Down's and ALS in particular, the presence of apoptosis is significant. The HD and PD the impact of apoptosis is less obvious but requires more Research. The expression of DNA is clear as evaluated by the TUNEL technique, cleavage is not enough evidence on its own to determine a Mechanism of the apoptosis. In neurotrophies, there is signs of neurotrophic support deficit in AD, although determination of whether such losses (e.g., from BDNF) caused or resulted from neuropathology is rather challenging. It is hard to determine the increase in neurotrophic activity can potentially be beneficial in the disease brain, so in this way the BDNF/TrkB system might play a major role. Yet, neurodegenerative illnesses are centered primarily on long-term therapy of interacting with the fundamental metabolic mechanism for neuronal death. Under certain circumstances, it could be performed with neurotrophies or similar molecules (IGF-I, melatonin), but would possibly be a more effective hope in future development of tiny compounds which transcend the blood-brain barrier & operate only with elements of the apoptotic biochemical machinery. Regardless of the therapeutic implications, considerable knowledge on the involvement of apoptosis in neuro- substantial conditions has been obtained in recent years. The task is now to find and exploit this information for new medication development, the biochemical pathways can cause apoptotic nerve cell death in neurodegenerative illnesses.

ACKNOWLEDGMENT

Authors are grateful to UIPS, Chandigarh University for providing all facilities and support.

REFERENCES

[1]. Trump BF. Characteristics and mechanisms of cell injury and cell death: the role of [Ca2+]i. *Mar Environ Res*. 1996;42(1-4):57-63. doi:10.1016/0141-1136(96)00074-8
[2]. Everson CA, Henchen CJ, Szabo A, Hogg N. Cell Injury and Repair Resulting from Sleep Loss and Sleep Recovery in Laboratory Rats. Published online 1929.
[3]. Extracts L, Attaleb M, Morjani H, Amzazi S, Mzibri M El. Antiproliferative Effect and Induction of Apoptosis by Inula viscosa L . and Human Cervical Cancer Cells.
[4]. Wide- W, Kinetics INT. APOPTOSIS : A BASIC BIOLOGICAL PHENOMENON WITH WIDE-. Published online 1972.
[5]. Hill MM, Adrain C, Duriez PJ, Creagh EM, Martin SJ. Analysis of the composition , assembly kinetics and activity of native Apaf-1 apoptosomes. 2004;23(10):2134-2145. doi:10.1038/sj.emboj.7600210
[6]. Cohen GM. Caspases : the executioners of apoptosis. 1997;16:1-16.
[7]. Elmore S. NIH Public Access. 2007;35(4):495-516.
[8]. Elmore S. Toxicologic Pathology. Published online 2014. doi:10.1080/01926230701320337
[9]. Liston P, Young SS, Mackenzie AE, Korneluk RG. Life and death decisions : the role of the IAPs in modulating programmed cell death. 1997;2(5):423-441.
[10]. D BMvEpZmIcJw. 14.pdf.
[11]. Kanehisa M, Goto S, Hattori M, et al. From genomics to chemical genomics: new developments in KEGG. *Nucleic Acids Res*. 2006;34(Database issue):354-357. doi:10.1093/nar/gkj102
[12]. Dixit AA and VM. Death Receptors : Signaling and Modulation. 2012;1305(1998). doi:10.1126/science. 281.5381.1305
[13]. Schnapp E, Breithaupt H. The A-T gene hunt genetics. 2019;(August):1-7. doi:10.15252/embr. 201948947
[14]. Deveraux QL, Reed JC. REVIEW IAP family proteins — suppressors of apoptosis. Published online 1999:239-252.
[15]. Hozak RR, Manji GA, Friesen PD. The BIR Motifs Mediate Dominant Interference and Oligomerization of Inhibitor of Apoptosis Op-IAP. 2000;20(5):1877-1885.
[16]. Lacasse EC, Baird S, Korneluk RG, Mackenzie AE. LaCasse EC , Baird S , Korneluk RG , MacKenzie AEThe inhibitors of apoptosis The inhibitors of apoptosis (IAPs) and their emerging role in cancer. 1999;(January):3247-3259. doi:10.1038/sj.onc.1202569
[17]. Chicheportiche Y, Bourdon PR, Xu H, et al. TWEAK , a New Secreted Ligand in the Tumor Necrosis Factor Family That Weakly Induces Apoptosis *. *J Biol Chem*. 1997;272(51):32401-32410. doi:10.1074/jbc.272.51.32401
[18]. Zhivotovsky B, Burgess DH. Proteases in apoptosis. Published online 1996:968-978.
[19]. Saelens X, Festjens N, Walle L Vande, Gurp M Van, Loo G Van, Vandenabeele P. Toxic proteins released from mitochondria in cell death. Published online 2004:2861-2874. doi:10.1038/sj.onc.1207523
[20]. Du C, Fang M, Li Y, Li L, Wang X. Smac , a Mitochondrial Protein that Promotes Cytochrome c – Dependent Caspase Activation by Eliminating IAP Inhibition. 2000;102:33-42.
[21]. Garrido C, Galluzzi L, Brunet M, Puig PE, Didelot C. Mechanisms of cytochrome c release from mitochondria. Published online 2006:1423-1433. doi:10.1038/sj.cdd.4401950
[22]. Yang J, Yang J, Liu X, et al. Prevention of Apoptosis by Bcl-2 : Release of Cytochrome c from Mitochondria Blocked Prevention of Apoptosis by Bcl-2 : Release of Cytochrome c from Mitochondria Blocked. 2012;1129(1997). doi:10.1126/science. 275.5303.1129
[23]. Chinnaiyan AM. The Apoptosome : Heart and Soul of the Cell Death Machine. *Neoplasia*. 1999;1(1):5-15. doi:10.1038/sj.neo.7900003

[24]. Loo G Van, Gurp M Van, Depuydt B, Srinivasula SM. The serine protease Omi / HtrA2 is released from mitochondria during apoptosis . Omi interacts with caspase-inhibitor XIAP and induces enhanced caspase activity. Published online 2002:20-26. doi:10.1038/sj/cdd/4400970
[25]. Schimmer AD. Inhibitor of Apoptosis Proteins : Translating Basic Knowledge into Clinical Practice. Published online 2004:7183-7190.
[26]. Joza N, Susin SA, Daugas E, et al. Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death. Published online 2001:549-554.
[27]. Bras M, Queenan B, Susin SA. Programmed Cell Death via Mitochondria : Different Modes of Dying. 2005;70(2).
[28]. Li LY, Luo X, Wang X. Endonuclease G is an apoptotic DNase when released from mitochondria. Published online 2001.
[29]. Sakahira H, Enari M. Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. 1998;391(JANUARY):1-4.
[30]. Cory S, Adams JM, Walter T, Hall E. THE BCL2 FAMILY : REGULATORS OF THE CELLULAR LIFE-OR-DEATH. 2002;2(September). doi:10.1038/nrc883
[31]. Schuler M, Green DR. Mechanisms of p53-dependent apoptosis. 29(200 I):684-688.
[32]. Fadok VA, Cathelineau A De, Daleke DL, Henson PM, Bratton DL. Loss of Phospholipid Asymmetry and Surface Exposure of Phosphatidylserine Is Required for Phagocytosis of Apoptotic Cells by Macrophages and Fibroblasts *. 2001;276(2):1071-1077. doi:10.1074/jbc.M003649200
[33]. Mazarakis ND, Edwards AD, Mehmet H. Apoptosis in neural development and disease. 1997;(July):165-170.
[34]. Wang Q, Zheng JQ. cAMP-Mediated Regulation of Neurotrophin-Induced Collapse of Nerve Growth Cones. 1998;18(13):4973-4984.
[35]. Hardy K, Spanos S. Growth factor expression and function in the human and mouse preimplantation embryo. *J Endocrinol*. 2002;172(2):221-236. doi:10.1677/joe.0.1720221
[36]. Razavi S, Nazem G, Mardani M, Esfandiari E, Esfahani S, Salehi H. Neurotrophic factors and their effects in the treatment of multiple sclerosis. *Adv Biomed Res*. 2015;4(1):53. doi:10.4103/2277-9175.151570
[37]. Kerschensteiner M, Stadelmann C, Dechant G, Wekerle H, Hohlfeld R. Neurotrophic cross-talk between the nervous and immune systems: Implications for neurological diseases. *Ann Neurol*. 2003;53(3):292-304. doi:10.1002/ana.10446
[38]. Chen S Der, Wu CL, Hwang WC, Yang DI. More insight into BDNF against neurodegeneration: Anti-apoptosis, anti-oxidation, and suppression of autophagy. *Int J Mol Sci*. 2017;18(3):1-12. doi:10.3390/ijms18030545
[39]. Heese K, Low W. Nerve Growth Factor , Neural Stem Cells and Alzheimer ' s Disease. Published online 2006:1-12. doi:10.1159/000094383
[40]. Liao J Bin, Wu DW, Peng SZ, et al. Immunomodulatory Potential of Patchouli Alcohol Isolated from Pogostemon cablin (Blanco) Benth (Lamiaceae) in Mice. 2013;12(August):559-565.
[41]. Rosser A, Svendsen CN. Stem cells for cell replacement therapy: A therapeutic strategy for HD? *Mov Disord*. 2014;29(11):1446-1454. doi:10.1002/mds.26026
[42]. Nielsen J. 51.pdf.
[43]. Vianney J. ScholarWorks at WMU Regulation of Glial Cell Line-Derived Neurotrophic Factor (GDNF) Production in Voluntary and Involuntary Muscle. Published online 2015.
[44]. Erickson JT, Brosenitsch TA, Katz DM. Brain-Derived Neurotrophic Factor and Glial Cell Line-Derived Neurotrophic Factor Are Required Simultaneously for Survival of Dopaminergic Primary Sensory Neurons In Vivo. 2001;21(2):581-589.
[45]. Bonner JF, Blesch A, Neuhuber B, Fischer I. NIH Public Access. 2011;88(6):1182-1192. doi:10.1002/jnr.22288.Promoting
[46]. Horger BA, Nishimura MC, Armanini MP, et al. Neurturin exerts potent actions on survival and function of midbrain dopaminergic neurons. *J Neurosci*. 1998;18(13):4929-4937. doi:10.1523/jneurosci.18-13-04929.1998
[47]. youssef Sari. 56.pdf.
[48]. Raivich G, Kreutzberg GW, Levi-montalcini R. Nerve growth factor and regeneration of peripheral nervous system. Published online 1993.
[49]. Y M, Sobue G, Y K, Terao S, Mitsuma T. Expression of mRNAs for Neurotrophic Factors (NGF , BDNF , NT-3 , and GDNF) and Their Receptors (p75 NGvR , TrkA , TrkB , and TrkC) in the Adult Human Peripheral Nervous System and Nonneural Tissues. 1996;21(8):929-938.
[50]. Tessarollo L, Vogel KS, Palko ME, Reid SW, Parada LF. Targeted mutation in the neurotrophin-3 gene results in loss of muscle sensory neurons. 1994;91(December):11844-11848.
[51]. Bradshaw RA, Murray-rust J, Ibarez CF, Mcdonald NQ, Lapatt R, Blundell TOML. Nerve growth factor : Structure / function relationships. Published online 1994:1901-1913.
[52]. Klein R, Nanduri V, Jing S, et al. The trkB tyrosine protein kinase is a receptor for brain-derived neurotrophic factor and neurotrophin-3. *Cell*. 1991;66(2):395-403. doi:10.1016/0092-8674(91)90628-C
[53]. Barde Y, Edgar D, Thoenen H. neurotrophic factor from mammalian brain. 1982;I(5):549-553. doi:10.1002/j.1460-2075.1982.tb01207.x
[54]. Leibrock J, Lottspeich F, Hohn A, et al. Molecular cloning and expression of brain-derived neurotrophic factor. *Nature*. 1989;341(6238):149-152. doi:10.1038/341149a0

[55]. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical Implications. *Arch Med Sci*. 2015;11(6):1164-1178. doi:10.5114/aoms.2015.56342
[56]. Papers JBC, Doi M, Fang H, et al. Transcriptional Activation of the Human Brain-derived Neurotrophic Factor Gene Promoter III by Dopamine Signaling in NT2 / N Neurons *. *J Biol Chem*. 2003;278(29):26401-26409. doi:10.1074/jbc.M211539200
[57]. Benarroch EE, Ca O. Brain-derived neurotrophic factor Regulation , effects , and potential clinical relevance. Published online 2015.
[58]. Kaplan DR, Miller FD. Neurotrophin signal transduction in the nervous system. *Curr Opin Neurobiol*. 2000;10(3):381-391. doi:10.1016/S0959-4388(00)00092-1
[59]. Walker F, Kato A, Gonez LJ, et al. Activation of the Ras/Mitogen-Activated Protein Kinase Pathway by Kinase-Defective Epidermal Growth Factor Receptors Results in Cell Survival but Not Proliferation. *Mol Cell Biol*. 1998;18(12):7192-7204. doi:10.1128/mcb.18.12.7192
[60]. Bonni A, Brunet A, West AE, Datta SR, Takasu MA, Greenberg ME. Cell Survival Promoted by the Ras-MAPK Signaling Pathway by Transcription-Dependent and -Independent Mechanisms. 1999;(December).
[61]. Lindsten T, Ross AJ, King A, et al. The combined functions of proapoptotic Bcl-2 family members Bak and Bax are essential for normal development of multiple tissues. *Mol Cell*. 2000;6(6):1389-1399. doi:10.1016/S1097-2765(00)00136-2
[62]. Vaillant AR, Mazzoni I, Tudan C, Boudreau M, Kaplan DR, Miller FD. 3-Kinase – Akt Pathway to Synergistically Regulate Neuronal Survival. 1999;146(5):955-966.
[63]. Corbit KC, Foster DA, Rosner MR. Protein Kinase Cδ Mediates Neurogenic but Not Mitogenic Activation of Mitogen-Activated Protein Kinase in Neuronal Cells. *Mol Cell Biol*. 1999;19(6):4209-4218. doi:10.1128/mcb.19.6.4209
[64]. Sue Goo Rhee, Yun Soo Bae. Regulation of phosphoinositide-specific phospholipase C isozymes. *J Biol Chem*. 1997;272(24):15045-15048. doi:10.1074/jbc.272.24.15045
[65]. Nakazawa T, Tamai M, Mori N. Brain-Derived Neurotrophic Factor Prevents Axotomized Retinal Ganglion Cell Death through MAPK and PI3K Signaling Pathways. 2002;43(10).
[66]. Stucchi G, Battevi N, Cairoli S, Consonni D. The prevalence of musculoskeletal disorders in the retail sector: an Italian cross sectional study on 3380 workers. *Med Lav*. 2016;107(4):251-262.
[67]. O'Brien S, Moore JO, Boyd TE, et al. 5-Year survival in patients with relapsed or refractory chronic lymphocytic leukemia in a randomized, phase III trial of fludarabine plus cyclophosphamide with or without oblimersen. *J Clin Oncol*. 2009;27(31):5208-5212. doi:10.1200/JCO.2009.22.5748
[68]. Kang MH, Reynolds CP. Bcl-2 Inhibitors: Targeting mitochondrial apoptotic pathways in cancer therapy. *Clin Cancer Res*. 2009;15(4):1126-1132. doi:10.1158/1078-0432.CCR-08-0144
[69]. Oltersdorf T, Elmore SW, Shoemaker AR, et al. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. *Nature*. 2005;435(7042):677-681. doi:10.1038/nature03579
[70]. Albershardt TC, Salerni BL, Soderquist RS, et al. Multiple BH3 mimetics antagonize antiapoptotic MCL1 protein by inducing the endoplasmic reticulum stress response and up-regulating BH3-only protein NOXA. *J Biol Chem*. 2011;286(28):24882-24895. doi:10.1074/jbc.M111.255828
[71]. Ocker M, Neureiter D, Lueders M, et al. Variants of bcl-2 specific siRNA for silencing antiapoptotic bcl-2 in pancreatic cancer. *Gut*. 2005;54(9):1298-1308. doi:10.1136/gut.2004.056192
[72]. 72. Paranjape AN, Balaji SA, Mandal T, et al. Bmi1 regulates self-renewal and epithelial to mesenchymal transition in breast cancer cells through Nanog. *BMC Cancer*. 2014;14(1):1-14. doi:10.1186/1471-2407-14-785
[73]. Roth JA, Nguyen D, Lawrence DD, et al. Retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer. *Nat Med*. 1996;2(9):985-991. doi:10.1038/nm0996-985
[74]. Chène P. P35 as a drug target in cancer therapy. *Expert Opin Ther Pat*. 2001;11(6):923-935. doi:10.1517/13543776.11.6.923
[75]. Wong RSY. Apoptosis in cancer: From pathogenesis to treatment. *J Exp Clin Cancer Res*. 2011;30(1):87. doi:10.1186/1756-9966-30-87
[76]. Boeckler F, Joerger A, Jaggi G, Rutherford T, Veprintsev D, Fersht A. Targeted rescue of a destabilized mutant of p53 by ar in silico screened drug. *Chemtracts*. 2008;21(6):236-237.
[77]. Rippin TM, Bykov VJN, Freund SMV, Selivanova G, Wiman KG, Fersht AR. Characterization of the p53-rescue drug CP-31398 in vitro and in living cells. *Oncogene*. 2002;21(14):2119-2129. doi:10.1038/sj.onc.1205362
[78]. Shangary S, Qin D, McEachern D, et al. Temporal activation of p53 by a specific MDM2 inhibitor is selectively toxic to tumors and leads to complete tumor growth inhibition. *Proc Natl Acad Sci U S A*. 2008;105(10):3933-3938. doi:10.1073/pnas.0708917105
[79]. Lain S, Hollick JJ, Campbell J, et al. Discovery, In Vivo Activity, and Mechanism of Action of a Small-Molecule p53 Activator. *Cancer Cell*. 2008;13(5):454-463. doi:10.1016/j.ccr.2008.03.004
[80]. Kuball J, Schuler M, Antunes Ferreira E, et al. Generating p53-specific cytotoxic T lymphocytes by recombinant adenoviral vector-based vaccination in mice, but not man. *Gene Ther*. 2002;9(13):833-843. doi:10.1038/sj.gt.3301709

[81]. Svane IM, Pedersen AE, Johnsen HE, et al. Vaccination with p53-peptide-pulsed dendritic cells, of patients with advanced breast cancer: Report from a phase I study. *Cancer Immunol Immunother*. 2004;53(7):633-641. doi:10.1007/s00262-003-0493-5
[82]. Ohnishi K, Scuric Z, Schiestl RH, Okamoto N, Takahashi A, Ohnishi T. siRNA targeting NBS1 or XIAP increases radiation sensitivity of human cancer cells independent of TP53 status. *Radiat Res*. 2006;166(3):454-462. doi:10.1667/RR3606.1
[83]. Wong RSY. Apoptosis in cancer: From pathogenesis to treatment. *J Exp Clin Cancer Res*. 2011;30(1):1-14. doi:10.1186/1756-9966-30-87
[84]. Grossman D, McNiff JM, Li F, Altieri DC. Expression and targeting of the apoptosis inhibitor, survivin, in human melanoma. *J Invest Dermatol*. 1999;113(6):1076-1081. doi:10.1046/j.1523-1747.1999.00776.x
[85]. Sharma H, Sen S, Lo Muzio L, Mariggiò MA, Singh N. Antisense-mediated downregulation of anti-apoptotic proteins induces apoptosis and sensitizes head and neck squamous cell carcinoma cells to chemotherapy. *Cancer Biol Ther*. 2005;4(7):720-727. doi:10.4161/cbt.4.7.1783
[86]. Liu Q, Dong C, Li L, Sun J, Li C, Li L. Inhibitory effects of the survivin siRNA transfection on human lung adenocarcinoma cells SPCA1 and SH77. *Chinese J Lung Cancer*. 2011;14(1):18-22. doi:10.3779/j.issn.1009-3419.2011.01.04
[87]. Yang CT, Li JM, Weng HH, Li YC, Chen HC, Chen MF. Adenovirus-mediated transfer of siRNA against survivin enhances the radiosensitivity of human non-small cell lung cancer cells. *Cancer Gene Ther*. 2010;17(2):120-130. doi:10.1038/cgt.2009.55