The evasion of cell death plays a significant role in cancer expansion and can also show resistance to radio and chemotherapy (Hanahan et al., 2011 and Cornmark et al., 2016). Thus, one latent approach of cancer treatment is to restore mechanism of functional cell death. Apoptosis is a vital biological process which plays a crucial role by clearing injured or undesirable cells in organisms for regulating homeostasis, growth and immune defense.

Extrinsic and intrinsic pathways are two main pathways of apoptosis that have been widely studied. The extrinsic pathway is promoted through binding of death ligands like TRAIL (TNF-related apoptosis-inducing ligand), TNFα (tumor necrosis factor α), Fas/Apo-1 to their equivalent death receptors (DR4/DR5, TNFR1 and CD95/FasR) on the top of cell plane. Recruitment of multimeric protein DISC on the selectively permeable membrane occurs due to binding of death ligands to their receptors. An adapter protein encloses in the DISC, it recruits procaspase 8 in system which leads to the autoactivation of caspase 8. Caspase 7 and caspase 3 activated by the cleavage of caspase-8 which leads to apoptosis.

The intrinsic pathway of apoptosis which is also known as mitochondrial pathway is distinguished by mitochondrial membrane permeabilization activated by stresses such as radiation or chemotherapy drugs. The mitochondrial pathway involves the oligomerization and translocation of B-cell lymphoma 2 protein such as Bcl-2 homologous antagonist killer (BAK) or Bcl-2 associated X protein (BAX). A pore is formed by BAX or BAK in the outer wall of mitochondria which causes discharge of Smac/DIABLO and cyt c into cytoplasm. Apoptosome a multi-protein complex forms by the cytochrome c collectively with the procaspase-9 and APAF1 in the cytoplasm and activates procaspase 9 into activated caspase 9. Afterwards, Activation of Caspase 3, caspase 7 and effector caspases are carried out through activated caspase 9. The Inhibitor of Apoptosis (IAP) proteins act as the final line of defense against apoptosis by inhibiting caspase-9, caspase-7 and caspase-3. IAP proteins prevent Smac/DIABLO from blocking caspase inhibition by XIAP (ML-IAP, cIAPs). The binding of Smac/DIABLO mimetics to IAP proteins prevent the inhibitory action by disrupting critical IAP-Smac and IAP-caspase interaction (Vucic et al., 2007). Activated caspase 3 and caspase 7 cut downstream cell demise activator which finally leads to apoptosis (Hanahan et al., 2011, Reed et al., 2002, and Bai et al., 2014). The extrinsic and intrinsic both apoptotic pathways converged which results into activation of caspase-7 and caspase-3. Hence, create a positive feedback loop for cellular suicide (Fig.1).

Significant regulators of apoptosis: IAP protein

Equilibrium between anti-apoptotic and pro-apoptotic mechanisms regulates whether cell demise signal be able to activate the execution of apoptotic program. In this equilibrium, anti-apoptotic proteins prevent apoptosis and pro-apoptotic proteins encourage apoptosis (Schimmer et al., 2004, 2006, 2007).
Nachmias et al., 2004 and Wei et al., 2008). Inhibitors of apoptosis (IAP) proteins are the members of anti-apoptotic family unit of proteins. So, IAP proteins play key roles in modulating apoptosis in various species.

IAP proteins were initially recognized in baculoviruses for their capability to prevent viral influenced cellular suicide (Crook et al., 1993, and Birnbaum et al., 1994). The IAPs can be differentiated based upon the presence of 1-3 domains of BIR (baculoviral IAP repeat) (Salvesen et al., 2002, Deveraux et al., 1999, Holcik, et al., 2001, Shiozaki et al., 2004). Several IAP proteins found in mammals include survivin (also known asBIRC5), neuronal IAP (NIAP, also known as BIRC1), X chromosome linked IAP (XIAP, also known as BIRC4), ubiquitin-conjugating BIR-domain enzyme apollon (Apollon, also known as BIRC6), cellular IAP1 (cIAP1, also known as BIRC2), IAP like protein 2 (ILP-2, also known as BIRC8), cellular IAP2 (cIAP2, also known as BIRC3), melanoma IAP (ML-IAP, also known as BIRC7) (Fig.2).

Among all, ML-IAP, cIAP1, cIAP2 and XIAP, play significant role in apoptotic regulation (Salvesen et al., 2002).

**Role of IAP proteins in Human cancer:** In a multitude of human cancers, prominent expression of cIAP and XIAP proteins have been found which allied to the chemical resistance and adverse prognosis in some cancers (Dubrez, et al., 2013). But in non-small cell lung cancer, the elevated expression of XIAP is linked with good prognosis (Ferreira et al., 2001). High levels of XIAP are connected with adverse prognosis in chronic lymphocytic leukemia, colorectal cancer, prostate cancer, breast carcinoma and several other human cancer types (Grzybowska-Izydorczyk et al., 2010, Guoan, et al., 2009, Moussata et al., 2012, Krajewska et al., 2003, Seligson et al., 2007, Zhang et al., 2011). Poor result in many myeloma patients are connected with elevated expression of cIAP1, cIAP2 and XIAP (Nakagawa et al., 2006). In MALToma NF-kB signaling activation is associated with combination of BIR domain of cIAP2 and MALT1 (Varfolomeev, 2006). The amplification of genes encoding cIAP1 and cIAP2 located at chromosome 11q21-22 occurs at elevated frequency in many human cancers, like cervical squamous cell carcinoma, hepatocellular carcinoma, esophageal squamous cell carcinoma and lung cancer along with many others (Imoto et al., 2002, Zender et al., 2006, Imoto et al., 2001, Dai et al., 2003). In bladder and colorectal cancer, poor endurance and advanced phase of cancer are connected with the high level of cIAP proteins (Krajewska et al., 2005, Che et al., 2012) and high cIAP1 levels are associated with resistance to radiation therapy in
cervical squamous cell carcinoma (Imoto et al., 2002).

IAPs are involved in human cancers not only limited to direct and indirect regulation pathways of apoptosis but also by the modulation of diverse non-apoptotic cell death pathways, mainly stem from their E3 ubiquitin ligase action as involvement of IAPs in human cancers. IAP proteins are central players in cell migration, motility, invasion and metastasis (Oberoi-Khanuja et al., 2013). Some studies recommend that metastasis and cell migration can also be promote by IAP proteins. IAP proteins like survivin and XIAP encourage metastasis and tumor cell invasion by activating Src kinase and focal adhesion kinase and NF-kB-integrin β1 signaling (Mehrotra, et al., 2010).

Decrease in cytoskeleton formation and polymerization of β-actin caused by genetic reduction of XIAP, which results in reduced cancer cell invasion and migration (Liu et al., 2011, Liu et al., 2012, Yu et al., 2012). Depletion of cIAP1 represses cell migration and cIAP1 has been regulate migration of cell in a caspase recruitment domain (CARD) dependent manner (Lopez et al., 2011).

According to several findings, IAP proteins can also negatively regulate the cancer cell migration (Dogan et al., 2008, Oberoi-Khanuja et al., 2008). In hela cells, reduction in IAP proteins increases development of lamellipodium in addition with microspikes which enhance the migration of tumor cell. For encouraging Rac1’s (Ras-related C3 botulinum toxin substrate 1) polyubiquitination at Lys147 followed by proteasomal degradation, cIAP1 and cIAP2 both directly bind with Rac in a nucleotide independent manner (Oberoi-Khanuja, et al., 2012). Reduction in cIAP1 and cIAP2 levels causes growth in Rac1 protein levels in tumor as well as normal cells, associated with enhancement in cell migration and extended morphology (Oberoi et al., 2012).

**IAP proteins regulate the NF-kB signaling pathway:** The transcription of wide range of genes which are involved in cell survival, inflammation and immunity is caused by the transduction of different stimulus by the transcription factors of the NF-kB family, c-Rel, RelB, RelA (p65). Nuclear Factor-kB1 and Nuclear Factor-kB2 are kinds of NF-kB transcription factors (Rothwarf et al., 1999, Almagro et al., 2012). They are compactly regulated by two vital post translational modifications, ubiquitination and phosphorylation, as for cellular survival and immunity there is high pertinence of pathway of NF-kB. The classical (canonical) pathway and alternative (non canonical) pathway are two NF-kB signaling pathways which can be usually differentiated by the signaling and the timing proteins which plays role in their activation (Fig. 3) (Scheidereit et al., 2006).

NF-kB proteins play a role as dimeric sequence-specific DNA-binding factors for regulation of target genes expression. Expression of target genes are associated with cell migration, death, survival, proliferation and invasion (Perkins et
NF-kB target genes are activated by p52 subunit which dimerizes with RelB. When cIAPs are absent, NF-kB inducing kinase (NIK) accumulates and phosphorylation of IKKα (IkB kinase complex) occurs and is accompanied by NF-kB2 p100 phosphorylation leading to cleavage of p52. Although, cIAPs prevent activation of downstream IKKα by controlling stability of NF-kB inducing kinase (NIK) through ubiquitylation. Consequently, cIAP proteins positively regulate the classical NF-kB signaling and negatively regulate the alternative NF-kB signaling.

In multiple myeloma, activation of noncanonical NF-kB pathway is caused by inactivating mutations of cIAP proteins. In the meantime, In vitro invasion of cancerous cell and in vivo metastasis of tumor is promoted through the XIAP when it associates with survivin for driving the NF-kB activation (Gyrd-Hansen et al., 2010). The combination of the MALT1 with BIR domain of c-IAP2/MALT1 fusion protein is essential for activation research, 7(8), 2468-2474.

CONCLUSION

IAP proteins play key roles in modulating apoptosis in various species. Also, IAP proteins suppress apoptosis in many species. As a novel cancer treatment, IAP proteins are accurate choice as they are vital regulators for survival and demises of cell. IAPs play central role in resistance to therapy and progression of disease and Therefore, IAPs represent novel therapeutic targets for cancer treatment.

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