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REVIEW ARTICLE

Role of metal complexes in inhibition of cancer growth factors

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ABSTRACT

Cancer is characterized by uncontrolled cell growth, representing a hallmark feature marked by sustained proliferation. This heightened proliferative capacity is primarily driven by the influence of growth factors. Scientific evidence suggests that growth factors play a crucial role in augmenting the transcription of specific proto-oncogenes, such as myc and fos. In the context of cancer development, these growth factors can be either produced by the cancer cells themselves or induce normal cells to release them through intricate signaling mechanisms. The functional diversity of growth factors encompasses various actions, but their predominant mode of operation is through the tyrosine kinase receptor pathway. Tyrosine kinase receptors, comprising integral membrane complexes with intrinsic kinase activity in their cytoplasmic domain, play a pivotal role in transducing signals initiated by the binding of specific growth factors (ligands). This binding event triggers the activation of the kinase function within the receptor, resulting in the phosphorylation of downstream targets on tyrosine and serine residues. Subsequently, this phosphorylation event recruits additional molecules into signaling cascades, amplifying the cellular response. Transition metals, such as Copper, Zinc, and Cobalt, integral to biological systems, play pivotal roles in normal physiological functions. However, dysregulation of these essential metals has been implicated in the pathogenesis of various disorders, including cancer. The narrative unfolds by elucidating the critical role of growth factors in cancer cell proliferation. Key growth factors, such as Transforming Growth Factor-β, Tumour Necrosis Factor-α and Insulin-like Growth Factors, are explored within the context of cancer progression. The intricate signaling pathways, particularly the Tyrosine Kinase Receptor pathway, are examined to understand how metal complexes may disrupt these pathways, impeding uncontrolled cell growth. Furthermore, this review provides an in-depth examination of medicinal inorganic chemistry, emphasizing the ability of transition metal complexes to form charged ions and induce hydrolysis reactions. The nuanced discussion underscores the necessity for precise dosages of metal-containing drugs to avoid undesirable toxicity, acknowledging the delicate balance required for optimal therapeutic responses. This comprehensive review delves into metal complexes of Cobalt, Copper, Zinc, and metal nanoparticles as promising inhibitors of cancer growth factors. By explicating the intricate interplay between metal complexes and growth factor pathways, this article contributes to the ongoing scientific exploration of novel and effective anticancer strategies.

Keywords: Growth Factors, Metal Complexes, Metal Nanoparticles, Copper, Zinc, Cancer

1. Introduction:

The enduring wisdom of Paracelsus (1493-1541), "Everything is poisonous, and nothing is harmless. The dose alone defines whether something isn't poison," resonates in the context of cancer treatment. The current arsenal of active anticancer agents spans diverse targets across multiple cellular and biological properties, steering away from conventional cytotoxicity towards the strategic design of selective[1-2]. While progress has been made, challenges persist, prompting exploration at the crossroads of structural biology and chemistry for innovative anticancer solutions. In nature, metal ions like zinc and copper are integral to numerous biological systems, playing pivotal roles in the normal functioning of organisms[3]. Transition metals such as copper, iron, and manganese participate in essential biological processes, ranging from electron transfer to catalysis and structural roles, often associating with active sites of proteins and enzymes[4]. However, dysregulation of these essential metals during normal biochemical processes has been linked to the development of various pathological disorders, including cancer[5]. These cellular functions necessitate trace metals in minute yet tightly regulated amounts. In contrast, metals like arsenic, cadmium, chromium, and nickel, while less beneficial, can induce a wide range of toxic side effects, including carcinogenesis[5-6]. Throughout history, metal-containing compounds have found utility in treating diverse disorders[7]. In the realm of medicinal chemistry, traditionally dominated by organic compounds, metal complexes have gained favor as both diagnostic tools and anticancer agents[8]. The accidental discovery of cisplatin i.e. cis-$[Pt^{II}(NH_3)_2Cl_2]$ stimulated research in anticancer agents. However, its clinical use is restricted due to dose-dependent toxicity, resistance, and a narrow spectrum of activity[9-10]. These limitations have propelled the search for platinum-based compounds with lower toxicity, higher selectivity, and a broader spectrum of activity, leading to the development of compounds like carboplatin and oxaliplatin, among others[11-12]. Beyond platinum analogs, attention has shifted to other metal complexes containing ions such as zinc (II), copper (II), gold, and copper chelating agents as potential anticancer agents[13-16]. Clinical trials investigating ruthenium-containing compounds underscore the rich potential of non-platinum metal-based compounds in cancer treatment[17-18]. Additionally, metals leveraging unique physiochemical properties serve as potent tools in cancer diagnosis[19]. Growth factors are important hall marker of cancer. Growth factors are proteins that stimulate the growth of specific tissues, playing a crucial role in cellular differentiation and division. They typically exert their influence through paracrine and autocrine signaling, although there is evidence suggesting an endocrine mode of action, contrary to the original belief. Autocrine mechanisms, in particular, are implicated in the significant role they play in the growth of cancer cells[20-21]. The modes of action of growth factors are diverse, with a predominant pathway being the tyrosine kinase receptor pathway. Tyrosine kinase receptors are membrane-bound complexes with intrinsic kinase activity in their cytoplasmic domain. Upon binding to specific growth factors (ligands), these receptors activate their kinase activity, leading to the

phosphorylation of downstream targets on their tyrosine and serine residues. This, in turn, initiates signaling cascades and recruits other molecules into the cellular response[20-21].

2. Cancer growth factors:

Cancer is characterized by uncontrolled cell growth, with sustained proliferation being a key feature[22]. This heightened proliferative capacity is largely facilitated by growth factors. Evidence indicates that growth factors can enhance the transcription of specific proto-oncogenes, such as *myc* and *fos*[23]. Cancer cells may either produce these growth factors themselves or prompt normal cells to release them through signaling mechanisms[22]. The actions of growth factors are diverse, but they predominantly operate through the tyrosine kinase receptor pathway. Tyrosine kinase receptors are integral membrane complexes possessing intrinsic kinase activity in their cytoplasmic domain. Upon binding to specific growth factors (ligands), these receptors activate their kinase function, leading to the phosphorylation of downstream targets on tyrosine and serine residues. This, in turn, recruits additional molecules into signaling cascades[21]. Growth factors can be classified in following classes[24].

2.1. PLATELET DERIVED GROWTH FACTOR FAMILY

Platelet derived growth factor (PDGF) is initially released from alpha-granules of platelets and act as a chemoattractant for fibroblasts and as mitogen for these cells[25]. PDGF stimulates production of collagenase by fibroblasts causing remodelling of matrix required for tissue repair[26]. It is also released from activated macrophages[27]. Platelet derived growth factor (PDGF) family of growth factor consists of 5 different disulphide linked dimmers PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD that act via 2 receptors PDGFRα and PDGFRβ[28]. Platelet derived growth factor receptors (PDGFR) are receptors with intrinsic tyrosine kinase activity that regulates several functions in normal cells[29]. PDGFR play a role in development of lungs, heart, CNS and kidney[30]. In addition to physiological functions, PDGF play pathological roles in disease such as atherosclerosis[31], glomerulonephritis[32] and cancer[33].

2.2. VASCULAR ENDOTHELIAL GROWTH FACTOR FAMILY

Humam vascular endothelial growth factor (VEGF) family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D and Placental Growth factor[34]. There are 3 receptor which are regulated by protein kinase for VEGF family of ligands: VEGFR-1, VEGFR-2, VEGFR-3. And two non-enzymatic receptors: Neuropilin-1 and Neuropilin-2[35]. VEGF is secreted by any cell that encounters hypoxia[36]. VEGF acts as a mitogen thereby being important survival factor for endothelial cells and monocyte motility[37]. VEGF changes permeability of endothelial cells by causing injury to help angiogenesis[38]. Major factors regulating VEGF includes growth factors, local environmental hypoxia, hormones and cytokines[39]. The key regulator of hypoxia induced angiogenesis is transcription factor Hypoxia-Induced-Factor (HIF-1)[40]. It was very early proposed that inhibiting angiogenesis can be effective antitumor strategy because tumour growth required for blood vessel formation[41]. VEGF mRNA is expressed in neoplastic cells whereas endothelial cells express VEGFR-1 and VEGFR-2 mRNA and

proteins[42]. The increase in blood vessel formation helps tumour to gain necessary oxygen and nutrient. Tumour angiogenesis is a hall mark of cancer which supports tumour growth and metastasis[43].

2.3. EPIDERMAL GROWTH FACTOR FAMILY

Epidermal growth factor family (EGF) is a complex network that modulates growth of cells. EGF is released by cells and then either by autocrine signaling i.e. stimulates its own growth or paracrine signaling i.e. stimulate growth of neighbouring cells[44]. Ligands known to bind to EGFR are Epidermal growth factor (EGF), Transforming Growth Factor-α (TGF-α), amphiregulin, heparin-binding EGF like growth factor, Betacellulin and Epiregulin[45]. EGFR are Receptor tyrosine kinases and they belong to ErbB family which consists of ErbB-1 (EGFR), ErbB-2 (HER-2 or Neu), ErbB-3, ErbB-4[46].

EGF has been known to be mitogenic for mesenchymal and epithelial cells[47]. EGF stimulus to normal cells causes them to transform into neoplastic cells by increasing the level of phosphotyrosine in proteins[48] and increase in sugar and amino acid metabolism. Expression of c-fos and c-myc is upregulated by EGF[49]. EGF has also been found to play a vital role in viral carcinogenesis as it enhances viral transformation of cells[50]. Chemical carcinogenesis of methylcholantherene in skin is enhanced by EGF[51]. EGF phosphorylates tyrosine residues of src, erb, abl, yes, fgr, ros, fes (fps) and fms[52].

2.4. FIBROBLAST GROWTH FACTOR FAMILY

In humans, the Fibroblast Growth Factor (FGF) family encompasses 23 polypeptide-encoding genes. Notable members include FGF-1 (acidic FGF), FGF-2 (basic FGF), FGF-6, and FGF-8. The FGF receptors, FGFR1-4, play crucial roles in both autocrine and paracrine signaling pathways[53]. Demonstrating mitogenic properties for both epithelial and mesenchymal cells, FGFs were identified as the first angiogenic factors[54], attributing to their high angiogenic activity[55]. FGFs enhance cellular motility and invasiveness[56]. Critical for the sustained self-renewal and pluripotency of human embryonic stem cells (HESCs), FGF signaling is indispensable[57]. In the context of haematopoiesis, FGF stimulates the growth of progenitor cells[58]. Notably, FGF-2 stimulation has been linked to the neoplastic transformation of cells[59]. Elevated FGF-2 levels in the microenvironment of metastatic prostate cancer contribute to the evasion of the antiproliferative effects of chemotherapy[60]. Furthermore, the myeloma-associated oncogene FGFR-3 exhibits upregulation in cancer cells from patients with Chronic Myeloid Leukaemia (CML)[56,61].

Moreover, various other growth factor families play pivotal roles in promoting cell proliferation and contributing to cancer. The Transforming Growth Factor-β (TGF-β) family, a group of secreted cytokines, plays a crucial role in influencing cellular proliferation and differentiation. Its impact extends to immunity, cancer, bronchial asthma, lung fibrosis, heart diseases, and diabetes[62]. Insulin-like growth factors (IGFs) are associated with the regulation of metabolism, growth, and survival[63]. The signaling pathway employed by IGF involves phosphoinositide-3-kinase (PI3K) and Akt or Ras and MAPK, mediating responses to various stimuli[64]. Hepatocyte Growth Factor (HGF), also known as Serum Factor (SF), exerts its actions by

binding to a specific receptor site, c-Met[65]. HGF binds to the extracellular α-chain of the c-Met receptor, inducing tyrosine phosphorylation of the terminal kinase domain and initiating downstream pathways[66]. Ephrin expression plays a regulatory role in development and tissue homeostasis. It is involved in the formation of tissue boundaries, assembly of neuronal meshwork's, remodelling of blood vessels, and organ size determination[67].

3. Properties of Metal Complexes:

The field of medicinal inorganic chemistry is comprehensive, encompassing the introduction or extraction of a metal ion into or from a biological system for therapeutic or diagnostic purposes[68]. A notable characteristic of metals is their ability to form positively charged ions in aqueous solutions, facilitating binding to negatively charged biological molecules. This property allows for fine-tuning the charge based on the coordination environment, resulting in the creation of species that can be cationic, anionic, or neutral[67,69]. Transition metal complexes, including Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+2}, Co^{+3}, Ni^{+2}, Cu^{+2}, Zn^{+2} play a significant role as anticancer agents. Additionally, metal ions with high electron affinity can induce hydrolysis reactions by polarizing coordinated groups[69]. In recent years, medicinal inorganic chemistry has garnered substantial attention for its role in designing anticancer agents[70-71]. While metals have historically been employed in treating various pathological disorders, the true potential of metal-based compounds in cancer treatment became evident with the landmark discovery of cisplatin in the 1960s. Given that the presence of metals in cellular conditions is rigorously regulated, the administration of metal-containing drugs must be carefully defined to achieve optimal therapeutic responses[72-73]. Improper dosages may lead to both excess and deficiency of metals, resulting in undesirable toxicity. This comprehensive review mainly focuses on metal complexes of Cobalt, Copper, Zinc and metal nanoparticles.

4. Cobalt and Cancer Growth Factors:

Cobalt is an essential trace element present in the human body. It is involved in important biological functions such as fatty acid and amino acid metabolism, haematopoiesis, and, in the form of vitamin B_{12} it is indirectly involved in synthesis of DNA. Interestingly, one cobalt complex containing Schiff base ligand (Doxovir) has recently passed phase II clinical trial for anti-viral treatment[74]. Several in vitro studies suggest that cobalt complexes possess promising anti-cancer activity[75]. Especially, cobalt complexes containing Schiff base ligands have been shown to possess more efficient anti-cancer activity against cancer cells such as MCF-7, A431 and HeLa than cis-platin[76-77]. In the case of cobalt (III) octahedral complexes, Schiff bases occupying the square planar positions than the remaining two axial positions can be utilized to tune their properties for bio-molecule interaction and biological applications. Changing the number and length of aliphatic chains in the coordinated ligands of some cobalt (III) complexes would strongly influence the mode of biomolecule interactions and anticancer activity[78-79]. Previously we have reported a novel cobalt complex i.e. Cobalt-N(2-hydroxyacetophenone) glycinate (CoNG)

(Figure-1) has a significant role in reversal of drug resistance[80].

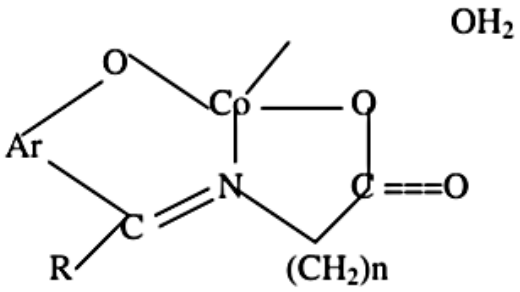

Figure 1: Chemical structure of novel cobalt complex, Cobalt-N(2-hydroxyacetophenone) glycinate (CoNG)[80].

5. Zinc and Cancer Growth Factors:

In experiments where mice were administered type II collagen to induce arthritis, the introduction of Zn showed a significant inhibitory effect on the formation of Th17 cells. Zn treatment was found to impede the activation of IL-6 and subsequent Th17 cell development in vitro through its interference with STAT3. Crucially, Zn binding caused a structural change in the alpha-helical conformation of STAT3, disrupting its interaction with JAK2 kinase and a phosphor-peptide carrying a STAT3-binding motif from the IL-6 signal transducer gp130 (Figure-2). The ultimate finding suggests that Zn functions by suppressing the activation of STAT3, a pivotal mechanism in the development of Th17 cells[81,83]. Simultaneously, substantial evidence exists to support the anti-cancer impact of Th17 lymphocytes. However, their effectiveness appears to be intricately linked to the disease's progression, showcasing differing roles in the early and late stages. Additionally, factors such as the cancer's origin, the involvement of inflammatory pathways, and the promotion of angiogenesis in its development significantly influence this dynamic. Equally important is the tumour's immunogenicity, as research has shown that the inhibition of tumour growth by Th17 lymphocytes is observable solely in immunogenic tumour types[82,84]. However, for IMR-32 cells insufficient zinc availability had a notable impact on the modulation of STAT1 and STAT3 in E19 rat brain and human neuroblastoma IMR-32 cells. This deficiency led to oxidative modifications of proteins, influencing the phosphorylation patterns of STAT1 and STAT3, hindering their nuclear translocation, DNA binding, and trans-activating activity. The findings propose a link between zinc deficiency-induced oxidative stress and the compromised tyrosine phosphorylation and nuclear movement of STAT1 and STAT3[85].

Zinc ions play a vital role in upholding the stability of the p53 protein and its binding affinity for DNA. Elevated levels of MT-1 and MT-2 trigger the displacement of zinc ions, resulting in the destabilization and deactivation of p53, subsequently hindering apoptosis. Clinical trials conducted on patients with colorectal cancer have validated this mechanism[86]. Zinc coordination has been shown to be crucial for the correct folding of the p53 core domain in laboratory settings. Disruption of this interaction significantly diminishes or entirely prevents p53 from binding to DNA and activating target genes[88]. NMR spectra analysis highlights alterations in the DNA-binding surface upon removal of the zinc ion. Furthermore, fluorescence anisotropy studies demonstrate that the absence of the zinc ion results in the loss of site-specific DNA-binding activity [87,89]

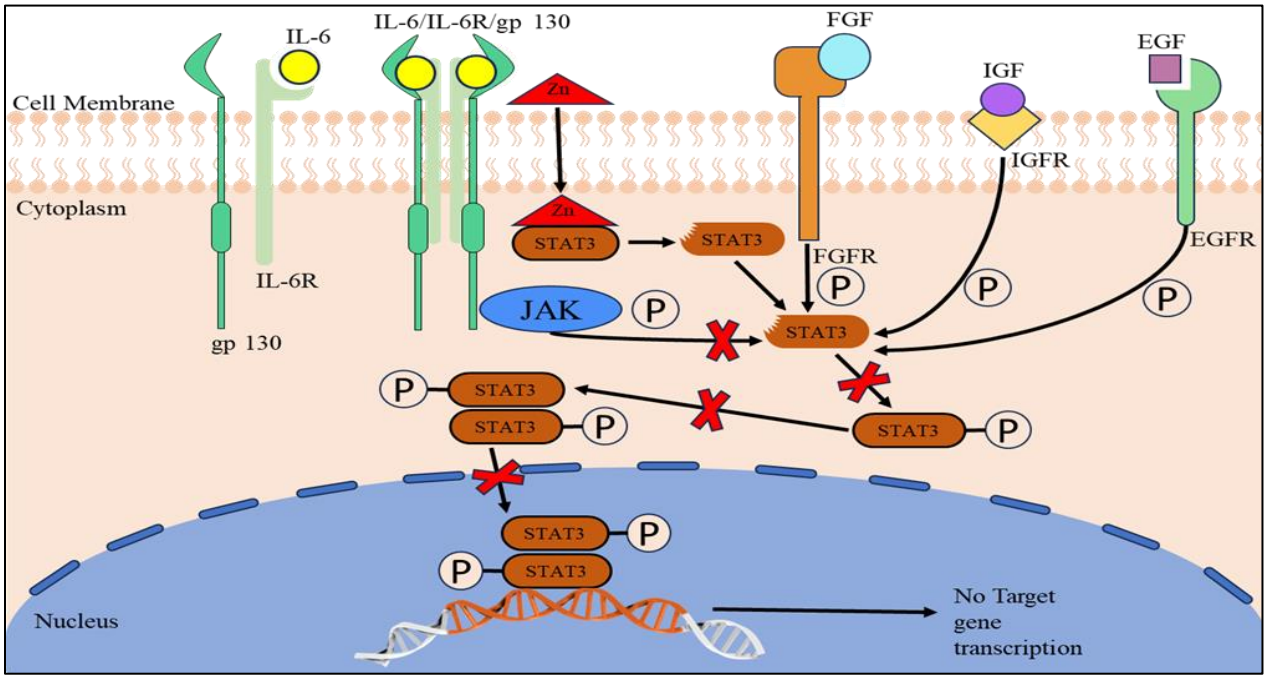

Figure 2: Zn preventing STAT3 nuclear transport. IL-6R and gp130 forms the IL-6/IL-6R/gp 130 complex which releases phosphorylated JAK. When Zn bind to the STAT3 protein and make conformational changes to the α-helical structure of the protein. FGFR, IGFR and EGFR could not phosphorylate STAT3 protein through JASK and STAT3 dimer formation is inhibited. As a result, it does not bind with the specific site in DNA and inhibits target gene expression by inhibiting the nuclear transport of STAT3 protein.

Multiple research endeavours have highlighted MT's role in inducing several anti-apoptotic B-cell lymphoma 2 (Bcl-2) oncogenes and the regulatory gene for the transcription factor c-myc. Simultaneously, it curtails the activity of proapoptotic proteins like caspase-1 and caspase-3. The correlation between heightened concentrations of MT-1 and MT-2 isoforms and decreased caspase-3 activity is linked to the requirement of zinc ions for caspase-3 functionality, analogous to the necessity observed in the case of the protein p53[90]. Numerous proteins involved in the removal of damaged bases or nucleotides rely on a zinc finger domain and are thus contingent on zinc for their function. Examples include the p53 suppressor protein and AP (Apurinic/apyrimidinic) endonuclease[91,92]. The identification of zinc binding within p53 originated from biochemical evidence and was solidified with the publication of a partial crystal structure of the protein[93]. Zinc plays a critical structural role in stabilizing the DNA-binding domain of p53, crucial for its DNA-binding activity (Figure-3)[94]. The evidence largely rests on the ability of metal chelators to strip zinc from p53, transforming the protein into a 'mutant-like' form that loses its specific DNA-binding ability. However, the reversible nature of this phenomenon hasn't been conclusively established. When zinc is chelated from p53 in vitro, it triggers swift cysteine oxidation and the formation of protein aggregates linked by disulfide bonds. Although thiol reduction dissolves these complexes, it doesn't suffice to restore the protein to its 'wild-type' conformation capable of DNA binding. In this study, a recombinant form of p53 lacking zinc was generated, displaying diminished DNA-binding affinity. This was achieved by using a chelator (EDTA, 200 mM) to prevent zinc incorporation and a thiol-reducing agent (DTT, 5 mM) to prevent disulfide formation

within the protein structure. Upon reintroduction of zinc, this protein transitioned from the 'mutant' PAb240+ form to the 'wild-type' PAb1620+ form, thereby regaining its high-affinity DNA-binding capacity. Experiments involving radioactive zinc confirmed the correlation between this effect and the incorporation of zinc within the protein structure[94].

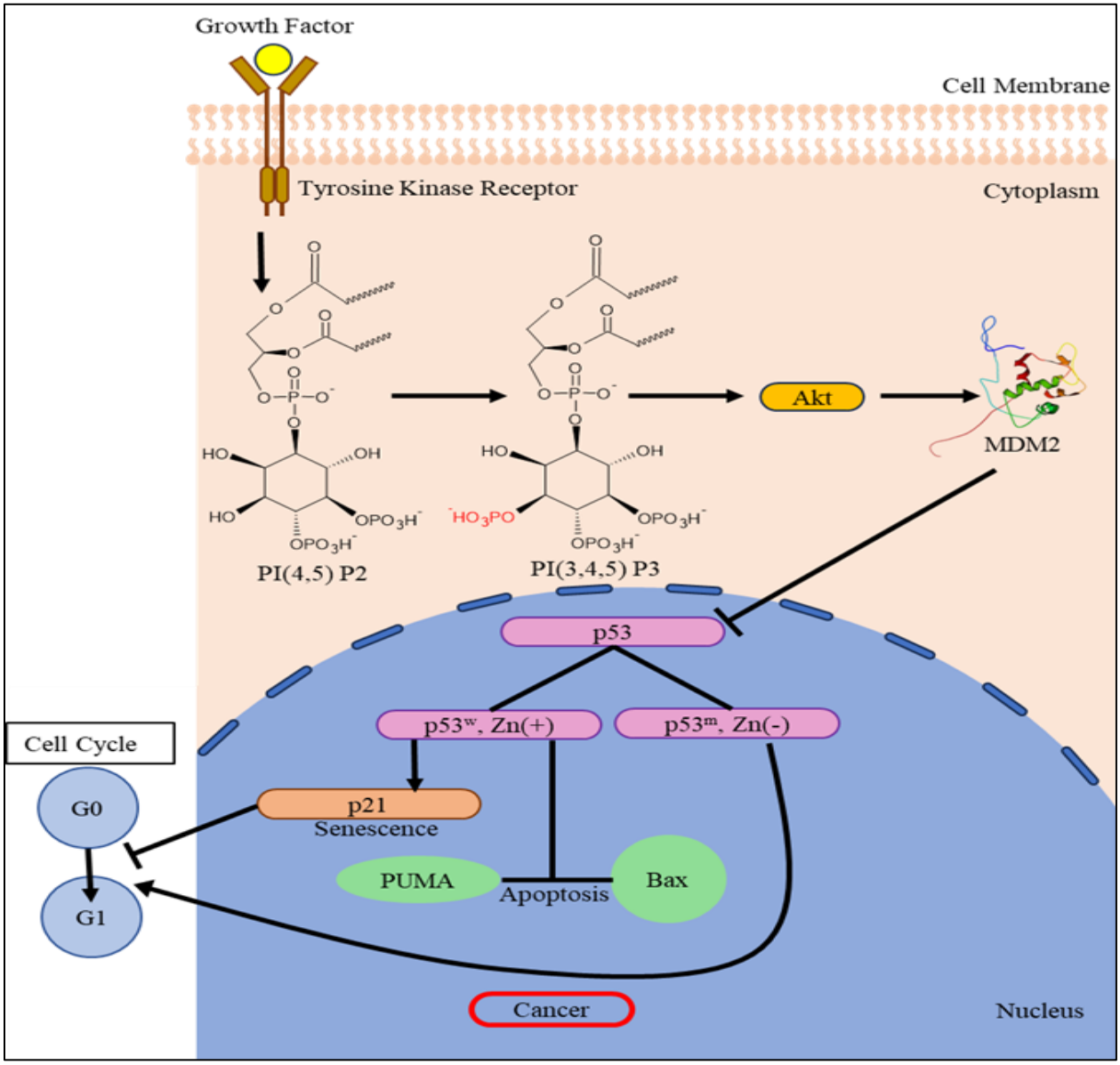

Figure 3: Cell cycle arrest due to presence of Zn. Growth factor signals activate tyrosine kinase receptors, leading to the phosphorylation of PI(4,5)P2 to PI(3,4,5)P3. This activates Akt, triggering MDM2-mediated inhibition of p53 and preventing apoptosis. Zn deficiency disrupts p53 folding, resulting in a mutant gene. In the presence of Zn, proper p53 folding activates p21, causing cell-cycle arrest. Zn deficiency allows cancerous cell proliferation.

Recently, Yousef and colleagues synthesized novel M (II) complexes using the chelating ligand L55 and assessed their capacity to hinder hepatocellular carcinoma cell growth. Comparing their cytotoxic effects revealed that the Zn complex-1 displayed lower IC50 values for both HeP-G2 (0.2457 μM) and MCF-7 (0.2013 μM) compared to L55

alone (with IC50 values of 0.4826 μM and 0.6224 μM, respectively). Furthermore, the Zn (II) complex exhibited antioxidative properties and demonstrated scavenging activity against hydroxyl and superoxide radicals (Figure-4)[97].

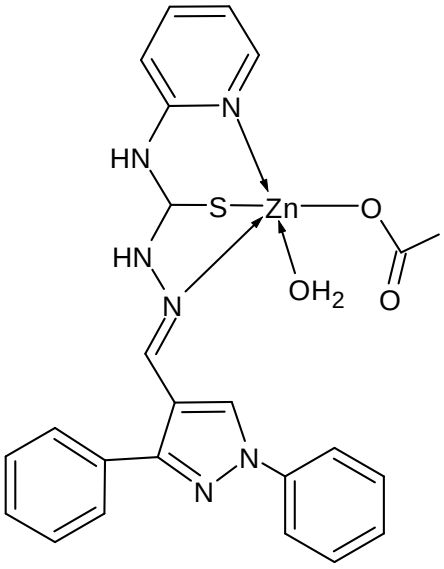

Figure 3: Zn (II) complex with chelating ligand L55

Zinc-phthalocyanine complexes (Figure-4) are widely known for their low toxicity and robust chemical and photochemical stability[100]. Researchers have explored enhancing Photodynamic Therapy (PDT) targeting efficiency by linking a specific anti-tumour agent to a photosensitizer. Jin-Ping Xue and collaborators introduced erlotinib-Zn (II) phthalocyanine complexes[98,100]. and Zn (II) phthalocyanine-coumarin conjugates[101]. Erlotinib, a small anti-cancer drug, targets the ATP binding domain of EGFR (Epidermal Growth Factor Receptor), prevalent in cancer cells, while 7-hydroxycoumarin impedes cell proliferation by reducing cyclin D1 release, frequently elevated in various cancer types[102]. Building on prior studies involving zinc (II) phthalocyanine conjugates where erlotinib was linked at the a-position using an oligoethylene glycol spacer, the researchers investigated the impact of both linker lengths (oligoethylene glycol chain) and substitution positions (a or b) within the phthalocyanine framework. They assessed the in vitro photodynamic activity and the specific affinity of a series of erlotinib-Zn (II) phthalocyanine conjugates, compounds 1–6, against Hep-G2 cells. Under dark conditions, all complexes demonstrated minimal cytotoxicity up to 50 mM, yet exhibited potent photo-cytotoxicity with IC50 values ranging from 12.44–91.77 nM (compared to the reference compound Zn-phthalocyanine IC50 43.30 ± 4.72 nM, using a low light dose (k = 670 nm, 80 mW cm^{-2}, 1.5 J cm^{-2})[99-102]. Notably, a-substituted compounds 2 and 1 displayed higher photo-toxicity (IC50 9.61 ± 2.49–44.50 ± 3.28 nM) than b-substituted compounds 3–6 (IC50 33.97 ± 3.97–91.77 ± 10.58 nM). Moreover, elongating the oligoethylene glycol chain slightly decreased the photo-cytotoxicity of compounds 1–162. The inclusion of the erlotinib component augmented cellular uptake and specificity for Hep-G2 cancer cell lines (known for EGFR overexpression), with compounds 2 and 5 (using a linker of n = 3) demonstrating the highest targeting ability[103].

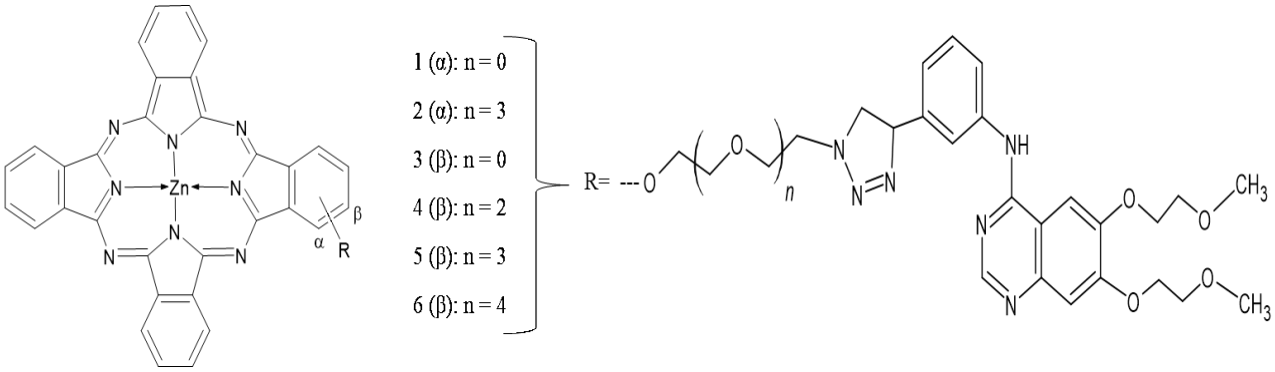

Figure 4: Zinc-phthalocyanine complexes

6. Copper and Cancer Growth Factors:

Copper is an essential component of various endogenous antioxidant enzymes. Its potential association with free radicals in the process of carcinogenesis have been subject of research[104]. DSF, a small molecule weighing 296.54 in molecular mass, has garnered increasing evidence of its efficacy in inhibiting various cancer types. Studies indicate its involvement in suppressing prostate cancer, lung cancer, breast cancer, liver cancer, ovarian cancer, and oesophageal carcinoma cell proliferation[105-109]. DSF has the ability to undergo rapid reduction in serum, forming two molecules of diethyldithiocarbamate. This compound serves as a potent chelator of transition divalent metal ions[110]. The anticancer potential of DSF has been established across diverse cancer cell models, primarily reliant on the creation of the $Cu(DDC)_2$ complex with divalent metal ions like Cu. In vitro experiments reveal that when DSF and Cu are combined, they promptly yield a highly oxidized intermediate form of DDC, known as bis(dialkyliminium)-tetrathiolane di-cation (Bitt-42+). This initial stage leads to the spontaneous breakdown of a small fraction of DSF into its anionic chelate form, DDC. Subsequent redox reactions between DDC and Cu^{2+} result in the stable formation of the $Cu(DDC)_2$ complex. This redox process and Fenton chemistry linked to the $Cu(DDC)_2$ complex generation trigger the production of Reactive Oxygen Species (ROS), ultimately prompting apoptosis in cancer cells. DSF/Cu demonstrates cytotoxicity against cancer cells and exhibits the capability to eliminate cancer stem cell (CSC) populations across various cancer types, with minimal to no toxicity observed in normal cells[111-114]. The mechanism behind DSF's anticancer effects appears to hinge on its dependence on copper, crucial for redox reactions. Cancer cells typically harbour elevated levels of copper due to the trans-membrane Cu transporter CTR1 transportation. DSF has the capability to form a complex with copper, facilitating its entry into cancer cells. This specificity allows DSF to selectively target these cells while sparing normal healthy cells expressing low levels of copper[112]. The interaction between DSF, DDC, and copper triggers the production of extracellular ROS, which subsequently prompt apoptosis in cancer cells[115]. Studies demonstrate the accumulation of DSF's metabolite, DDC, and its copper complex

$Cu(DDC)_2$ within cancer cells, inducing ROS generation and consequent apoptosis. The production of both extracellular and intracellular ROS is heavily reliant on the intact thiol group, which plays a role in copper chelation[115-120]. In breast cancer cells subjected to treatment with the DSF/Cu complex, researchers observed continuous activation of the MAPK pathway. This activation was subsequently channelled towards initiating ROS-induced apoptosis. Additionally, the use of MAPK pathway inhibitors resulted in a reduction of the cytotoxic effect caused by the DSF/Cu complex. These findings strongly suggest the involvement and significance of the MAPK pathway in mediating ROS-induced apoptosis triggered by the DSF/Cu complex[111]. Studies revealed that DSF/Cu exhibited the ability to inhibit proteasome activity specifically in breast cancer models without affecting normal breast cells. This inhibition of proteasome activity by the DSF/Cu complex resulted in the buildup of poly-ubiquitinated proteins and the formation of cytotoxic protein aggregates. These aggregates comprised crucial proteins like IκB, p27, Kip1, and c-Myc, leading to the interruption of cell-cycle progression and eventual induction of apoptosis[121]. Proteasomes play a crucial role in the activation of the NF-κB pathway. They are instrumental in the degradation of the inhibitor molecule, IkB (inhibitor of κB), a process that leads to the liberation of the NF-κB p50/p65 heterodimer from the inhibitory complex. This liberation allows the p50/p65 heterodimer to translocate into the nucleus, where it functions as a transcriptional regulator[122]. When DSF/Cu impedes the proteasome system, it results in sustained inhibition of NF-κB by IκB, preventing the nuclear translocation of NF-κB. This scenario contributes to favouring apoptosis or sensitizing cancer cells to anti-cancer drugs. Notably, DSF has showcased significant relevance in this context, as demonstrated by Wang et al. (2003). Their study revealed that when DSF was administered alongside 5-fluorouracil, it substantially inhibited NF-κB activity. This inhibition enhanced the apoptotic effect of 5-fluorouracil on colorectal cell lines, specifically DLD-1 and RKO[123]. For more than ten years, the link observed between elevated ALDH activity and the cancer stem cell (CSC) phenotype has served as a catalyst for researchers. This association has spurred efforts to develop precise ALDH inhibitors with heightened clinical promise. The aim is to efficiently suppress CSCs and impede tumour progression through targeted interventions[124]. DSF exhibits the capacity to induce apoptosis in breast cancer stem cells (CSCs) by specifically inhibiting ALDH1 activity[111]. In combination with cisplatin, DSF amplifies its cytotoxic effect by targeting the stemness of CSCs derived from breast cancer cell lines (Figure-5). This is achieved through the inhibition of stemness-related transcription factors such as Sox, Nanog, and Oct, alongside the suppression of ALDH activity in ALDH + stem-like cells1[25-126]. Guo et al. (2019) showcased DSF's ability to sensitize cisplatin-resistant ovarian ALDH+ stem-like cells to cisplatin treatment. This sensitization was achieved by suppressing ALDH activity and triggering apoptosis[128]. Furthermore, DSF demonstrates efficacy in reversing cisplatin resistance in testicular germ cell tumours by inhibiting ALDH activity[127]. Xu et al.'s research revealed that the DSF/Cu complex induced

apoptosis not only in MM cells but also in MM progenitor cells. Additionally, it notably triggered cell cycle arrest, specifically in the G2/M phase, within MM.1S and RPMI8226 cells. The study also demonstrated through JC-1 assays and protein blotting that DSF/Cu disrupted mitochondrial membrane integrity and activated cystatin-8 cleavage in MM cells. These findings strongly suggested the activation of both exogenous and intrinsic apoptotic pathways by DSF/Cu. Importantly, in MM mice models, DSF/Cu exhibited significant efficacy by markedly reducing tumour volume and extending overall survival compared to the control group. These results underscored the promising clinical potential of DSF/Cu in the treatment of multiple myeloma, demonstrating potent anti-myeloma activity both in vitro and in vivo[129].

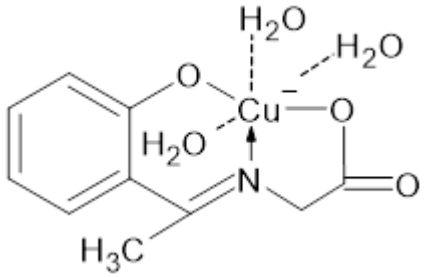

Figure 4: Copper N-(2 Hydroxy acetophenone) glycinate[140].

Copper N-(2 Hydroxy acetophenone) glycinate or CuNG (Figure-4) demonstrates the potential to up-regulate IFN-γ, leading to subsequent apoptosis of tumour cells, even bypassing the multidrug-resistant (MDR) phenotype. This suggests a clinical application for this copper chelate in immunotherapy against various drug-resistant cancers. CuNG appears to leverage the immune system for inducing apoptosis in drug-resistant cancer cells both in vivo and in vitro. Cancer often induces immunotolerance and immunosuppression, impacting its progression. In both in vivo and in vitro settings, CuNG treatment prompts splenocytes from EAC/Dox-bearing mice to release IFN-γ and TNF-α, known inducers of cancer cell apoptosis. Remarkably, CuNG gradually reverses immunosuppression, as indicated by the restoration of lymphoproliferative response. While the specific involvement of cytotoxic T cells and natural killer cells in this apoptosis induction is under investigation, it's known that IFN-γ can reverse T-cell tolerance and sensitizes tumours to radiation therapy[130-141].

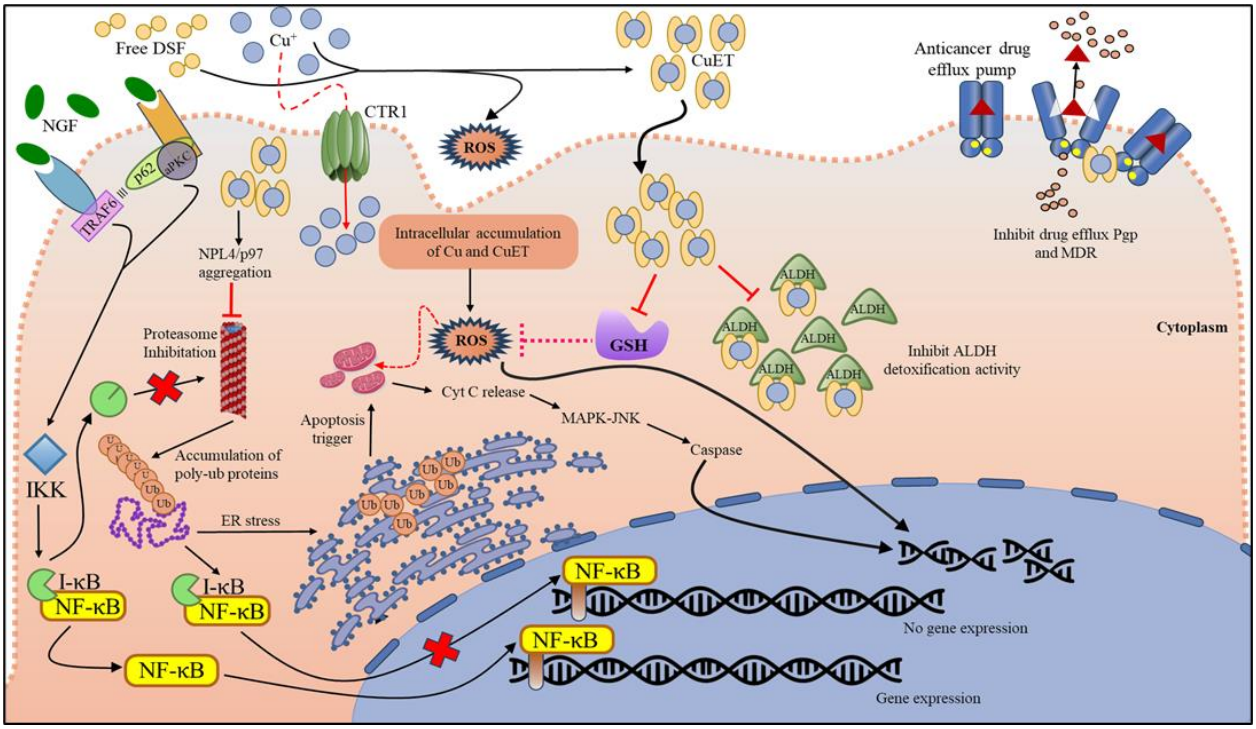

Figure 5: Function of DSF/Cu complex in cancer inhibition. DSH/Cu induces ROS stress, inhibiting proteasome and preventing IκB degradation. Undegraded IκB binds NF-κB, hindering nuclear transport and gene expression. NGF activates NF-κB via p75NTR or TrkA, binding ALDH in cancer cells, impeding detoxification. Proteasome inhibition causes poly-ub protein accumulation, inducing ubiquitin and oxidative stress, releasing Cyt-C and triggering apoptosis.

Gu et al. synthesized four terpyridine copper (II) complexes (Figure-6) that exhibited notable cytotoxicity against various cancer cell lines, particularly BEL-7402 cells, while demonstrating minimal toxicity towards normal human liver cells[141]. Their research delved into the mechanisms underlying these complexes' actions, revealing their capacity to induce G0/G1 phase arrest and modify the expression of cell cycle-related proteins. Additionally, these complexes up-regulated Bax expression while down-regulating Bcl-2 expression, triggering the release of cytochrome c and activation of the caspase cascade. This cascade ultimately led to mitochondrial-mediated apoptosis, showcasing substantial anti-tumour efficacy in a mouse xenotransplantation model featuring BEL-7402 tumour cells[141].

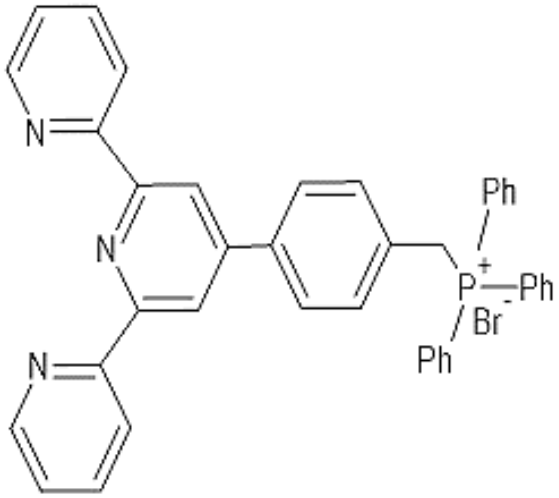

Figure 6: Terpyridine copper (II) complex[141].

7. Metal Nanoparticles and Cancer Growth Factors:

Traditional treatments rely on compounds that regulate the cell cycle, impede cell growth, and exert cytotoxic effects, often causing unwanted side effects[142]. Unfortunately, resistance to these

therapies is common among various malignant tumours[143]. Consequently, silver nanoparticles (AgNPs) offer promise in cancer treatment due to their distinctive physicochemical properties. Directing drug delivery specifically to cancer cells using AgNPs can enhance treatment effectiveness and reduce side effects[144]. The mechanisms by which silver nanoparticles and their combinations with antitumor agents work involve ROS and inducing oxidative stress, causing DNA damage, halting the cell cycle, and prompting cancer cell death via both apoptotic and non-apoptotic pathways[145-147]. Numerous investigations have demonstrated the potential of AgNPs to arrest the cell cycle at various phases, predominantly observed in tumour cell accumulation at the G2/M phase following exposure to AgNPs[148-149]. Their capacity to induce DNA double-strand breaks and increase the sub G0/G1 DNA content within AgNPs-treated cells, indicating apoptotic characteristics, has also been identified[147]. Additionally, studies have highlighted the impact of AgNPs on regulatory protein expression associated with cell cycle modulation. Notably, pivotal transcription factors, including the well-recognized tumour suppressor p53, have been implicated. p53 plays crucial roles in intracellular mechanisms such as DNA damage response and repair, cellular metabolism regulation, autophagy, aging, and programmed cell death (Figure-8).

Hembram et al. (2020) investigated the impact of hybrid Quinacrine-Based silver and gold nanoparticles on various cell lines, both tumour and non-tumour, revealing minimum inhibitory concentration values ranging from 0.5 to 27 µg/mL. Specifically studying SCC-9 cells (squamous cell carcinoma), they delved into the alterations in protein levels associated with DNA repair, replication, and cell cycle regulation (Figure-7). The study highlighted significant reductions in the expression of cyclins E1, B1, and A2. Cyclin A2 and Cdc-2 (Cdk1)/Cdk2 complexes play roles in cell transition from the S phase to the G2 phase. Post-nanoparticle administration, levels of Cip/Kip proteins like p21 and p27, as well as checkpoint kinases (Chk1), decreased notably (except for Chk2, which paradoxically showed increased expression, likely due to compensatory activation). Additionally, the application of nanoparticles reduced the activity of Cdc25-A phosphatase, responsible for activating Cdks to maintain cell cycle progression. These alterations, coupled with effects on other DNA repair-related proteins, collectively contributed to inhibiting tumour cell growth and inducing a cell cycle arrest in the S phase[149-151]. It's been observed that AgNPs treatment in fibroblasts led to reduced production of laminin-1 and collagen-1 and hindered cell migration, demonstrating strong inhibitory effects on stromal fibroblasts[132]. While these findings show promise, further exploration into the mechanisms is needed, especially on diverse stromal cell types like macrophages or endothelial cells, to better understand the impact of AgNPs within the tumour's cellular environment. Notably, in vivo studies have revealed that AgNPs exhibit a stronger anti-tumour effect in immunocompetent mice compared to immunodeficient ones, indicating that AgNPs treatments trigger the anti-tumour immune response within the tumour microenvironment[146]. There's limited information on AgNPs effects on tumour-

associated macrophages, although studies have shown that AgNPs of various sizes boost mRNA levels of IL-1b and IL-8 and prompt the production of reactive oxygen species (ROS) in macrophages[147]. This is noteworthy therapeutically, as these features align with M1-polarized macrophages, known for their capability to initiate anti-tumour responses[148]. Some research has highlighted the necessity of lysosomal entrapment for increased release of Ag ions. The observation that AgNPs ionize more readily in acidic pH environments supports the idea that Ag ions are the primary factors driving the effects triggered by AgNPs[151]. Silver ions have been recognized for their role in generating reactive oxygen species (ROS), which in turn induce considerable oxidative stress, activating pathways that lead to cell death[152-153, 157]. Notably, neutralizing AgNPs-induced ROS with antioxidants can mitigate or even prevent the cytotoxicity triggered by AgNPs, underscoring the significance of ROS in AgNPs toxicity[154-155]. However, inducing oxidative stress alone might not fully replicate AgNPs toxicity. Reports suggest that while cisplatin and AgNPs treatments result in similar levels of ROS generation and equivalent anti-proliferative effects, cisplatin-induced cell death includes both apoptosis and necrosis, whereas AgNPs treatments induce apoptosis exclusively[156].

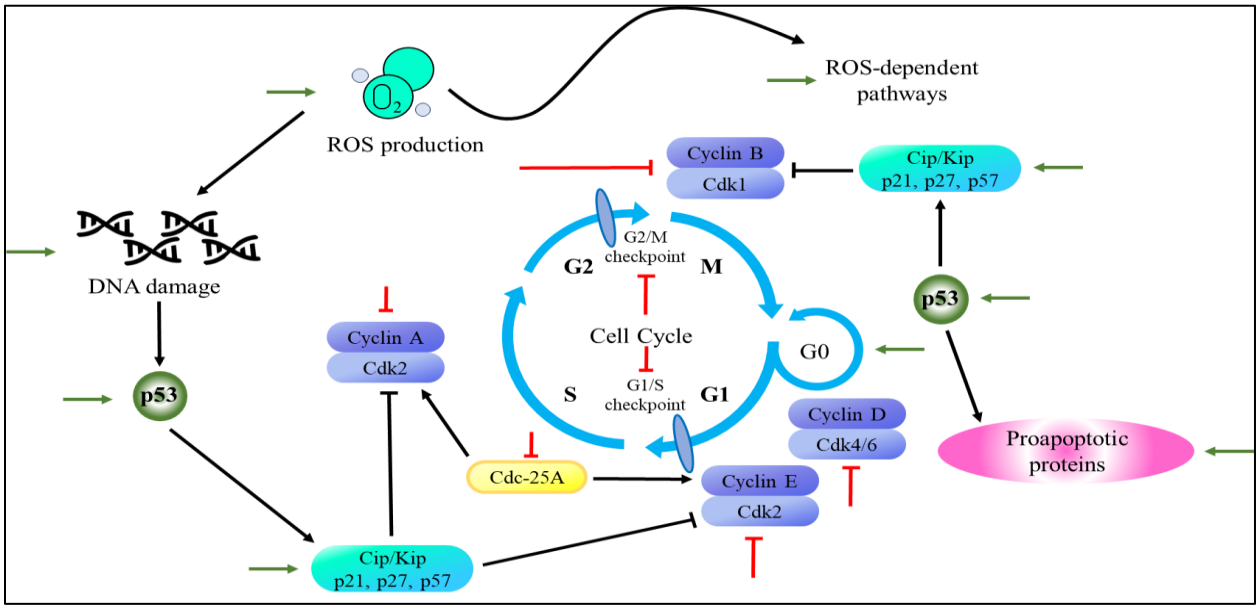

Figure 7: Cell cycle regulation modified by AgNPs. AgNPs activate ROS, DNA damage, and pro-apoptotic factors (green arrow), inducing cell death. They also inhibit key cell cycle complexes (red arrow), causing checkpoint arrests and amplifying apoptosis through p53 activation.

The epidermal growth factor receptor (EGFR) tends to be excessively expressed in about 60% of pancreatic cancers, prompting exploration into the combination of cetuximab and gemcitabine in Phase II trials for this disease[158]. In their work, Patra et al, showcased the potential of achieving high intra-tumoral gold concentrations (4500 μg g^{-1}) using this strategy, in contrast to the 600 μg g^{-1} seen with untargeted GNPs, while also minimizing accumulation in the liver or kidney[159]. Their GNP–cetuximab–gemcitabine

nanocomplex outperformed individual agents or their combined use, both in vitro and in vivo. Even at low doses (2 mg kg^{-1}), this complex restrained tumour growth by over 80% in an orthotopic pancreatic cancer model, surpassing the 30% inhibition observed using the non-conjugated agents in combination[159].

Jiang et al, developed citrate-coated GNPs within a controlled size range of 2 to 100 nm, functionalized with multiple trastuzumab antibodies[160]. This facilitated targeted binding and cross-linking of the human epidermal growth factor receptor (HER)-2 in human SK-BR-3 breast cancer cells. Larger nanoparticles exhibited a higher protein-to-nanoparticle ratio compared to smaller, more curved particles, resulting in more robust trastuzumab binding. The study identified an optimal nanoparticle size range of 40–50 nm for cellular entry. Smaller particles disengaged from the cell membrane, while larger ones appeared to diminish the necessary membrane wrapping for Receptor-Mediated Endocytosis (RME). Moreover, the 40 nm GNP–HER particles facilitated the internalization of the HER-2 receptor complex into the cytoplasm, leading to a 40% reduction in surface HER-2 expression—an effect not seen with trastuzumab binding alone. This reduction subsequently led to decreased expression of downstream kinases like protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) and a twofold increase in trastuzumab cytotoxicity. Despite using extremely low concentrations of GNPs (fM concentrations), GNP–HER was clearly observed in cytoplasmic lysosomes. This study emphasized that GNPs might not only serve as passive drug carriers but also influence drug–cell interactions, potentially enhancing therapeutic effects[160].

Gold nanoparticles (AuNPs) of certain sizes possess the ability to notably impede cell proliferation and induce cell death, encompassing apoptosis, necrosis, and autophagy. These effects stem from mechanisms involving protein denaturation, damage to cellular organelles, genotoxicity, oxidative stress, and immune reactivity[161]. Furthermore, AuNPs demonstrate anti-angiogenic effects by engaging with the heparin-binding domains found in pro-angiogenic factors such as VEGF, b-FGF, and PDGF[161].

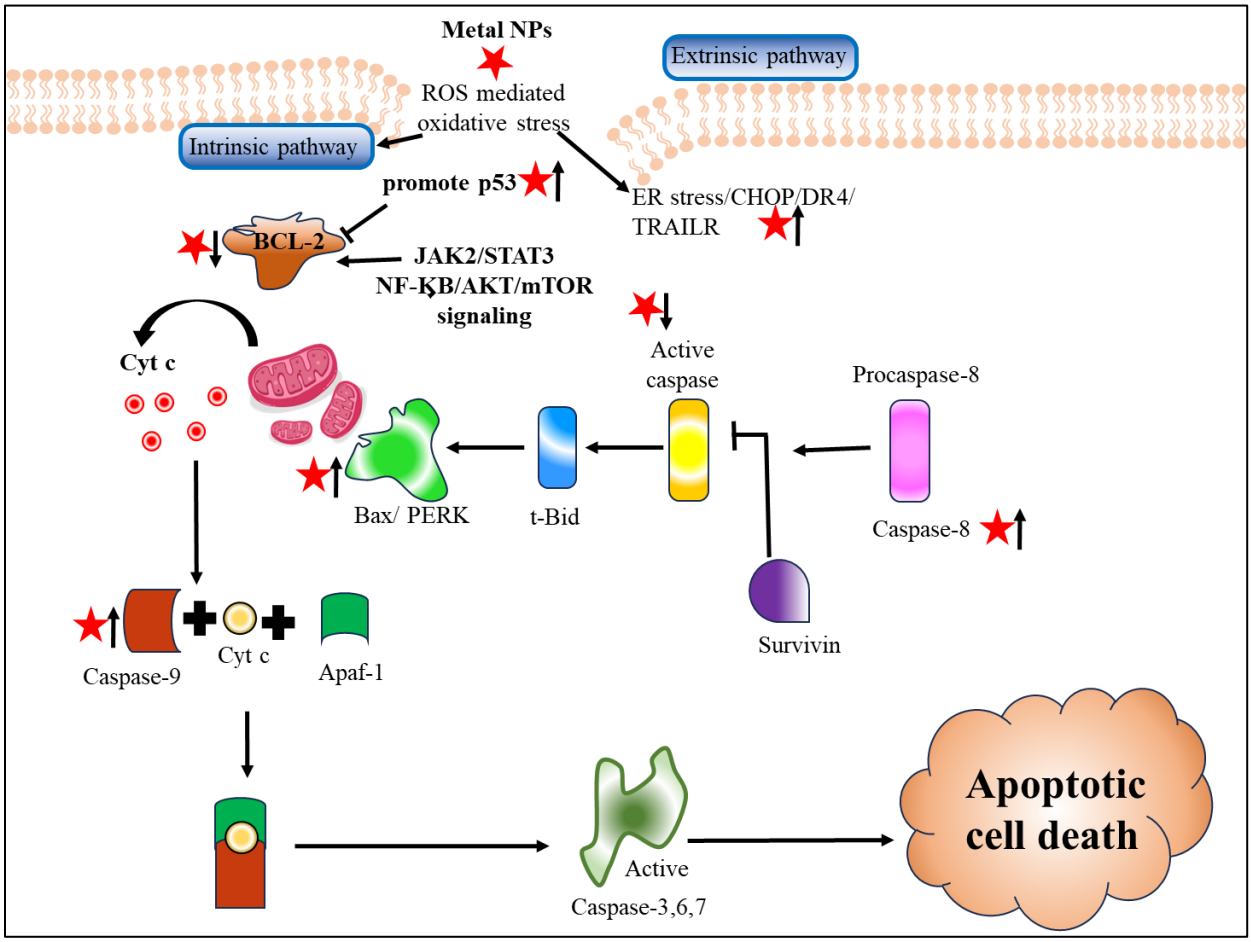

Figure 8: Metal NPs induce ROS mediated oxidative stress. Metal NPs induce ROS-mediated oxidative stress via intrinsic and extrinsic pathways. In the intrinsic pathway, p53 inhibits BCL-2, triggering Cyt c release, activating Caspase-8, and promoting apoptosome formation. Caspase-9, Cyt c, and Apaf-1 signal to Caspase-3, 6, 7, leading to apoptosis. The extrinsic pathway involves significant endoplasmic reticulum stress.

Zhang et al, developed lysine-free recombinant EGF mutants by replacing two intrinsic lysine residues with either serine (S) or arginine (R). This modification aimed to enhance the anti-cancer effects of EGF-GNPs conjugates by adjusting the orientation of EGF on the nanoparticle surface. Among the evaluated EGF mutants (RS, SR), the GNP conjugate of the SR mutant displayed improved biological activities and better growth inhibition in the EGFR-overexpressing skin cancer cell line A431. Biochemical analyses suggested that the enhanced activity of the SR mutant wasn't solely due to orientation control but was also linked to increased binding activities of the mutant to EGFR. These findings support the strategy of manipulating the configuration of the EGF molecule on the nanoparticle surface to develop more potent EGF-GNP conjugates, highlighting SR-GNPs as a potential candidate for cancer therapy[162].

8. Conclusion:

In conclusion, this review highlights the intricate interplay between metal complexes and growth factor pathways, offering insights into the potential of metal-based compounds as promising inhibitors of cancer cell proliferation. The fundamental role of growth factors in driving uncontrolled cell growth, a hallmark of cancer, has been explored, with a

focus on key players such as Transforming Growth Factor-β, Tumour Necrosis Factor-α, and Insulin-like Growth Factors. The Tyrosine Kinase Receptor pathway, a central signaling cascade activated by these growth factors, has been examined in detail, providing a foundation for understanding how metal complexes may disrupt these pathways and impede cancer progression. Transition metals, including Cobalt, Copper, and Zinc, integral to normal physiological functions, have been discussed in the context of cancer pathogenesis. The review underscores the delicate balance required for optimal therapeutic responses, emphasizing the necessity for precise dosages of metal-containing drugs to avoid undesirable toxicity. The exploration of medicinal inorganic chemistry reveals the potential of metal complexes to serve as effective anticancer agents, contributing to the ongoing quest for innovative solutions in cancer treatment.

Furthermore, this article delves into the emerging field of metal nanoparticles as inhibitors of cancer growth factors, expanding the repertoire of potential therapeutic interventions. The enduring wisdom of Paracelsus regarding the significance of dosage in determining toxicity resonates throughout, guiding the discussion on the nuanced use of metal-containing compounds in cancer therapy. As research progresses at the crossroads of structural biology and chemistry, the insights provided in this comprehensive review contribute to the foundation of knowledge in the quest for novel and effective anticancer strategies.

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