Anti-Cancer Activities of Cu(II) Ion Solution in Progression and Development against Cancer and Tumor Cells

By Dr. Tsuneo Ishida

Abstract- Copper plays important role of cancer cell progression and development, malignant cell growth, and angiogenesis in invasive and metastatic growths. Specially, angiogenesis and autophagy have been worthy of new blood vessel formations and fusion proteins respectively for malignant and tumor cell growths. Schiff base copper(II) complexes have anti-proliferative activity against cancer cells. Cu²⁺ ions play an important role as pro-cancer factor in tumor tissues especially in tumor angiogenesis, invasion, and metastasis. Specially, Cu²⁺ ions as Cu-chelating complex can inhibit formation of new blood vessel of tumor cell against angiogenesis in cancer. Promotion and development of cancer tissues have been proceeding with homeostatic imbalances of copper, in which can be caused by the uptake of excessive amounts of copper and some genetic defects. Cancer cell killing via ROS that superoxide anion O₂−, hydroxyl radical •OH, hydrogen peroxide H₂O₂ mainly may be performed under cellular Cu²⁺ ions induced ROS generations in tumor cells. Finally, Cu²⁺-H₂O₂ induced DNA base-pairs inhibition can be regarded as being undergone to DNA damages due to Cu²⁺- complex formations within DNA base-pairs G≡C, A=T by Cu²⁺ substitutions in hydrogen bonds of DNA base-pairs.

Keywords: copper( I) and copper(II) ions, cancer and tumor cells, angiogenesis, reactive oxygen species (ROS), DNA base-pairs.

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I. Introduction

Copper is essential trace element that has the catalysis of a wide range of enzymatic activities, including those involved in the processes of energy production such as cytochrome oxidase, the cell response to oxidant injuries of Cu-Zn superoxide dismutase(SOD). In healthy human adults, the necessity copper daily dietary intake is said to be 1~2 mg. Cu^{2+} ion is reduced to Cu^{+} and then carried into cells by various transmembrane transporters. Copper and zinc are essential for optimal innate immune function and nutritional copper deficiency leads to increased susceptibility to bacterial infection. In the blood, the major copper carrying proteins is ceruloplasmin and the rest of copper is transported by albumin and histidine. Formation of new blood vessels by a tumor enable tumor growth, invasion, and metastasis facilitates easily to occur. Then, organic chelators of copper can passively reduce cellular copper and serve the role as inhibitors for angiogenesis. Depletion of copper has been shown to inhibit angiogenesis in a wide variety of cancer cell and xenograft system. Anti-angiogenic strategies of blood vessel for vasculogenesis, arteriogenesis, and angiogenesis are performed, in which are the embryological formation of new blood vessels, the remodeling of an existing artery to increase its cross-section in response to increased blood flow, and the budding of new capillary branches from existing blood vessels. The progenitor cells migrate to sites of vascularization and differentiate into endothelial cells, forming the vascular plexus. Especially, copper has been suggested as an important co-factor for angiogenesis. It is also a major copper ion that having been found in variety of tumor tissues and are involved in tumor angiogenesis processes on copper-mediated tumor proteasome inhibition. Several clinical trials using copper chelation as either an adjuvant or primary therapy have been conducted. Copper can influence the major stages of tumorigenesis-initiation, promotion, progression, invasion, and metastasis. Copper ions also play a significant role for autophagy of anticancer immunity and immunogenicity, autophagy of tumor antigen, and autophagy in cancer immunotherapy based on preclinical references. Further, copper dependent oxidative damage can be prevented by chelation with the antioxidants dipeptides which with imidazole ring chelate copper. As cancer cells exist probably under significant oxidative stress, the cytotoxic levels could be a successful anticancer approach, in which leads to increases of reactive oxygen species (ROS)^8 stress and ROS (O_2^− to H_2O_2) and oxygen by generations of copper-zinc SOD enzymes.

On the other hand, cancer is one of the leading causes of mortality and represents a tremendous burden on patients and societies. Colorectal cancers are associated with one of the highest morbidity and mortality rates in both men and women. Cancer arises from a single cell, in which malignant tumors are described as monoclonal, meaning that each tumor arises from a single cell. Cancer cells are characterized by increased proliferation and reduced apoptosis. The development of a malignant tumor from a normal cell usually inhibitions forth the driving force in cancer progression may be various molecular such as...
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The underlying molecular mechanism remains unclear. Tumor microenvironment, K-ras mutations, and Haplo-insufficiency as a driving force are new findings highlighting to investigate cancer invasion and metastasis. Recently, it is worth noting that copper chelation and Cu-polymer compounds kill the cancer cells with copper-binding protein formations. Thus, copper is a vital mineral essential for many biological processes, in which copper also plays an important role in promoting physiological and malignant angiogenesis. Copper deficiency as an anti-cancer strategy is that in an early (phase II) clinical trial have led to ongoing phase II evaluation of the copper chelator Tetrathiomolybdate (TM, as an anti-angiogenic agent) in patients with advanced cancers. The TM may be most beneficial for patients with minimal disease burden in the metastatic setting, in which ongoing phase studies as well as future trials will attempt to exploit this knowledge to define the role of TM in cancer treatment. The other, the vast majority of all Cu in healthy humans is associated with enzyme prosthetic groups or bound to proteins. Excess or toxicity of Cu, which is associated with the pathogenesis of hepatic disorder, neurodegenerative changes and other disease condition, can occur when Cu homeostasis is disrupted.

In this review, it has become revealed on the standpoint of the results obtained from Cu(II) ions solutions against bacteria whether Cu(II) ions and its compounds may be directly suppressed against the cancer and tumor cells.

### Table 1: MIC measurements of Cu(II) commercial solution agents against E.coli as a bacteriostatic action by liquid medium method

<table>
<thead>
<tr>
<th>Cu(II) solution agent</th>
<th>Cu(II) solution concentration (mg/L)</th>
<th>MIC 50 mg/L above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original conc 500 mg/L</td>
<td>50 25 12.5 6.25 3.13 1.56 0.78 0.39 0.20 0.10</td>
<td>+ + + + + + + + +</td>
</tr>
</tbody>
</table>

+ (+) : Visible bacterial growth  
- (-) : No visible bacterial growth

### Table 2: MIC, MBC, and CFU of Cu(II) in Cu(NO₃)₂·3H₂O solution against S.aureus as a bactericidal action

<table>
<thead>
<tr>
<th>Antibacterial agent Cu(NO₃)₂·3H₂O solution</th>
<th>Cu(II) concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5000 2500 1250 625 313 156 78 39 20 9.8</td>
</tr>
<tr>
<td>MIC</td>
<td>- - - - + + + + + + + +</td>
</tr>
<tr>
<td>MBC</td>
<td>- - - - + + + + + + + +</td>
</tr>
<tr>
<td>CFU (cfu/mL)</td>
<td>&lt;10 &lt;10 &lt;10 1.1 × 3.1 × 4.0 × 4.5 × 5.1 × 5.5 × 5.3 10² × 10⁸ × 10⁸ × 10⁸ × 10⁸ ×</td>
</tr>
</tbody>
</table>

(+) : Bacterial growth (visible turbidity), (-) : No visible bacterial growth

Cu(II) ions are important as antibacterial agents for bacteriostatic and bactericide actions in bacterial cells. Table 1 shows the bacteriostasis as disinfection agent inhibiting the bacteria growth and multiplying organism of Cu(II) ion, in which minimum inhibitory concentration, MIC= 50 mg/L above was obtained for Cu(II) ion concentration range of 0.10~50 mg/L against E.coli. Table 2 indicates the results as bactericide action, in which MIC=625 mg/L and minimum bactericide concentration, MBC=1250 mg/L were obtained for Cu(II) ion concentration range of 9.8~5000 mg/L against S.aureus. The killing curve of Cu(II) ions is shown in Fig.1 (measurement’s error=±6%), in which killing effects for the copper (II) ions appear sufficiently. Killing mechanisms of Cu(II) ion solutions against bacteria are outlined below.  1. Bacteriolysis of S.aureus peptidoglycan(PGN) cell wall by Cu(II) ions is ascribed to the inhibition of PGN elongation due to the damages of PGN biosynthesis; transglycosylase (TG), transpeptidase (TP) and the activations of PGN autolysins. The other, 2. bacteriolysis of E.coli outer membrane cell wall by Cu(II) ions is attributed to the destruction of outer membrane structure and to the inhibition of PGN elongation due to the damage of PGN biosynthesis TP and the activations of PGN autolysins.
In the cancer and tumor cells, the killing modes are elucidated, it must be clear in this study that the inhibitions of progression and development, invasion, and metastasis of tumor cell may occur by Cu²⁺ induced autophagy fusion proteins in cancer and tumor cells.

III. Cancer Development and Progression

Cancer process is comprised of initiated cancer, development and progression of cancer, proliferation, invasion, and metastasis. Progression process of canerous changes is considered for the cancer and tumor cells in the following:


Copper becomes an essential cofactor for cancer cell proliferation, differentiation, invasion, and metastasis, and apoptosis and necrosis.

Carcinogenesis follows the activation of oncogenes and the deactivation of tumor suppression genes. Apoptosis is highly regulated process of cell death in the development and maintenance of a normal cell population in mature organism. Deregulation of apoptosis pathways is thus a key feature of carcinogenesis. This chapter describes the anti-cancer activities of Cu²⁺ transfer process into initiation, promotion, malignant cell, cell invasion and metastasis against cancer and tumor cells.

a) Cancer prevention and initiated process

Clioquinol (CQ)-CuCl₂ mixture indicates a formation of a stable CQ-Cu complex, and 1,10-phenanthroine promotes copper complexes into tumor cells and induces apoptosis by inhibiting the proteasome activity. Catechins, the dietary phytochemicals present in green tea and other beverages, are considered to be potent inducers of apoptosis and cytotoxicity to cancer cells, in which the antioxidant properties make cancer induction lowering and impeding oxidative injury to DNA. The cellular DNA breakage was found to be significantly enhanced in the presence of copper ions. These Cu complexes play role of cancer prevention.

b) Promotion

Initiation process: copper(II) ions inactivate catalyst enzyme with forming Cu⁺ ions.

\[ \text{Cu}^{2+} + \text{SH} \rightarrow \text{SCu}^{(I)} + \text{H}^+ \]

Oxygen in the cell varies reductive superoxide anion, that generates hydrogen peroxide.

\[ \text{O}_2^- + \text{e}^- \rightarrow \text{O}_2^- \]
\[ 2\text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \]
\[ \text{O}_2^- + \text{H}_2\text{O}_2 \rightarrow \text{OH}^- + \cdot\text{OH} + \text{O}_2^- \]
\[ \text{O}_2 + \text{e}^- + \text{H}^+ \rightarrow \cdot\text{HO}_2 \]
\[ \cdot\text{HO}_2 \rightarrow \text{H}^+ + \text{O}_2 \]

\[ \text{Cu}^{2+} \rightarrow \text{Cu}^{+} \]

\[ \text{O}_2^- \rightarrow \text{O}_2 \]

\[ \cdot\text{OH} \rightarrow \text{H}_2\text{O} \]

\[ \text{H}^+ + \text{O}_2 \rightarrow \text{HO}_2 \]

\[ \text{HO}_2 \rightarrow \text{H}^+ + \text{O}_2 \]
Cu\(^{2+}\) ions are in turn reduced to Cu (I) ions by superoxide anion O\(_2^-\). The copper (I) ions can reduce hydrogen peroxide H\(_2\)O\(_2\) to hydroxyl radical \(\cdot\)OH.

\[
\begin{align*}
\text{Cu}^{2+} + \text{O}_2^- &\rightarrow \text{Cu}^+ + \text{O}_2 \\
\text{Cu}^+ + \text{H}_2\text{O}_2 &\rightarrow \text{Cu}^{2+} + \cdot\text{OH} + \text{OH}^- \\
\end{align*}
\]

c) Progression

Progression of cancer or tumor cell is considered that the uncontrolled cell growth for a carcinogenesis, oncogenesis, epigenesis\(^{26}\) and the migration for intercellular ion channels\(^{27}\) are focused on the identification. Epigenetics in carcinogenesis, progression, and metastasis occurring from cancer stem cell have investigated that many epigenetic changes such as hypomethylation of oncogenes, hypermethylation of tumor suppressor genes, are known to be associated with many cancers. The other, the intracellular ion channels have emerged as oncogenic proteins, since they have an aberrant expression in cancers compared to normal tissues and contribute to several hallmarks of cancer. Carcinogenesis follows the activation of oncogenes and the deactivation of tumor suppression genes.

Cu\(^{2+}\) induced initial cancer cell ROS production and oxidative stress against tumor cell\(^{28}\).

In free radicals (O\(_2^-\), H\(^{+}\), OH\(^-\), \(\cdot\)OH) and H\(_2\)O\(_2\) are formed as follows\(^{29}\):

\[
\begin{align*}
\cdot\text{O}_2^- + 2\text{H}^+ + e^- &\rightarrow \text{H}_2\text{O}_2 \\
\text{H}_2\text{O}_2 + e^- &\rightarrow \text{HO}^- + \cdot\text{OH} \\
\text{OH} + e^- + \text{H}^+ &\rightarrow \text{H}_2\text{O} \\
2\text{H}^+ + \cdot\text{O}_2^- + \cdot\text{O}_2^- &\rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \\
\text{H}_2\text{O} &\rightarrow \text{OH}^- + \cdot\text{H} + e^- \rightarrow \text{H}_2\text{O}_2 \\
\end{align*}
\]

In the cell wall, reacting with polyunsaturated fatty acids(L=Organic ligand):

\[
\begin{align*}
\text{LH} + \text{OH}^- &\rightarrow \text{L}^+ + \text{HOH} \\
\text{L}^+ + \text{O}_2 &\rightarrow \text{LOO}^- \\
\text{LH} + \text{LOO}^- &\rightarrow \text{L}^+ + \text{LOOH} \\
\end{align*}
\]

Reactive oxygen species (ROS) O\(_2^-\) and H\(_2\)O\(_2\) generated in cell wall permeate into cell membrane and cytoplasm, in which in cell membrane high reactive \(\cdot\)OH and OH\(^-\) are formed by Haber-Weiss and Fenton reactions.

Haber-Weiss reaction\(^{30}\): \(\text{H}_2\text{O}_2 + \text{O}_2 \rightarrow \cdot\text{OH} + \cdot\text{OH}^- + \text{O}_2\)

Fenton reaction\(^{27}\): \(\text{Cu}^+ + \text{H}_2\text{O}_2 \rightarrow \cdot\text{OH} + \cdot\text{OH}^- + \text{Cu}^{2+}\)

Furthermore, new ROS productions occur by Fenton-like type. L=Ligand

\[
\begin{align*}
\text{LCu(I)} + \text{H}_2\text{O}_2 &\rightarrow \text{LCu(II)} + \cdot\text{OOH} + \text{H}^+ \\
\text{LCu(II)} + \text{H}_2\text{O}_2 &\rightarrow \text{LCu(I)} + \cdot\text{OH} + \text{OH}^- \\
\end{align*}
\]

The other, relation of oxidative stress and autophagy has been investigated for copper ion in Cu\(_2\)O, CuO crystals. The aqueous systems as following reaction\(^{32}\):
which is partial action sites of glycan saccharide chains. L is coordinated molecular.

\[
\begin{align*}
\text{Cu}^{2+} + LH & \rightarrow \text{CuL}^+ + H^+ \\
\text{CuL}^+ + LH & \rightarrow \text{CuL}_2 + H^+ \\
\text{Cu}^{2+} + 2LH & \rightarrow \text{CuL}_2 + H^+
\end{align*}
\]

Peptide copper complex may be formed as 3N-Cu-O, Cu(Gly-L-Ala)H₂O. Specially, Cu²⁺ ions react with such as cross linked molecular penta glycine(Gly)₅, copper-glycine complex may be formed.

Amino acid : Cu²⁺ + Gly⁻ → Cu(Gly)⁺,
Cu(Gly)⁺ + Gly⁻ → Cu(Gly)₂,
Peptido : Cu²⁺ + GlyGly → Cu(GlyGly),
Cu(GlyGly) + Gly⁻ → Cu(GlyGlyGly)⁻.

b) Autophagy in cancer cell
Autophagy plays an important role in cancer and tumor cells. However, how autophagy contributes to cancer ontogenesis and progression has turned out to be more complex than expected. It must be clear whether Cu²⁺ ions induced autophagy or necrotic cell death. Autophagy is to be function as tumor suppression of damaged organelles/proteins, and to confer stress tolerance that can maintain tumor cell, and to be a mechanism of cell death. MCF-7 cells influenced with tested Cu(II) complexes produced LC3 protein after 72 hours incubation indicating autophagy in MCF-7 cancer cells. Further, the specific nanomedicine induced phage fusion protein in cancer cell occur, that has shown significant improvements in the therapeutic activity of currently existing drug delivery system, such as liposomal doxorubicin. Thus, this fact is implicated that in the cancer and tumor cells, the killing modes are elucidated, it must be clear in this study that the process of autophagy.

c) Cu²⁺ ions, copper complexes and copper-chelating suppress tumor development and angiogenesis in the cancer cell
Tumors are to grow and thrive that they must develop a blood supply. Thus, it is said that every increment in tumor growth requires an increment in capillary growth, in which neovascularization or mechanism by that tumor cells elicit new blood vessel growth from the surrounding tissue. Angiogenesis is a complex process with many different growth factor and inhibited by a diverse range of proteins. The molecules secreted by tumors act on stromal cells in a paracrine fashion, so that can have different activities with the production and secretion of antiangiogenic proteins. Copper is required for high levels of angiogenesis, in which copper requirement is due to many angiogenic factors. Angiogenesis relies on the coordination with many different activities in copper complex and copper-chelating for suppressor tumor.

Copper as a neovascular agent is required for angiogenesis, in which micro-molar amounts of Cu(10⁻⁶ M), thus appeared to control endothelial cell migration and angiogenesis. Copper was shown to stimulate blood vessel formation in the avascular cornea of rabbits, only recently have clinical trials established that Cu privation by diet or by Cu chelators diminishes a tumor's ability to mount an angiogenic response. Nanoparticles of copper(NanoCu) stimulate angiogenesis at molecular level. NanoCu affect the development of blood vessel and muscles in a different manner than Cu salts, in which have pro-angiogenic properties at the systemic level, to a greater degree than CuSO₄ salt. The other, NanoCu also were confirmed that demonstrating significant effects on mRNA concentration and on mRNA gene expression of all pro-angiogenic and pro-proliferative genes measured.

Tetrathiomolybdate(MoS₄²⁻,TM) is a very promising antiangiogenic agent, and a potent metal chelator that binds Cu to proteins such as serum albumin, forming a complex that is only sparingly taken up by cells. The underlying concept for TM efficacy as an anticancer agent is that when the copper status is in the window, cellular copper needs are met and toxicity is avoided. Copper deficiency induced TM, depletion of copper and copper-lowering were significantly impaired tumor growth and angiogenesis, encouraging results in canine study of advanced and metastatic cancer. Further, the copper-chelating agents are efficient for Trientine Dihydrochloride (trientine), suppressor tumor development and angiogenesis.

d) Copper-nucleotide interaction and Cu²⁺-DNA: Cu²⁺ substitution to hydrogen bond in DNA base pairs
Cu²⁺ ion induced occurrence of generations of ROS and hydrogen peroxide H₂O₂ in tumor cells damages DNA in tumor, in which formation of DNA
damage resulting from a release of catalytic copper and binding of copper to DNA with generation of ·OH radicals, and by reaction of H$_2$O$_2$ with the metal produces the strand breaks in DNA as well as DNA base modifications and deoxyribose fragmentation.

It has been found that in aqueous solution coordination of Cu$^{2+}$ to the N7 and N1 sites of purine rings is pH dependent and coordination to N7 diminishes as pH of the solution increases. The sites of action tending to bind purine base A(adenine), G(guanine) and pyrimidine base C(cytosine), T(thymine) of nucleic acid bases for individual metals are indicated, depending on acid dissociation constant pK$_a$. According to the theory, it is shown in Fig.2, that is represented to substituting of Cu$^{2+}$ ions into hydrogen bonds in DNA base-pairing G≡C and A=T pairs. Thus, it may be considered that DNA damages due to copper complexes formation within DNA base-pairs G≡C, A=T occur in cytoplasm of cancer cell.

e) Copper complexes induced the killing, the regulation, the suppressor against cancer and tumor cells

Copper compounds, complexes, and chelation act beneficial for specific malignant tumors. The anticancer activity of Cu(II) depending disulfiram(DS) is high against cancer cell of metastatic liver cancer, prostate cancer that supplementing with Cu, DS is highly toxic to cancer cell.$^{46,47}$ Anticancer activity is exhibited by copper(I) complex possessing pyridine-type ligands(pyridine, bipyridine, phenanthroline etc.) or such where copper(I) ion is coordinated to phosphine ligands.

These both types of ligands to one molecule would make it possible to create a compound with an increased activity against cancer cells.$^{48}$ The novel Cu(II) compound with a binucleating ligand containing a phenol scaffold and two triaza crown binding sites that is occurring within DNA cleavage on cancer cell growth and induces apoptotic cell death of Capan-1 pancreatic cancer cells.$^{49}$ Also, the anticancer action of Casiopenias, copper coordinated complexes of Cu(N-N)(A-A)NO$_3$, (A-A=N-O,O-O)) with perceptible antineoplastic effects on human malignant glioma had been investigated.$^{50,51,52}$ The result is that the Casiopenia III-ia significantly inhibited cell proliferation and cell death, inducing autophagy and apoptosis of glioma cells, which correlated with the formation of autophagic vacuoles, over expression of Bax and Bid proteins. New uses for old copper binding drugs$^{53}$ is approached to discover new application for a specific cancer cell death inducer, including pro-angiogenic process.
Furthermore, the copper chelation kills the cancer and tumor cells, in which an alternative Cu-chelators\(^5\) and TPEN-copper complex using a cyclic amino metal chelator\(^3\) could inhibit and suppress neovascularization, increase of apoptosis in tumor growth, and angiogenesis. Copper chelating complex can serve as anti-angiogenic agent and ROS generators to inhibit tumor growth. Killing of cancer cell is induced via ROS mainly consisting of singlet oxygen, \(\cdot\) OH, and \(\cdot\) O\(_2\). As the summary of above-mentioned results, Table 3 represents the anti-cancer activities for \(\text{Cu}^{2+}\) ions migration into initiation, progression, proliferation, invasion, and metastasis against cancer and tumor cells.

**Table 3:** Anti-cancer activities of \(\text{Cu}^{2+}\) ions for the initiation, progression, proliferation, invasion and metastasis against cancer and tumor cells

<table>
<thead>
<tr>
<th>Cu(^{2+}) ion solution</th>
<th>Prevention</th>
<th>Promotion</th>
<th>Progression</th>
<th>Proliferation and Invasion</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carcinogenesis</td>
<td>Tumorigenesis initiation</td>
<td>Oncogenes</td>
<td>Angiogenesis</td>
<td>Transendothelial migration</td>
</tr>
<tr>
<td>Cu(^{2+})</td>
<td>ROS and SOD</td>
<td>Initial tumor formation and growth</td>
<td>Haber-Weiss reaction</td>
<td>Cu lowering with proteasome</td>
<td>Anti-angiogenesis</td>
</tr>
<tr>
<td>(\text{CuCl}_2) mixture</td>
<td></td>
<td></td>
<td>(\text{Cu}^{2+} + \text{O}_2^- + \text{H}_2\text{O}_2)</td>
<td>DNA damages</td>
<td>Inhibitor of angiogenesis</td>
</tr>
<tr>
<td>1,10-phenanthroline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anti-metastatic effects: EMT-Cu(^{2+})</td>
</tr>
<tr>
<td>Catechins-Cu(^{2+})</td>
<td>(\text{Cu}^{2+} + \cdot\text{SH} \rightarrow \text{SCu(} \text{I}) + \text{H}^+)</td>
<td>(\cdot\text{Cu}^{2+} + \cdot\text{OH} + \text{H}_2\text{O}_2)</td>
<td>(\cdot\text{OH} + \cdot\text{OH} + \cdot\text{O}_2)</td>
<td>DNA damages</td>
<td>Anti-metastasis by Cu(_2\text{O(Cu)})</td>
</tr>
<tr>
<td>Autophagy for cancer prevention (Cu(_2\text{O crystal})</td>
<td>(\text{O}_2 + \text{e} \rightarrow \text{O}_2^-)</td>
<td>(\cdot\text{OH} + \cdot\text{OH} + \cdot\text{O}_2)</td>
<td>(\cdot\text{OH} + \cdot\text{OH} + \cdot\text{O}_2)</td>
<td>DNA damages</td>
<td>Suppression of tumor growth by Cu depletion</td>
</tr>
<tr>
<td>(\text{Cu}^{2+})</td>
<td>(\cdot\text{OH}, \text{H}_2\text{O}_2)</td>
<td>(\cdot\text{OH}, \text{H}_2\text{O}_2)</td>
<td></td>
<td>DNA damages</td>
<td></td>
</tr>
<tr>
<td>(\text{Cu}^{2+})</td>
<td>Anti-angiogenesis</td>
<td>Anti-angiogenesis</td>
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<td>Anti-angiogenesis</td>
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<td>Inhibitor of angiogenesis</td>
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<td>Inhibitor of angiogenesis</td>
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<td>Anti-metastatic effects: EMT-Cu(^{2+})</td>
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<td>Anti-metastasis by Cu(_2\text{O(Cu)})</td>
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<td></td>
<td>Suppression of tumor growth by Cu depletion</td>
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<td>Nano Cu, Cu-chelation, and Cu-complexes</td>
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<td></td>
<td>induced necrotic cell death</td>
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</tbody>
</table>
V. Conclusions

Cu^2+ ions have numerous roles in cancer prevention, initiation of carcinogenesis, progression of uncontrolled cell growth, malignant tumor cell growth, invasive growth as malignancy, and metastasis of down-regulation of cell adhesion and cell-cell attachment, by Cu(I)/Cu(II) redox reaction cycles and Cu^2+ ion induced ROS productions. Angiogenesis and autophagy play an important role in cancer and tumor cells. Schiff base copper(II) complexes have anti-proliferative activity against cancer cells. Cu^2+ ions play an important role as pro-cancer factor in tumor tissues, especially in tumor angiogenesis, invasion, and metastasis. Cu^2+ ions as Cu-chelating complex can inhibit formation of new blood vessel of tumor cell against angiogenesis in cancer. Promotion and development of cancer tissues have been proceeding with homeostatic imbalances of copper, in which can be caused by the uptake of excessive amounts of copper and some genetic defects. Cancer cell killing via ROS that superoxide anion O_2^-, hydroxyl radical ·OH, hydrogen peroxide H_2O_2 mainly may be performed under cellular Cu^2+ ions induced ROS generations in tumor cells. Finally, Cu^2+-H_2O_2 induced DNA base-pairings inhibition can be regarded as being undergone to DNA damages due to Cu^2+-complex formations within DNA base-pairs G=C, A=T by Cu^2+-substitutions in hydrogen bonds of DNA base-pairs.

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