

# Highly Bactericidal Silver (I) against Bacteria and Anti-Cancer Activity of Ag<sup>+</sup> ions for Regulation of Cancer/Tumor Cell Growth

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## Abstract

Since highly bactericidal silver (I) ions against bacteria have been obtained, as highly accurate results, prospect effects of silver (I) ions for regulation of cancer and tumor cell growth can be expected to occur even at apoptotic conditions. This mini-review article is reported that as an availability for most highly bactericidal effect of Ag<sup>+</sup> ions, the regulation of cancer cell growth may be able to be achieved by Ag<sup>+</sup> ions-mediated hydrolyzing and degrading functions.

Bactericidal effects of silver (I) ions on bacteriolyses of bacterial cell walls by activation of peptidoglycan (PGN) autolysins and silver ion-mediated cancer cell hydrolyzing and degrading activity by endolysins have been analyzed. Bacteriolysis against *Staphylococcus aureus* (*S. aureus*) PGN cell wall by Ag<sup>+</sup> ions is caused by the inhibition of PGN elongation due to regulation of PGN synthetic transglycosylase (TG) and transpeptidase (TP), and the enhancement of activation of PGN autolysins of amidases. On the other hand, bacteriolysis and destruction against *Escherichia coli* (*E. coli*) cell wall by Ag<sup>+</sup> ions are caused by the destruction of outer membrane structure due to degradative enzymes of lipoproteins at N- and C-terminals, and by the inhibition of PGN elongation owing to inactivation of PGN TP synthetic enzyme endopeptidase and enhancement of the activations of PGN hydrolases and autolysins of amidase, peptidase, and carboxypeptidase.

Ag<sup>+</sup> ions-mediated cancerous cell hydrolyzing enzyme that binds to and degrades intact cancer cells of the producing organism are classified as autolysins or endolysins (phage lysin), resulting that the hydrolase activity is an essential as regulator of cancer and tumor cell growth and hydrolase activation may be promoted the apoptosis and the necrosis of cancer cells, and subsequently lead to cancer cell death by this hydrolase. Thus, highly bactericidal Ag<sup>+</sup> ions against bacteria and effect of Ag<sup>+</sup> ions for cancer cell growth regulation or cell death can be able to realize at the same time.

Silver ions induced ROS generations such as O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, •OH, OH<sup>-</sup> producing in bacterial and tumorous cells occur and lead to oxidative stress. DNA damages may be due to linear coordinated Ag<sup>+</sup> complex formations by Ag<sup>+</sup> substitution within double and triple hydrogen bonds in DNA base pairs.

**Keywords:** *Silver(I) ion; Bacteriolysis; PGN autolysin; Hydrolase and degradation; Cancer and tumor cell*

**Received Date:** October 27, 2018; **Accepted Date:** November 05, 2018; **Published Date:** November 12, 2018

**Citation:** Tsuneo Ishida, Highly Bactericidal Silver (I) against Bacteria and Anti-Cancer Activity of Ag<sup>+</sup> ions for Regulation of Cancer/Tumor Cell Growth. *Cancer Med J* 2018; 1(1) 24-36.

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## Abbreviations

ABNC: Active but Nonculturable; A: Adenine; AgNPs: Silver Nanoparticles; Bap1: BRCA1-Associated Protein-1; C: Cytosine; ENPs: Engineered Nanoparticles; *E. coli*: *Escherichia coli*; G: Guanine; LP: Lipoprotein; LPS: Lipopolysaccharide; MTs: Metallo-Thioneins; MBC: Minimum Bactericidal Concentration; MIC: Minimum Inhibitory Concentration; NAG: N-Acetyl Glucosamine; NAM: N-Acetyl-Muramic Acid; NAAA: N-Acylethanolamine-Hydrolyzing Acid Amidase; OM: Outer Membrane; OMP: Outer Membrane Protein; PGRPs: Peptidoglycan Recognition Proteins; Pal: Protein-Associated Lipoprotein; PGN: Peptidoglycan; RBBP9: Retinoblastoma-Binding Protein 9; ROS: Reactive Oxygen Species; Sal: Salinomycin; *S. aureus*: *Staphylococcus aureus*; T: Thymine; TG: Transglycosylase; Tol: Tol Protein; TP: Transpeptidase; UCH-L1: Ubiquitin C-Terminal Hydrolase-L1.

## Introduction

The high antibacterial effects of silver (I) ions such as silver salts and silver nanoparticles (AgNPs) have been noticed, should be sufficient to control the majority of bacterial pathogen, and are widely utilized as antibacterial agents. Released biologically active  $\text{Ag}^+$  shows a strong affinity for sulfhydryl groups and other anionic ligands of proteins, cell membranes, and debris that  $\text{Ag}^+$  binds protein residues on cell membranes of sensitive bacteria and is absorbed intracellularly by pinocytosis of concentration of 60 ppm  $\text{Ag}^+$  that  $\text{Ag}^+$  actively absorbed from silver nitrate or silver sulphadiazine induces and binds the cysteine-rich proteins metallothioneins (MTs) [1]. Bactericidal activity of  $\text{Ag}^+$  ions is apparent to be strong from the experimental data that minimum inhibitory concentration (MIC) = 8 ppm, minimum bactericidal concentration (MBC) = 32 ppm for  $\text{Ag}^+$  in silver sulfate solutions against *S. aureus* are obtained [2], the other, MIC = 625 ppm, MBC = 1250 ppm for copper nitrate solutions against *S. aureus* are gained [3]. Silver exists as silver metal and silver ions of different oxidation states of +1, +2, +3, and +4 that the most common states of silver are silver (0) metal and silver (I) ion and both of them interact with thiols in no redox reaction involved that  $\text{Ag}^{2+}$ ,  $\text{Ag}^{3+}$  and  $\text{Ag}^{4+}$  form state are not of relevance for aqueous solutions and under environmental and biological conditions [4]. Recently, with proceeding development in nanotechnology, silver nanoparticles (AgNPs) call attention to potential treatments such as food storage by broad antibacterial effects, prevention of serious diseases, and medical applications [5]. The toxicity of AgNPs is mainly due to release to free silver ions. On the other hand, the antibacterial activity and mechanism of action have been gradually clarified that silver ions may cause *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) bacteria to reach an active but non-culturable (ABNC) state and eventually die, and also have been indicated to the mechanism of inactivation of pathogens by damages and destruction of the bacterial cell membrane [6,7]. The high antibacterial activity factor of  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  ions may be thought to be caused by binding bacterial surface proteins, cell membrane, and metal-binding complex formations [8]. However, bactericidal elucidation by metal-binding enzyme degradation due to inhibition of peptidoglycan (PGN) elongation and relationships between PGN synthesis and PGN hydrolase/autolysin has been remained still unclear.

In this review, antibacterial effect of silver (I) ions and subsequently cancer hydrolyzing and degrading enzymes could be elucidated with the attentions of PGN elongation due to inhibition of PGN syntheses and activation of PGN hydrolases/autolysins. Firstly, bacteriolytic mechanisms for Gram-positive *S. aureus* thick PGN layer and Gram-negative *E. coli* outer membrane-connecting thin PGN layer cell walls are discussed with remarkable PGN autolysins. Secondly,  $\text{Ag}^+$  ions induced cancer leading to cause of cancer/tumor cell death are described as application of bacterial PGN autolysins to cancer cell apoptosis and necroptosis. Thirdly,  $\text{Ag}^+$  ions-mediated hydrolyzing, degrading, and autolysin/endolysin for

growth control and death of cancer and tumor cells. Lastly, it has revealed that productions of reactive oxygen species (ROS) lead oxidative stress or cell death against *S. aureus*, *E. coli*, and tumor cells.

### **PGN Autolysin, Autophagy and Cancer Apoptosis, Necroptosis**

#### **PGN syntheses and PGN hydrolyzing autolysins against *S. aureus* and *E. coli* cell walls**

The surface envelope cell structures of *S. aureus* as representative of Gram-positive bacterium and *E. coli* as representative of Gram-negative bacterium, molecular structures of these cell walls, molecular structure of PGN, and PGN syntheses and autolysins have been examined. Further, the reaction and the behavior of metallic ions and bacterial cell, and molecular bonding manner also were pursued.

*S. aureus* surface layer consists of teichoic acids, lipoteichoic acids, and thick PGN envelope cell wall [9]. In the molecular structure of *S. aureus* PGN cell wall, there are action sites of transglycosylase (TG) and transpeptidase (TP) mainly on thick PGN layer. The TG is the synthetic enzymes of N-acetylglucosamidase cleavage between NAG (N-acetylglucosamine) and NAM (N-acetylmuramic acid), and N-acetylmuramidase cleavage between NAM and NAG on glycan chain. The TP is the synthetic enzyme cleavage between Glycine and D-alanine on PGN crosslinking. The other, there are PGN autolysins of N-acetylmuramyl-L-alanine amidase cleavage, DD-endopeptidases cleavages between Glycine and Glycine on pentaglycine (Gly)<sub>5</sub>, and in addition, lysostaphin cleavage between Glycine and Glycine on PGN cross-linking [3]. PGN synthesis requires glycosyltransferases to polymerize the glycan chain and DD-transpeptidase to crosslink the peptides, and PGN cleavage of PGN hydrolases and autolysins is required for reductive cell division and cell separation that amidase has a prominent role in septum cleavage, but lytic transglycosylases and endopeptidases contribute to cell separation, and their role is probably understated owing to their greater redundancy, in which they play vital role in regulating cell wall growth as well as other lysis phenomena [10].

On the other hand, *E. coli* cell wall consists of lipid A, lipopolysaccharide, porin proteins, outer membrane of lipo-protein, and thinner 2-7 nm PGN layer in 30-70 nm periplasmic space [9]. Degradative enzymes of lipoproteins at N- and C-terminals are endopeptidase between phospholipid-lipoprotein bond and amidase between L-Ala-NAM bond via *E. coli* outer membrane, lipoprotein to PGN. In the molecular bonding manner of *E. coli* cell wall and peri-plasmic PGN, there are *E. coli* PGN synthetic enzymes TG of glucosaminidase cleavage, muramidase cleavage on glycan chain, and TP of endopeptidase cleavage on cross-linking. The other, PGN hydrolases and autolysins are degradative enzymes of amidase cleavage, peptidase cleavage, and carboxypeptidase cleavage [3]. Penicillin-binding protein 2 and RodA (encoded downstream of the PBP2 gene) are required for the PGN synthesis of glycan strands during elongation and the periplasmic amidase cleave only one-sixth of the PGN that is turned over by the lytic transglycosylases [11]. *E. coli* has at least 13 periplasmic PGN hydrolases (autolysins), which can collectively cleave almost any glycoside and amide bond [10]. Interactions of PGN molecular structure with PGN syntheses and PGN autolysins influence in any event the bacteriolytic cell walls.

#### **Autophagy and cancer metastasis**

Anti-cancer activity of silver (I) ions occurs in each region for the initiation, progression, proliferation, invasion, and metastasis against cancer and tumor cell development [12]. Metastasis is a key step of cancer progression that indicates a more advanced stage and a poorer prognosis that when over-activated under certain circumstances, excess autophagy results in cell death which the apoptosis serves as an important process for inhibiting metastasis [13]. The anti-metastatic role of

autophagy in cancer metastasis may be regulators of apoptosis, autophagy, and necroptosis involved in the regulation of cancer metastasis, accompanying with characteristic cancer cell hydrolyzing and degrading enzymes.

## Discussions

### Bacteriolysis of PGN Cell Wall by Silver (I) ions against *S. aureus*

For the sake of growth of *S. aureus* PGN cell wall, there is necessarily required for the adequate balance between PGN synthesis and PGN autolysin. When the balance was broken to be imbalanced, bacteriolysis and destruction of the cell wall should be occurred. Hence, it become to be apparent that bacteriolysis of *S. aureus* PGN cell wall by silver ions is caused by inhibition of PGN elongation due to inactivation of PGN synthesis and enhancement of activation of PGN autolysins, with similar bacteriolytic phenomenon for *E. coli* cell wall [10].

### *S. aureus* PGN Synthetic Enzymes of TG and TP

The released  $Ag^+$  ions that penetrated from AgNP into bacterial cells, can inhibit the growth of Gram-positive *B. subtilis* bacterium which exerts toxicity by damaging cellular membrane, degrading chromosomal DNA, lowering reductase activity, and reducing protein expression [14]. Wall teichoic acids are spatial regulators of PGN cross-linking biosynthesis TP [15], and silver ions could inhibit both TG and TP enzymes of the PGN that  $Ag^+$ -induced bacteria may inactivate PGN synthesis transglycosylase TG [16] and transpeptidase TP [17,18]. Lysostaphin-like PGN hydrolase and glycylglycine endopeptidase LytM may function as TP enzyme [19].

$Ag^+$ ions	<i>S. aureus</i> Cell Wall	
	Teichoic acid, Lipoteichoic acid	Peptidoglycan layer, Proteins
$Ag^+$	$Ag^+, O_2^-, H^+, H_2O_2$	$Ag^+, O_2^-, H^+, \cdot OH, H_2O_2, \cdot HO_2, \cdot NO, ONOO^-$
	<ul style="list-style-type: none"> <li>· Wall teichoic acids are spatial regulators of PGN cross-linking biosynthesis TP.</li> </ul>	<ul style="list-style-type: none"> <li>· <math>Ag^+</math>-induced bacteria may inactivate PGN synthesis transglycosylase TG and transpeptidase TP.</li> <li>· Activations of PGN autolysins of N-Acetylmuramyl-L-alanine Amidase, Amidase MurA, Lytic Amidase LytA, enzymatically active domain of autolysin LytM, Metalloenzyme AmiE, and Lysostaphin-like PGN hydrolase and glycylglycine endopeptidase LytM.</li> <li>· Bacteriolysis of <i>S.aureus</i> cell wall caused by inhibition of PGN elongation due to activations of amidases and DD-endopeptidase LytM. (DNA molecular is damaged by <math>O_2^-</math> and <math>H_2O_2</math> and leads to oxidative stress.)</li> </ul>

**Table 1:** Antibacterial activities of  $Ag^+$  ions for bacteriolytic process of *S. aureus* PGN cell wall.

### $Ag^+$ Induced Amidase of *S. aureus* PGN Autolysins

Lytic activity was inhibited by glucosamine, NAG,  $Hg^{2+}$ ,  $Fe^{3+}$ , and  $Ag^+$  [20], and  $Ag^+$  binding Rv3717 showed no activity on polymerized PGN and but, it is induced to a potential role of N-Acetylmuramyl-L-alanine Amidase [21], PGN murein hydrolase activity and generalized autolysis; Amidase Mur A [22], Lytic Amidase Lyt A [23], enzymatically active domain of autolysin Lyt M [24], metal-dependent metalloenzyme Ami E [25] as prevention of the pathogen growth. The activations of these PGN autolysins could be enhanced the inhibitions of PGN elongation simultaneously, with bacteriolysis of *S. aureus* PGN cell wall. Hence, bacteriolysis of *S. aureus* PGN cell wall by  $Ag^+$  ions are caused by inhibition of PGN elongation due

to inactivation of PGN TG or TP and enhancement of activation of PGN autolysins of amidases.  $O_2^-$  and  $H_2O_2$  permeate into membrane and cytoplasm, and then, DNA molecular is damaged by oxidative stress [26]. From above mentioned results, antibacterial activities of  $Ag^+$  ions for bacteriolytic process of *S. aureus* PGN cell wall are shown in Table 1.

## **Bacteriolysis and Destruction of *E. coli* Cell Wall by Silver (I) ions**

### **Permeability of Silver Ions into *E. coli* Cell Wall**

*E. coli* cell wall is comprised of lipopolysaccharide (LPS), lipoproteins (LP), and peptidoglycan (PGN) as thinner layer within periplasmic space. When permeability of silver ions in the *E. coli* cell wall, highly anionic LPS with hydrophobic lipid A, core polysaccharide, O-polysaccharide, is liable to be explosive, inhibition of LPS biosynthesis may be possibility to occur by active hydrolases [27]. The Omp A, Omp C, Omp F porins of lipoproteins have metallic cation selective and hydrophilic membrane crossing pore, to be effective for silver transfer [28]. Ag-resistant mutants of *E. coli* display active efflux of  $Ag^+$  and are deficient in porins that active efflux may play a major role in silver resistance, which is likely to be enhanced synergistically by decreases in OM permeability [29]. Physicochemical interaction of *E. coli* cell envelopes suggested that the adsorption of the cell wall or envelope to clay has masked or neutralized chemically reactive adsorption sites normally available to metal ions that metal binding capacity of metal cation bridging in isolated envelopes was determined by atomic adsorption spectroscopy [30].

Silver adsorption by *E. coli* cells displays metallothioneins (MTs) anchored to the outer membrane protein Lam B that the complete MT sequences are anchored by their N-termini and C-termini to the permissive site 153 of the protein [31]. Recently,  $Ag^+$  ions into *E. coli* cell wall are elucidated to be occurred *E. coli* under ionic silver stress which  $Ag^+$ -dependent regulation of gene expression is transpeptidase acting on the structural integrity of the cell wall [32]. The addition of glucose as an energy source to starved cell activated the Ag efflux on the increased Ag accumulation in Ag-susceptible and -resistant strain. Silver (I) ions reactive with thiol, and then generates silver (I) thiolate compounds. Silver ion complexes with both inorganic and organic thiols with redox reaction involved that with inorganic thiols like  $HS^-$  and  $S^{2+}$ , it is possible to form many species such as  $AgSH$ ,  $[Ag(SH)_2]^-$  and  $[Ag_2(SH)_2S]^{2-}$  depending on the concentration of the anions present [33].



### **Destruction of outer membrane structure of *E. Coli* by degradative enzymes of lipoproteins at C- and N-terminals**

Tol protein (Tol)- protein-associated lipoprotein (Pal) system is composed of five proteins that Tol A, Tol Q, and Tol R are inner membrane proteins, Tol B is a periplasmic protein, and Pal, the peptidoglycan-associated lipoprotein, is anchored to the outer membrane [34].  $Ag^+$  ions induced Tol-Pal complex is antimicrobial agents widely used, it has recently been demonstrated to be essential for bacterial survival and pathogenesis that outer membrane structure may be destroyed [35,36]. It is unclear whether both amidase and endopeptidase of lipoprotein at C-, and N-terminals are simultaneously activated by  $Ag^+$  ions. However, outer membrane may be thought to be destroyed probably by predominant activation of lipoprotein-amidase.

### **Damage of *E. coli* PGN synthetic enzyme of silver-protein amidase in periplasmic space, and amidase, peptidase, and carboxypeptidase of PGN autolysins**

Silver ions may be accumulated in *E. coli* periplasmic space, in which the silver ions are spent to the activation of bacteriolysis of the cell wall and efflux activity to extracellular cell. Then, lipoprotein-endopeptidase may be degradative by  $\text{Ag}^+$  binding proteins [37]. The other, it is unclear that the silver-induced PGN biosyntheses TG/TP should be inhibited by the silver ions [38-40]. However, silver ions inactivate TP of endopeptidase by because of destructive observation of bacterial cell walls [32]. Silver ions could activate *E. coli* PGN autolysins of amidase, peptidase, carboxypeptidase [41,42], such as silver depending PGN autolysin, AmiC [43], AmiD [44], Muramidase [45], Amino acid amidase [46], Carboxy-peptidase A [47], zinc metalloenzymes AmiD [48], Amidase zinc-containing amidase; AmpD [49], zinc-present PGLYRPs [50], Carboxypeptidase-degraded aldolase [51], CarboxypeptidaseY [52] serve to be effective for the PGN autolysins. It is particularly worth noting that enhancement of the activities of autolysins is characterized on PGN carboxypeptidase and TP-endopeptidase [41] requiring divalent cations.

Accordingly, the inhibition of PGN elongation had occurred by silver ion induced activities of PGN hydrolases and autolysins. Thus, antibacterial mechanism is found that bacteriolysis and destruction of *E. coli* cell wall by silver ions are caused by the destruction of outer membrane structure owing to the activation of amidase of lipoprotein at C-, and N-terminals, and inhibition of PGN elongation due to the damage of PGN synthetic enzyme of silver-protein amidase in periplasmic space, and PGN autolysins of amidase, peptidase, and carboxypeptidase. As mentioned above antibacterial activities of  $\text{Ag}^+$  ions for bacteriolysis and destruction of *E. coli* cell wall are represented in Table 2.

$\text{Ag}^+$ ion	<i>E. coli</i> cell wall		
	Lipopolysaccharide (LPS) Lipid A, Core polysaccharide	Outer Membrane Lipoprotein, Porins Omp F, A, C	Periplasmic Space Thin PGN layer
	$\text{Ag}^+, \text{O}_2^-, \text{H}^+, \text{H}_2\text{O}_2$	$\text{Ag}^+, \text{O}_2^-, \text{H}_2\text{O}_2, \cdot\text{OH}$	$\text{Ag}^+, \text{O}_2^-, \text{H}_2\text{O}_2, \text{OH}^-, \cdot\text{OH}$
$\text{Ag}^+$	<ul style="list-style-type: none"> <li>• Negative charge</li> <li>• Hydrophobic Lipid A</li> <li>• Inhibition of LPS biosynthesis</li> <li>• <math>\text{Ag}^+ + \text{-(SH)}^- \rightarrow \text{AgSH}</math> (depending concentration)</li> </ul>	<ul style="list-style-type: none"> <li>• Porin proteins of hydrophilic channels</li> <li>• Destruction of outer membrane structure due to degradative hydrolases of lipoprotein at C- and N-terminals</li> <li>• <math>\text{LOO}\cdot, \text{L}\cdot</math> (Fatty acid)</li> </ul>	<ul style="list-style-type: none"> <li>• Ag accumulation and Efflux activity</li> <li>• Periplasmic enzymes</li> <li>• Damage of PGN bio-synthesis TP of Endo-peptidase enzymes and activation of PGN autolysins</li> <li>• Bacteriolysis by inhibition of PGN elongation due to activation of <i>E. coli</i> PGN autolysins of amidase, peptidase, and carboxypeptidase.</li> </ul>

**Table 2:** Antibacterial activities of  $\text{Ag}^+$  ions for bacteriolysis and destruction of *E. coli* cell wall.

#### $\text{Ag}^+$ ions induced cancer leading to cause of cancer/tumor cell death

Silver nanoparticle (AgNPs) possess unique cytotoxic features that AgNPs with size of 5 nm and 35 nm can kill osteosarcoma cells independently from their actual p53 status and induce p53-independent cancer cell apoptosis [53]. AgNPs with 2.6 nm and 18 nm size decreased viability, proliferation and caused death of pancreatic cancer cells in a size- and concentration-dependent manner that cellular uptake of AgNPs resulted in apoptosis, autophagy, necroptosis and mitotic catastrophe [54]. AgNPs also have anticancer activity of endoplasmic reticulum stress, oxidative stress and mitochondrial impairment triggering cell death by apoptosis and autophagy activation [55]. Engineered nanoparticles (ENPs) with sizes no

larger than 100 nm are able to enter the human body and accumulate in organs such as brain, liver, lung, testes, and cause toxic effects, and ENPs cytotoxicity in living cells, sizes, shapes, surface charges, agglomeration status all play a deciding ENP safety and suitability for such roles, in which ENPs induce cell apoptosis with potential cancer therapy [56].

### **Ag<sup>+</sup> ions-mediated hydrolyzing activity leading to cause of cancerous cell death**

Hydrolase activity is an essential regulator of growth of cancer and tumor cell that the enzyme activity drives the functional contribution of this protein to tumor-cell growth which retinoblastoma-binding protein 9 (RBBP9) as a tumor-associated serine hydrolase that displays elevated activity in pancreatic carcinomas [57]. Thus, RBBP9-mediated suppression of TGF- $\beta$  signaling is required for E-cadherin expression as loss of the serine hydrolase activity leads to a reduction in E-cadherin levels and a concomitant decrease in the integrity of tumor cell-cell junctions [57]. The hydrolases have enzyme-mediated hydrolytic activation that play degradative role of tumor cell. As the main compartment for intracellular degradation and subsequent recycling of cellular constituents, the lysosomes receive both hetero- and autophagic cargo, which in the degradative lumen of this organelle find their final destination. The degradation is carried out by a number of acid hydrolases such as phosphatase, nucleases, glycosidases, peptidases, sulfatases, and lipases capable of digesting all major cellular macromolecules [58]. The physical disruption, including leakage of lysosomal hydrolases into the cytosol, led to programmed cell death and necrosis. Numerous regulatory proteins direct the addition of ubiquitin to lysine residues on target proteins, and there are countered by an army of deubiquitinating enzymes. BRCA1-associated Protein-1(Bap1) helps to control cell proliferation by resulting HCF-1 protein levels and by associating with gene involved in the G1-S transition [59]. Therefore, silver ions induced carboxy-terminal hydrolase activation may be promoted the apoptosis and the necrosis of cancer cells. However, Ag<sup>+</sup> ion-mediated hydrolyzing and degrading method is incompletely yet established without information for Ag<sup>+</sup> ions-associated enzymes. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) increases cellular ROS levels and promote tumor invasion, in which silencing UCH-L1, as well as inhibition of H<sub>2</sub>O<sub>2</sub> generation by catalase, a NOX inhibitor, suppressed the migration potential of B16F cells, indicating that UCH-L1 promotes cell migration by up-regulating H<sub>2</sub>O<sub>2</sub> generation [60]. The other, gold nanorod induced apoptosis specifically in cancer cells by affecting lysosome and mitochondria [61]. Lysosomes are membrane-bound organelles containing that function in the degradation of macromolecules delivered via the endocytic, phagocytic, and autophagic pathways, in which AgNPs induced cell death was increased by bafilomycin A1 treatment, and the perturbation of lysosomal pH by AgNP exposure may play a role in AgNP agglomeration and subsequent cellular damage in cancer cell and moderate lysosomal permeabilization can result in apoptosis or apoptosis-like cell death [62].

Elongated nanoparticle aggregates and generated hundreds of pN (pico Newton) to dramatically damage the plasma and lysosomal membranes, whereas the physical disruption, including leakage of lysosomal hydrolases into the cytosol, led to programmed cell death and necrosis [63]. Accordingly, the perturbation of lysosomal pH by AgNP exposure may play a role in AgNP agglomeration and subsequent cellular damage in A549 cells. The microbial amidases enzymes are in great demand for use as therapeutic agents against many dreadful diseases that in the presence of these enzymes, the tumor cells failure to survive which L-asparaginase and L-glutaminase can use as potent antitumor or antileukemic drugs [64]. Identification of N-acyl ethanolamine-hydrolyzing acid amidase (NAAA) inhibitors has been able to reduce cell proliferation and migration and cause cell death on different bladder cancer cell lines [65]. Further, the use of antibody-enzyme conjugates for cancer therapy [66] that Lyt A-like N-acetylmuramoyl-L-lanine amidases [67] such as lytic amidase Lyt A [68], Lyt A autolysin [69], autolysin Lyt A [70], and autophagy [71], and murein lytic cleavage agents on glycan-chain-like as chimeric phage endolysin

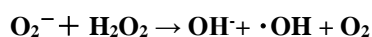
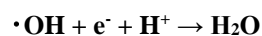
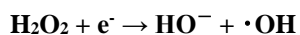
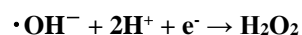
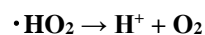
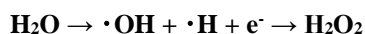
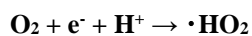
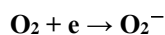
such as Ply187 [72] and LysPA26 [73] in cancer therapy. These works provide a novel strategy of designing magnetic nanomedicines for mechanical destruction of cancer cells. Comparing with bacterial PGN autolysins, the research of cancer cell hydrolases will become important as significant advancement for cancer and tumor cells in future. Table 3 shows anticancer activities of Ag<sup>+</sup> ions-mediated cancer cell hydrolyzing, degrading, and autolysin/endolysin enzymes for malignant cell formation, proliferation, and metastasis of tumor cells.

Ag <sup>+</sup> ions	Progression, Proliferation, and Metastasis of Cancer and Tumor Cell		
	Malignant Cell Formation	Proliferation	Metastasis
Ag <sup>+</sup>	Ag <sup>+</sup> O <sub>2</sub> <sup>-</sup> , •OH, H <sub>2</sub> O <sub>2</sub>	Ag <sup>+</sup> O <sub>2</sub> <sup>-</sup> , •OH, H <sub>2</sub> O <sub>2</sub>	Ag <sup>+</sup> O <sub>2</sub> <sup>-</sup> , •OH, H <sub>2</sub> O <sub>2</sub>
	<ul style="list-style-type: none"> <li>•AgNPs induced ROS anti-angiogenesis</li> <li>•Hydrolyzing enzymes and regulation of tumor cell growth</li> </ul>	<ul style="list-style-type: none"> <li>• Sal + AgNPs with autophagy inhibit proliferation</li> <li>•AgNPs induced ROS anti-angiogenesis</li> <li>•Hydrolyzing and degrading enzymes for regulation of proliferation</li> </ul>	<ul style="list-style-type: none"> <li>•AgNPs induced ROS anti-angiogenesis</li> <li>•AgNPs of size 10 nm minute.</li> <li>•Phage-derived hydrolyzing, degrading enzymes of regulator of tumor cell growth and metastasis</li> </ul>

**Table 3:** Anticancer activities of Ag<sup>+</sup> ions-mediated cancer cell hydrolyzing, degrading, and autolysin/endolysin enzymes for malignant cell formation, proliferation, and metastasis of tumor cells.

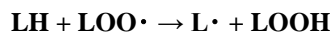
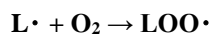
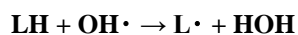
### Production of reactive oxygen species (ROS) and oxidative stress against *S. aureus*, *E. coli*, and tumor cell

For the penetration of Ag<sup>+</sup> ions to PGN cell wall, the ROS production such as superoxide anion radical O<sub>2</sub><sup>-</sup>, hydroxyl radical •OH, hydrogen peroxide H<sub>2</sub>O<sub>2</sub> occurred from superoxide radical O<sub>2</sub><sup>-</sup> molecular [74]. Silver ions reacted with -SH, and H<sup>+</sup> generates. In *E. coli*, free radicals O<sub>2</sub><sup>-</sup>, OH<sup>-</sup>, •OH and H<sub>2</sub>O<sub>2</sub> are formed as follows [75]. In tumor cell, ROS are mainly produced in the mitochondria in cells. Increasing ROS to selectively kill cancer cells are that components of the antioxidant pathway are selectively essential for tumor growth [76].





**In cell wall, reacting with polyunsaturated fatty acids:**



Ag<sup>+</sup>-containing Peptidoglycan Recognition Proteins (PGRPs) induce ROS production of H<sub>2</sub>O<sub>2</sub>, O<sup>-</sup>, HO<sup>•</sup>, and then the ROS occur the oxidative stress, and killing by stress damage and DNA damages within base-pairs [77].

**Conclusions**

(1) Ag<sup>+</sup>-induced *S. aureus* may inactivate PGN synthesis transglycosylase TG and transpeptidase TP. Bacteriolysis of *S. aureus* PGN cell wall, in which wall teichoic acids control PGN synthesis cross-linking TP, is due to the inhibition of PGN elongation by enhancing the activities of PGN autolysins; amidase AmiA and AmiE, and PGN hydrolase Lysostaphin-like endopeptidase of Glycine-Glycine bond cleavage.

(2) Bacteriolysis and destruction of *E. coli* cell wall are due to the damage of LPS synthesis, destructing of outer membrane structure by degrading of lipoprotein at C-, N-terminals, owing to inhibition of PGN formations by inactivation of carboxypeptidase and TP-endopeptidase, and activities of PGN autolysins of amidase, peptidase and carboxy-peptidase.

(3) Ag<sup>+</sup> ions-mediated hydrolase activity is an essential as regulator of cancer and tumor cell growth. Tumor cell-hydrolyzing enzymes that bind to and degrade intact cancer cells of the producing organism are classified as autolysins or endolysins (phage lysin) by Ag<sup>+</sup> ions-mediated hydrolyzing and degrading functions, resulting that hydrolase activation may be promoted the apoptosis and the necrosis of cancer cells, and subsequently lead to cancer cell death by this hydrolase. Thus, it is splendid that highly bactericidal Ag<sup>+</sup> ions against bacteria and effect of Ag<sup>+</sup> ions for cancer cell growth regulation or cell death may be able to realize at the same time. However, the mechanism of action remains unclear.

(4) Silver ions-induced ROS generations such as O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, •OH, OH<sup>-</sup> producing in bacterial cell walls and cancer cells occur, and subsequently lead to oxidative stress. These ROS and H<sub>2</sub>O<sub>2</sub> give the damages cell membrane proteins and DNA molecular in cytoplasm. The DNA damages may be due to linear coordinated Ag<sup>+</sup> ion complex formations by Ag<sup>+</sup> substitution within double and triple hydrogen bonds in DNA base pairs.

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