

Promising Targets for Prospective Antibacterial Therapy

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Abstract

Antibiotic resistance has gained increasing attention in recent years due to ability of bacterial species to rapidly develop defense mechanisms that can either destroy or expel out antibiotics from the bacterial cell. The raising concern about the dwindling effectiveness of antibiotics has led to a 'nightmare' situation where common bacterial infections remained untreatable. Several classes of antibiotics have been developed earlier that specifically acts on bacterial cellular processes such as transcription and translation. However, in recent years bacteria tend to evolve multiple evasive strategies that rendered most effective antibiotics futile. Thus, development in next generation antibiotics lies in disruption of evasive strategies that confers antibiotic resistance. Targeting vital components of bacterial cells including cell wall components, quorum sensing systems, metabolic genes, cell division machinery, transcription, translation, protein secretion systems, pilus assembly and efflux pumps holds great promise towards development of novel antibacterial agents. This mini review article identifies the benefits and discusses the potential bacterial targets that could be used in the development of potent antibiotics. The targets described in this article have also been proven to decrease the tenacity of multidrug resistant bacteria and holds promise in combating multi drug resistance.

Keywords: Multidrug Resistance; Bacterial Infections; Drug Targets; Antibacterial Agents; Next Generation Antibiotics

Introduction

Antimicrobial drug saves countless of human lives by combating infectious diseases [1]. Antibiotics can be classified as bactericidal and bacteriostatic compounds. Bactericidal compounds cause cell death in bacteria, whereas bacteriostatic compounds tend to inhibit the growth of bacteria. Excessive use or abuse of antibiotics has been reported to induce selection pressure on bacteria that enforces them to develop resistance against conventional antibiotics [2]. In recent years, many Gram-negative and Gram-positive bacteria have evolved resistance to wide array of antibiotics. The most critical group of multi-drug resistance bacteria that poses threats to humans includes *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Salmonella enterica*, *Shigella* spp., *Vibrio cholerae*, *Chlamydia* spp, Methicillin-resistant *Staphylococcus aureus* (MRSA) [3-5]. Thus, the global health impact of antibiotic resistance together with rapid depletion of antibiotic arsenal has revived interest on discovery and development of new antimicrobial drugs [6-8]. There are several antibiotics that targets essential cellular processes in bacteria. Some of potential targets includes quorum sensing (QS) system [9-11], biofilms [12,13], transcription machinery [14], elongation factors [15], protein synthesis [16], DNA gyrase [3] and protein secretion systems [2]. This mini review article summarizes different cellular processes in bacteria that could be used as potential target for development of novel antibiotics.

Inhibiting cell wall synthesis and its components

Cell wall synthesis in bacteria is divided into 3 phases- namely, synthesis of the nucleotide precursors (phase I), synthesis of the lipid-linked intermediates (phase II) and polymerization reactions (phase III). Most antibacterial drugs have been developed against phase III pathway involved in cross linking of cell envelope and structure formation [17]. Glutamate racemase (GR) has been considered as an important target for development of cell wall inhibitor as it catalyzes the interconversion of L-glutamate (L-Glu) to D-glutamate (D-Glu), thereby affecting the peptidoglycan synthesis of bacterial pathogens. GR inhibitors such as pyrazolopyrimidinediones and pyridodiazepine amines have shown promising results in inhibiting the growth of bacteria [17]. Teichoic acid (TA) is a cell wall component found in Gram-positive bacteria, that includes wall teichoic acid (WTA), connected to peptidoglycan, or lipoteichoic acid (LTA). Teichoic acid biosynthetic pathways seem to be an important target for development of antibacterial drug. Earlier studies have shown that targeting teichoic acid biosynthesis resulted in growth inhibition of MRSA in presence of methicillin. Teixobactin is an antibacterial drug known to induce damage to cell membrane by interfering with peptidoglycan and teichoic acid biosynthesis pathways [18]. In *Streptococcus pneumoniae*, TacL acts as a putative LTA ligase, which is required for LTA assembly. Strains deficient in TacL lacks LTA attenuated virulence in mouse models. Thus, TacL has proven to be a potential antibacterial target [19]. Mutation in cell wall synthesis genes *dapF* and *mrcB* induces susceptibility of bacterial cells to cefoxitin (FOX) which makes them an attractive candidates for prospective antibacterial therapy [20].

WTA is an important component of MRSA that confer resistance against β -lactam. Inhibition of Tar enzymes involved in WTA biosynthesis makes MRSA and more susceptible to β -lactams. Thus, development of inhibitors to WTA biosynthesis are considered to be an effective strategy to treat MRSA and MRSE infections. MnaA, a 2-epimerase modulates substrate levels of TarO and TarA wall teichoic acid (WTA) biosynthetic enzymes through interconversion of Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) and UDP-N-acetylmannosamine (UDP-ManNAc). Loss of MnaA adversely affects WTA and induces β -lactam hypersensitivity in both MRSA and MRSE [21]. WecA (polyprenyl phosphate-GlcNAc-1- phosphate transferase) in *Mycobacterium tuberculosis* (Mtb) catalyzes the conversion of UDP-GlcNAc to decaprenyl-P-P-GlcNAc that is involved in biosynthesis of mycolyl arabinogalactan in Mtb. WecA inhibitors block cell wall synthesis in *M. tuberculosis* and thus acting as a potent antimycobacterial. Screening of drugs for WecA inhibitor have resulted in discovery of UT - 01320, that effectively kills the intracellular Mtb in macrophages [22].

Lipophilic benzoic acids with electron-withdrawing ring substituents has proven to be effective in preventing the growth of *S. aureus* and *B. subtilis* through inhibition of cell wall synthesis enzymes such as undecaprenyl diphosphate synthase (UPPS) and undecaprenyl diphosphate phosphatase (UPPP). Trifluoromethoxy analog 11 has shown more potent antibacterial activity than bacitracin which acts as cell wall synthesis inhibitor [23]. Cell envelope synthesis factors belonging to polyprenyl phosphate N-acetyl hexosamine 1-phosphate transferase (PNPT) superfamily such as MraY, WecA, TarO, WbcO, WbpL, RgpG, and GP could also be used as potential targets for antibacterial therapy. Inhibitors for MraY like muraymycin D2 (MD2) have shown *in vivo* antimicrobial activity against *M. tuberculosis*, MRSA, and vancomycin-resistant Enterococcus (VRE) [24].

Targeting bacterial quorum sensing system

Establishment of bacterial infections generally starts with the formation of biofilms. Biofilm formation affects the life cycle of bacteria and affords protection against physical and environmental stresses [25]. Nosocomial infections (hospital-acquired infections) have been increasingly associated with biofilm formation on implanted medical devices [11]. Many bacteria residing within biofilm regulate their cooperative activities and physiological processes through a specialized mechanism called quorum sensing (QS). Quorum sensing aids bacterial cells to communicate with each other through the production, detection and response to an extracellular signaling molecules called auto inducers. Many species of bacteria use quorum sensing mechanisms to coordinate gene expression based on density of their local population within the biofilm. The bacterial quorum sensing system harbours two component regulatory systems- sensor histidine kinase and response regulator that coupled with each other and regulate wide variety of biological processes such as cell viability, stress responses, virulence and antibiotic resistance [26]. Thus, targeting quorum sensing system would provide one feasible ways of treating common and chronic bacterial infections.

DevR and DevS two-component system in *M. tuberculosis* mediates bacterial adaptation to hypoxic condition, which is essential for the initiation and maintenance of dormant bacilli during latent tuberculosis. In recent years, mycobacterial two-component system have been widely exploited for the development of antimycobacterial agents. Novel peptide inhibitor (DevRS) mimicking DevR has been discovered earlier that specifically impaired with the transcriptional regulation and survival of *M. tuberculosis* under hypoxia through inhibition of DevS autokinase activity [27]. Interestingly, development of quorum regulator SarA targeted compound 2-[(Methylamino)methyl] phenol has proven to be effective in inhibiting biofilm formation through down regulation of virulence genes (fnbA, hla and hld) in *S. aureus* that makes it an effective antibacterial agent for treatment of MRSA infections [25].

N-acyl L-homoserine lactones (AHLs) is a signaling molecule that mediates the communication process between Gram-negative bacteria. The AHL lactonase enzyme family possesses hydrolytic activity toward a broad spectrum of AHLs that could serve as an attractive candidate for antibacterial therapy. A novel cold-adapted N-acylhomoserine lactonase (Aii810) derived from metagenome strongly attenuated virulence factors and biofilm formation of *P. aeruginosa* through degradation of N-butyryl-L-homoserine lactone and N-(3-oxododecanoyl)-L-homoserine lactone, which offers attractive ways for using Aii810 as effective therapeutic agents for treatment of *P. aeruginosa* infection [9]. Ajoene, a sulfur rich natural compound derived from garlic has shown to inhibit small regulatory RNAs (sRNA), RsmY and RsmZ in *P. aeruginosa* and RNAlII in *S. aureus* that controls virulence factors such as hemolysins and proteases [10]. An active hydrophobic pentadecanal long chain fatty aldehyde discovered from the Antarctic marine bacterium *Pseudoalteromonas haloplanktis* TAC125 possessed auto inducer AI-2 like activities that inhibits the biofilm formation in *S. epidermidis* [28].

Interference with metabolic genes

Drug resistant bacteria usually thrive as persister cells within bacterial population. It is interesting to note that decreased TCA cycle has been shown to correlate with increased resistance against β -lactam in clinical *S. epidermidis*. *P. aeruginosa* showed increased antibiotic tolerance under nutrient deprivation through utilization of ppGpp-dependent mechanism. Thus, metabolic pathways and their associated genes could be considered as promising drug targets for antibacterial therapy [29]. Most pathogens are dependent on their respective hosts to get essential micronutrients through transport systems. Disruption of nutrient transport mechanisms can inevitably disrupt nutrient uptake and metabolic pathways leading to growth inhibition of bacterial cells [30]. Folic acid synthesis enzyme dihydropteroate synthase (DHPS) is another important target widely exploited as an antimicrobial drug. Low levels of DHPS reduces cellular folate and cause cell death [31]. ATP production is one of the most important metabolic processes essential for bacterial growth and survival. Mutations in ATP synthase subunits has shown to induce susceptibility in polymyxin-resistant strains of *S. aureus* treated with oligomycin A [32]. Thus, targeting F₀F₁ ATP synthase in pathogens could be considered as another possible way to prevent bacterial infections [31].

Targeting bacterial cell division

Bacterial cell division represents a potential target for development of novel antimicrobial drugs. Filamentous temperature sensitive protein Z (FtsZ) is a protein that assembles into a ring at the site of septum and facilitates bacterial cell division. FtsZ is a prokaryotic homologue to the eukaryotic protein tubulin. The evolutionarily conserved nature of this protein makes it an attractive candidate for the development of broad spectrum antibacterial agents [33,34]. A novel class of natural products called the chrysopaentins has shown to inhibit Z-ring formation through inhibition of FtsZ protein in live bacteria, which open up the possibility of exploiting these compounds as FtsZ inhibitor to treat bacterial infections [35]. Another class of natural products called alkyl gallates have shown to exhibit antibacterial activity against both Gram-positive and Gram-negative bacteria including *Salmonella*, MRSA and *B. subtilis*. Heptyl gallate is an effective FtsZ inhibitor that disrupts FtsZ assembly and affects the membrane permeability in *B. subtilis* [34]. Quinazoline derivatives of zantrin, a well-known inhibitor of FtsZ's GTPase activity shown has been to inhibit FtsZ at micromolar concentrations [36]. Kil Peptide derived from bacteriophage lambda disrupt the FtsZ protofilaments and thus act as a phage derived FtsZ inhibitor in *E. coli* [37].

Antisense oligonucleotides containing locked nucleic acids (LNAs) possessed high affinity for FtsZ mRNA with low toxicity profile implicating its potential application as effective FtsZ inhibitors. A locked nucleic acid (LNA) conjugated to peptide (KFF)3K known as peptide-LNA (PLNA) has been shown to exhibit specific activity against FtsZ mRNA and reduced FtsZ protein levels in MRSA [38]. Rhodomirtone, a natural extract from *Rhodomyrtus tomentosa* leaves has been shown to impair cell division proteins (FtsA and SepF) and inhibit GTPase activity of FtsZ protein in *B. subtilis* [33]. A Non-cytotoxic taxane SB-RA-2001 inhibited the proliferation of *B. subtilis* 168 and *M. smegmatis* cells through inhibition of Z-ring formation [39]. A thiazole orange derived compound known as 2-((E)-4-hydroxystyryl)-1-methyl-4-((Z)-(3-methylbenzo[d]thiazol-2(3H)-ylidene) methyl) quinolin-1-ium iodide was shown to inhibit the dynamic assembly of FtsZ protein and Z-ring formation in MRSA, vancomycin-resistant *Enterococcus* and *E. coli* [40].

Inhibiting bacterial transcription

Bacterial RNA polymerase has been considered as another important target for development of antibacterial agent due to its direct involvement in gene transcription and highly evolutionarily conserved nature among different bacterial species. Blocking or altering the function of RNA polymerase may have direct impact on bacterial cell viability. Bacterial RNA polymerase has been exploited widely for the development of antisense agents such as peptide nucleic acids (PNAs) that could effectively targets both Gram-negative and Gram-positive pathogens. The α -subunit of RNA polymerase encoded by *rpoA* is highly important for promoter recognition, stability, assembly of core enzyme and initiation of transcription. Failure to initiate transcription has detrimental effects on bacterial cell growth. An antisense approach to antibacterial therapy has been developed against *rpoA* using a peptide nucleic acid covalently conjugated to HIV-TAT cell penetrating peptide (GRKKRRRQRRRYK), which reduced the expression of MRSA USA300 toxins-hemolysin and Panton-Valentine leukocidin (PVL) [5]. DNA gyrase has proven to be another important target for development of antimicrobial agent as it introduces negative supercoils and reduces positive supercoils of DNA in an ATP-dependent manner. DNA Gyrase is composed of two A (GyrA) and two B (GyrB) subunits that could be considered as potential target of fluoroquinolones. In recent years, gyrase inhibitors have been clinically tested and validated for its potential application as antibacterial agents. Earlier studies have shown that DNA gyrase and topoisomerase IV inhibitor, AZD0914 effectively interact with the TOPRIM domain of GyrB. Structure activity relationship (SAR) and *in vitro* studies have uncovered the novel DNA gyrase inhibitors like MRL - 770 and its two analogues, MRL - 423 and MRL - 1082 for use as potential antibacterial agent [3]. Sigma factors of bacterial RNA polymerase can also be used as potential target for development of antibacterial drugs. Bacteriophage-encoded proteins, P7 that infects *Xanthomonas oryzae* has shown to effectively interact with β and β' subunit of the RNA polymerase leading to displacement of $E\sigma^{70}$ -promoter complex ($\alpha 2\beta\beta'\omega\sigma$; $E\sigma$), inhibition σ^{54} mediated promoter recognition and transcription initiation [14,41]. Chlamydia phage ϕ CPG1 capsid protein Vp1 has been shown to decrease mRNA levels of ERK1 & 2 and pro-inflammatory cytokines (IL-8 and IL-1) in cells infected with *Chlamydia trachomatis* and thus inhibiting the growth of sexually transmitted bacteria [42].

Inhibiting bacterial protein synthesis

Protein synthesis is a ubiquitous process that regulates gene expression and bacterial cell survival. Targeting bacterial ribosomal components and protein synthesis has thus been promising approaches to prospective antibacterial drug development. Aminoglycosides inhibits bacterial protein synthesis through codon misreading and inhibition of tRNA-mRNA complex translocation. Aminoglycosides also affect protein translation by direct interaction with decoding A-site of rRNA. Paromomycin derivative 4'- O-(Alkyl) 4,5- Di substituted 2-Deoxystreptamines has shown greater selectivity to 16S rRNA and low affinity to eukaryotic ribosomes, which inhibited growth of MRSA AG041 [43]. However, most bacterial cells can develop resistance to antibiotics by employing a set of enzymes called aminoglycoside modifying enzymes (AMEs). The activities of AMEs has been reported to decrease in the presence of triazole linkers that aid in linking and binding of neomycin dimers to A site of bacterial ribosomes. Thus, development of linkers and aminoglycoside dimers resistant to AMEs is one possible approach to overcome aminoglycosides resistance by bacterial pathogens [44]. Translation stalling peptide sequences such as SecM, ErmBL and TnaC interact directly with nascent peptide at the exit tunnel, thus making the ribosomal exit site an effective target for the design of novel antibacterial. N-10 endocyclic amine derivatives of azithromycin containing an indole moiety have been shown to inhibit protein translation in *E. coli* by binding to ribosome A751 residue [45].

Antibacterial agents such as aminomethylcycline and Omadacycline are ribosomal inhibitors that targets 70S ribosomes and exhibit potent antibacterial activity against MRSA, hemolytic streptococci, *S. pneumoniae*, *H. influenzae*, and Legionella [46]. Alkyl substituted derivatives like N-benzyl substituted 3'-(R)- 3'-aminomethyl-3'-hydroxy spectinomycins showed increased antibacterial activity by binding to 30S ribosomes of *S. pneumoniae*, *H. influenzae*, *L. pneumophila*, and *Moraxella catarrhalis*, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* [47]. Viomycin is a protein synthesis inhibitor that affects protein synthesis by binding to ribosomal A-site and competes with elongation factor G (EF-G) [48]. Translation elongation factor P (EF-P) rescues the bacterial cell from any ribosomal stalling at consecutive prolines. EF-P activity requires post-translational β -lysyl modification of Lys34 in *E. coli* and *S. enterica*, whereas *Shewanella oneidensis* and *P. aeruginosa* requires post-translational modification of Arg32 with rhamnose. These posttranslational modifications are essential for survival of *Neisseria meningitidis* containing orthologue of rhamnosyl modification enzyme (EarP). Thus, EarP could be considered as one of the promising target to treat *N. meningitidis* infections [15]. In *M. tuberculosis*, translational events such as initiation and elongation are controlled by interaction of 50S ribosomal proteins L12 and L10. T766 and T054 are small molecules inhibitor that binds specifically to L12 and disrupt L12 - L10 interaction in *M. tuberculosis*, which could be considered as potential target for development of antimycobacterial agent [16]. Solithromycin, an antibacterial agent showed turnover of 23S rRNA and 16S rRNA in methicillin-sensitive and methicillin-resistant strains of *S. aureus*, *S. pneumoniae*, and *H. influenzae* [49].

Targeting bacterial protein secretion system

Most bacterial pathogens rely on dedicated protein secretion system to secrete virulence proteins into the host system. The type III secretion system (T3SS) acts as a needle apparatus to transport virulence factor and is evolutionarily conserved across Gram-negative pathogens, which could be used as potential target for design of novel antibacterial drugs [50]. *Salmonella* pathogenicity island-1 (SPI-1), Ysc and Ysa T3SS of *Yersinia*, Sct T3SS of *Chlamydia* and T3SS transcriptional regulators of *Pseudomonas* and *Shigella* are the well-studied T3SS systems. In recent years, T3SS has become one of the most promising targets and researchers have made effort to design inhibitors specific to T3SS. Salicylidene acylhydrazides (SAHs) is the well-studied T3SS inhibitor that possessed broad spectrum antibacterial activity against *Chlamydia*, *Shigella*, *Salmonella* and *E. coli*. Another class of compounds called as thiazolidinone shown to inhibit T3SS of *Yersinia*, type II secretion system in *Pseudomonas* and type IV pili secretion system of *Francisella sp.* [2]. Piericidin A1 and its derivative Mer-A 2026B obtained from marine actinobacterium has been shown to inhibit the T3SS system in *Yersinia pseudotuberculosis* and NF- κ B activation in host cells [50]. Similarly, phenoxyacetamides MBX 1641 and MBX 1642 has shown potent activities against *P. aeruginosa* T3SS system at low micromolar concentrations [4]. The final stage of protein synthesis is ribosome recycling, where ribosome is split into 30S and 50S subunits with the help of ribosome recycling factor (RRF) and GTPase elongation factor G (EF-G) making them available for the next round of protein synthesis. Fusidic acid has shown to inhibit the ribosome splitting processes that halts peptide elongation in bacterial cells [51]. Since, resistance to Fusidic acid has been reported in recent years that warrants development of new drugs to overcome the resistance.

Phage therapy

Phage therapy has garnered significant attention in recent years owing to its host specificity, biofilm penetration and low cytotoxicity profiles as compared to conventional antibiotics. Phage therapy uses bacteriophages to treat bacterial infection. It mainly aims at bacterial lysis using phage proteins, holin and endolysin (lysin) [52]. ABgp46, a recently discovered phage lysin has shown broad spectrum antibacterial activity against multi drug resistant *A. baumannii*, *P. aeruginosa*, and *S. typhimurium* [52]. Polysaccharide depolymerases are phage derived enzymes proven to be effective in removal of extracellular polysaccharide (EPS), which inhibits the growth of bacterial biofilm rendering them susceptible to antibiotics. Hybrid or chimeric enzymes have also been developed from phages. A chimera of T4 lysozyme with the bacterial toxin pesticin has shown to target FyuA in some *Yersinia* and pathogenic *E. coli* strains. Artilysin, a chimera of sheep myeloid antimicrobial peptide and N-terminus of an endolysin showed potent antimicrobial activity against *P. aeruginosa* and other multidrug-resistant strains. Virion-associated peptidoglycan hydrolase (VAPGH, or tail-associated lysin) is another phage derived

protein showed antibacterial activity against several MDR strains [53]. A chimeric protein CHAPSH3b developed from virion-associated peptidoglycan hydrolase (VAPGH) of phage vB_SauS-phiIPLA88 (HydH5) and cell wall binding domain of lysostaphin have proven to be effective in downregulating autolysin gene, AtlA and preventing biofilm formation of *S. aureus* [54].

Targeting bacterial appendages

A pilus is a hair-like appendages found on the surface of many bacteria, whose activity is responsible for bacterial translocation, motility, virulence and biofilm formation. Targeting assembly of pilus could be an effective approach for development of novel antibacterial agent. Type IV pili (TFPs) are necessary for these functions in *P. aeruginosa*. D3112 protein gp05 or Tip, a phage derived protein has shown to inhibit twitching motility in bacteria. Blocking activity of PilB is crucial for TFP assembly and regulation by ATPase activity. Thus, PilB may be considered as an important target for development of novel antimicrobials [55]. Plasmid encoded resistance genes poses a global public health threat as they are rapidly transferred among bacterial species and confer antibiotic resistance. Protein g3p obtained from a replicating M13 phage interfere with bacterial conjugation and transfer of F plasmid encoding tetracycline resistance in *E. coli*, which offers an attractive way to stop dissemination of plasmids mediated antibiotic resistance [56].

Targeting efflux pumps

Efflux pumps are proteinaceous transporters associated with multidrug resistance in many bacterial species. In recent years, efflux pumps are considered as potential target in the design of future antibiotics. Rv1258c efflux pump in *M. tuberculosis* promotes intracellular survival of bacterium within macrophages and conferred resistance to spectinomycin. In recent years, spectinamides or modified spectinomycins have been designed to overcome clearance by Rv1258c and promote inhibition of *M. tuberculosis* [57]. Boeravinone B, a compound isolated from the roots of *Boerhavia diffusa* showed inhibitory action against NorA efflux pump in *S. aureus* [11]. AcrAB-TolC RND (resistance-nodulation-division) efflux pumps are abundant in Enterobacteriaceae family acting as drug/proton antiporters in conferring multi drug resistance. Lack of AcrAB-TolC efflux systems have been shown to reduce virulence and induce drug susceptibility in *S. enterica* seovar Typhimurium [13]. The Bcr/Cfl eff system in *Proteus mirabilis* gave rise to swarming motility and crystalline biofilms on catheters leading to catheter blockage. Floxetine and thioridazine are efflux pump inhibitors that inhibit Bcr/Cfl eff system and reduces the virulence properties of *P. mirabilis* [12].

Conclusion

The key step in antibacterial drug development processes lies in understanding the basic bacterial processes and designing agents with novel mechanism of action against the specific targets would potentially disrupts bacterial cell multiplication and survival. Targeting the bacterial cellular machinery and other key events essential for bacterial cell survival seems to offer promising approach to development of potential antibacterial drugs. Studies involving structure activity relationships, molecular modeling, high throughput drug screening and *in vitro/in vivo* drug validation could also add benefits to development of potential next generation antibiotics to tackle bacterial infections.

Conflict of Interest

All authors declare no conflicts of interest.

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Volume 14 Issue 7 July 2018

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