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Booklets

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Title: Importance of peptidoglycan hydrolases, bactericidal enzymes produced by lactic acid bacteria, in the reduction of antibiotic resistance

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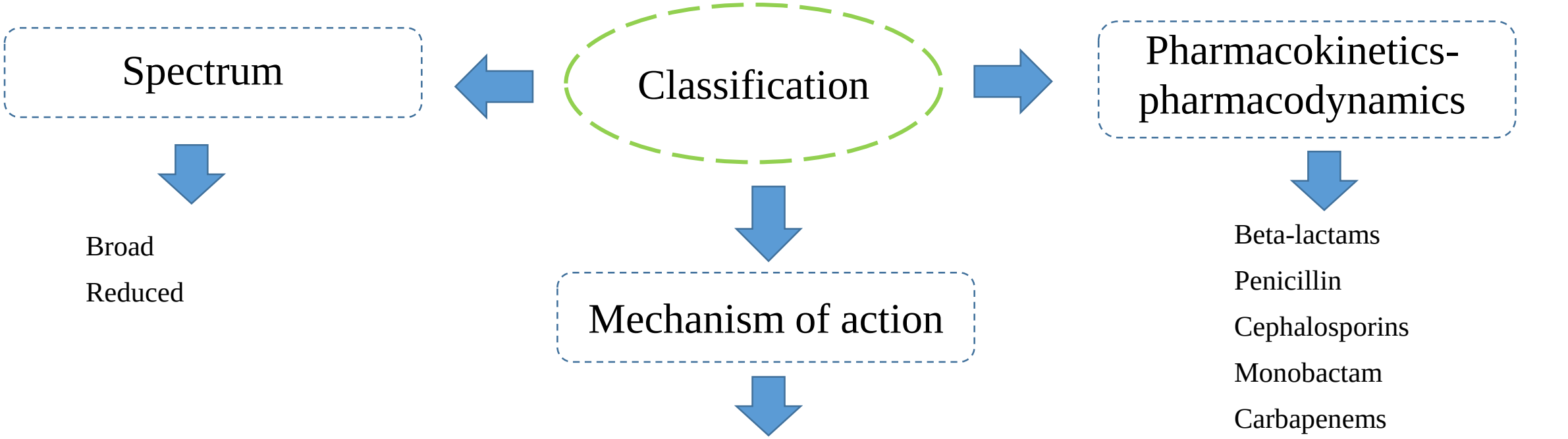
Antibiotics

Its induced the death or inhibiting the growth of bacteria and fungi, and the replication of viruses are defined as antimicrobial



Worlwide problem of antibiotic use

Antibiotic resistance (AR)

Natural expression of bacterial evolution and genetics

Mechanisms of transferring resistance genes

- Transformation
  - The transfer of genes from free DNA of a previously lysed bacterium to another
- Conjugation
  - The transfer of genetic material contained in plasmids from one bacterium to another via pili
- Transposition
  - The transfer of genetic material from one bacterium to another by a phage

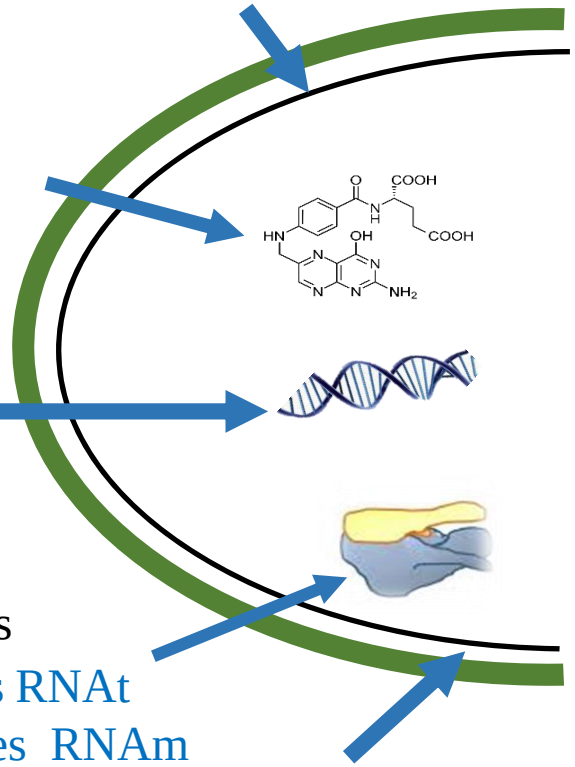
Factors that favor AR:

- The inappropriate use of antimicrobials
- The low quality of active compounds
- The lack or deficiency of infection prevention and control programs
- The inability of laboratories to detect resistance
- The inadequate surveillance and insufficient regulation of antibiotic use

Mechanism of bacterial resistance to antibiotics

Antibiotic targets

Resistance mechanisms to antibiotics



Cell wall

Folate synthesis

DNA / RNA synthesis

Fluoroquinolones

DNAg

Rifamycins RNAp

Protein synthesis

Tetracyclines RNAt

Aminoglycosides RNAm

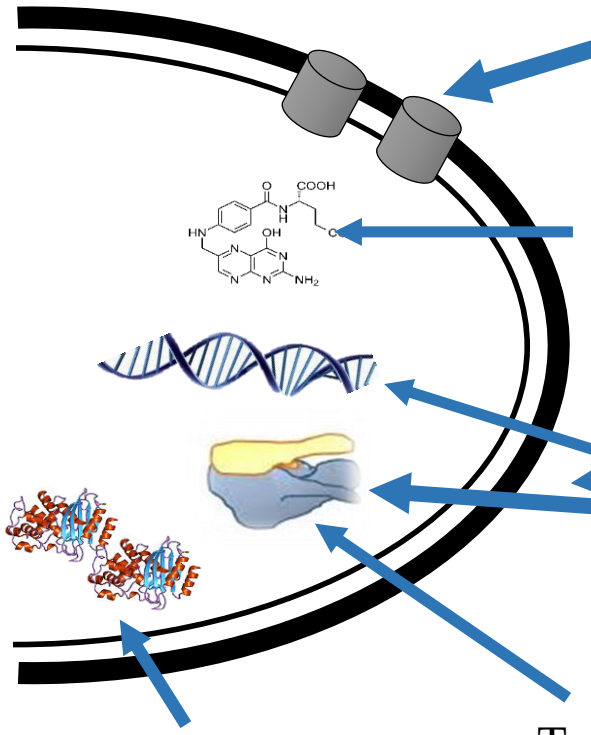
Macrolides

Chloramphenicol

Binding of amino acids

Cellular membrane

Polymyxins



Efflux pumps

Metabolic routes

Target modification

Target protection

Enzyme inactivation

Enzyme production

Examples of recent cases of antibiotic resistance

2014-2015:

Acinetobacter baumannii showed of resistance to fluoroquinolones, amikacin, trimethoprim/sulfamethoxazole, imipenem, meropenem, cephalosporins and tetracyclines

2016:

Enterococcus faecalis and *Enterococcus faecium* strains, which showed resistance to ampicillin, streptomycin, penicillin, vancomycin, gentamicin, erythromycin and quinupristin and dalfopristin

2017:

Pseudomonas aeruginosa showed of resistence to to ampicillin, ceftriaxone, chloramphenicol, cefotaxime cephalothin, nitrofurantoin, kanamycin, streptomycin and tetracycline

2017:

Escherichia coli showing resistance to amikacin, ampicillin, levofloxacin, cephalothin, cefotaxime, ceftriaxone, chloramphenicol, gentamicin, netilmicin, nitrofurantoin, cefepime, trimethoprim sulfamethoxazole, tetracycline, kanamycin and streptomycin

2018:

strains of *Staphylococcus aureus* and 12 strains of coagulase-negative *Staphylococcus* showing methicillin resistance

Worlwide action plan on antibiotic resistance

Priority 1: CRITICAL	Priority 2: HIGH	Priority 3: MEDIUM
Carbapenem-resistant *Acinetobacter baumannii* Carbapenem-resistant *Pseudomonas aeruginosa* Carbapenem-resistant *Enterobacteriaceae*, producers of extended-spectrum beta-lactamases.	*Enterococcus faecium*, resistant to vancomycin *Staphylococcus aureus*, methicillin-resistant, intermediate susceptible and vancomycin resistant *Helicobacter pylori*, resistant to clarithromycin *Campylobacter spp.*, resistant to fluoroquinolones *Salmonellae*, resistant to fluoroquinolones *Neisseria gonorrhoeae*, cephalosporin-resistant,	*Streptococcus pneumoniae*, not penicillin sensitive Ampicillin-resistant *Hemophilus influenzae* Fluoroquinolone-resistant *Shigella spp.*

WHO in 2017 published the first list of priority AR pathogens

Development of the presence of antimicrobial resistance in Mexico

1998

Streptococcus pneumoniae Showed show resistance to penicillin and to cephalosporins, macrolides, ciprofloxacin, trimethoprim-sulfamethoxazole, chloramphenicol and tetracyclines

2009

Multidrug-resistant *Salmonella typhimurium* strains

2011

Increasing resistance to clarithromycin was reported in *Helicobacter pylori*

2012

Antimicrobial resistance in *Campylobacter spp*

Alternative for controlling antibiotic use

Use of microorganisms with antimicrobial activity

Preservation of various food products

Lactic acid bacteria

GRAS

Produce

- Hydrogen peroxide
- Carbon dioxide
- Reuterine
- Reutericicline
- 2-pyrrolidone
- 5- carboxylic acid
- Bacteriocins
- Peptidoglycan hydrolases (PGH)

Lactobacillus bulgaricus ATCC 11842 and *Lactobacillus helveticus* ATCC 15807 that have bactericidal activity against *Escherichia coli, Salmonella enteritidis* and *Shigella dysenteriae*

Proteins of lactic acid bacteria with biological activities

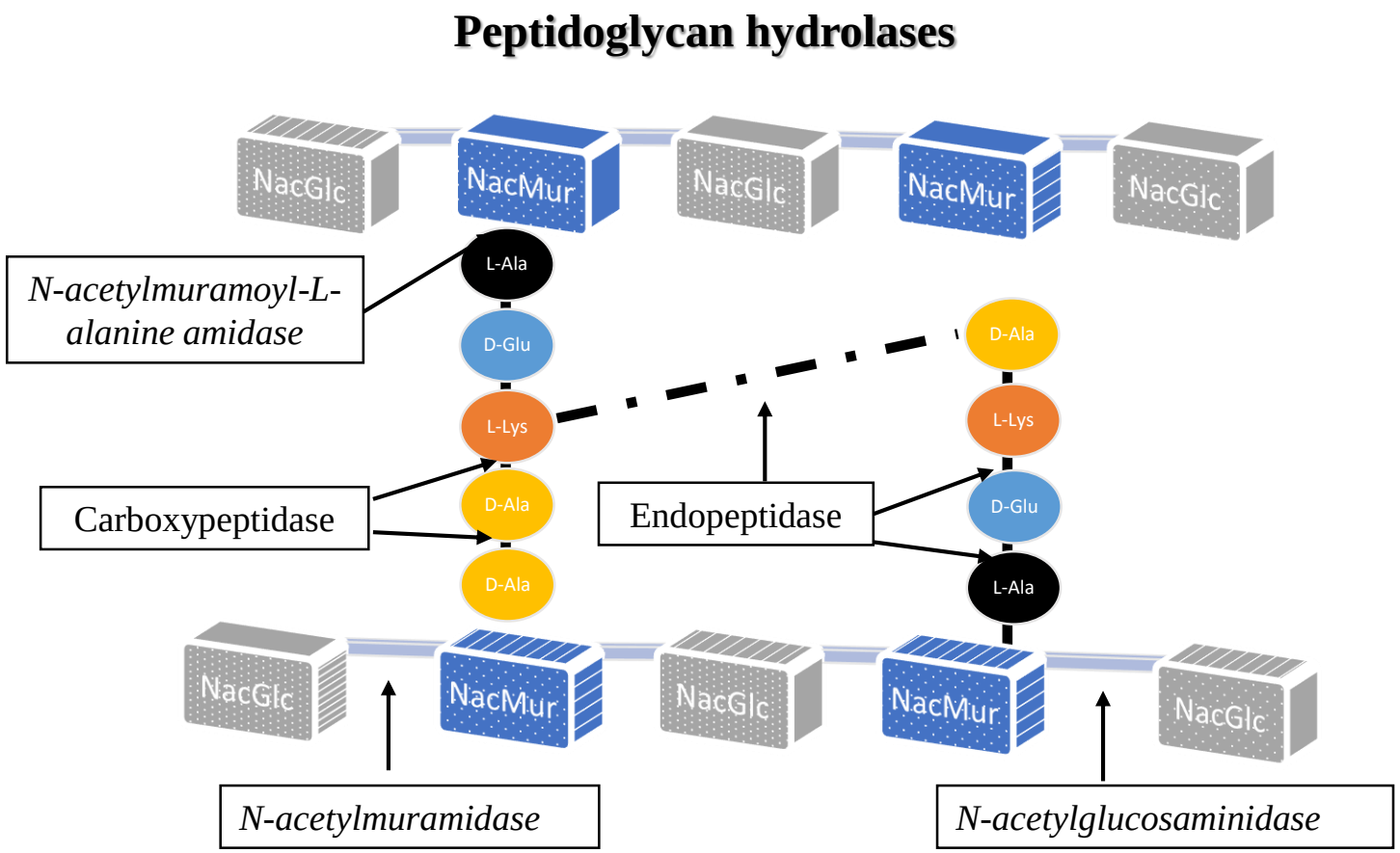
Metabolite	Producing microorganism	Reference
Diacetyl	Most of the BAL	Montville and Winkowski, 1997
Reuterin	*L. reuteri* *L. coryniformis*	Magnusson and Schnürer, 2001
BLIS: Bacteriocin-like and inhibitory substances	Most of the BAL	Montville and Winkowski, 1997
Bacteriocins	Most of the BAL	Nes, et al., 1996
Cyclic dipeptides: Cyclo-PhePro Cyclo-PheOHPro Cyclo-GlyLeu	*L. coryniformis* *L. plantarum* *L. pentosaceus*	Magnusson and Schnürer, 2001
Bioactive peptides	Most of the BAL	Visser, S. et al., 1986. Fedorov et al., 2003
PGH	Most of the BAL	Cibik and Chapot-Chartier, 2004, Lortal and Chapot-Chartier, 2005 Turner et al., 2007

LAB have the ability to inhibit the growth of certain altering and/or harmful microorganisms in food or even within the community

Peptidoglucan hydrolases (PGH)

Enzymes that hydrolyzed in a controlled way the peptidoglycan bond inhibiting the growth of bacteria that represent a public health problem.

Classification



The classification of PGHs depends on the type of bond they hydrolyze in the PG

Catalytic domains of peptidoglycan hydrolases

The characterized PGHs have a modular structural organization with two domains: a catalytic domain containing the active site of the enzyme and a cell wall binding domain

Catalytic domains

Catalytic domains are specialized for cleavage of a specific peptidoglycan bond.

N-acetylmuramoyl-L-alanine amidase	Endopeptidase	Carboxypeptidase	N-acetylglucosami-nidase	N-acetylmurami-dasa
Amidase 2 (PF01510)	Peptidase M23 (PF01551)	Peptidase_S66 (PF02016)	Glucosaminidase (PF01832)	Glico_hydro_25 (PF01183)
Amidase 3 (PF01520)	CHAP (PF05257)	VanY (PF02557)		SLT (PF01464)
Amidase 5 (PF05382)		Peptidase_S11 (PF02113)		Transglucosylase (PF06737)
CHAP (PF05257)		Peptidase_S13 (PF00768)		

Cell wall binding domains

Cell wall binding domains are of great importance for the catalytic efficiency of PGHs. One of their main functions is the binding of proteins to the cell wall and the targeting of the enzyme to its site of action

Binding domains	Joint sites	XFAM access number
Big_4	Variety of bacterial surface proteins.	PF07532
CBM_5_12	Carbohydrate Binding Modulus (CBM)	PF02839
ChW	Proteins containing ChW repeats (tryptophan)	PF07538
Collagen	Triple helix repeat proteins	PF01391
CpL_7	The CW_7 repeats form a cell wall binding motif.	PF08230
Cu_amine_oxidN1	Oxidation of primary amines to aldehydes	PF07833
Cw_binding_1	Repeats in P15057 recognition of choline-containing cell walls	PF01473

27 surface domains that can be found in bacteria

PGH production by lactic acid bacteria

The most reported production of PGH is *Lactobacillus*. One species can produce two or even three enzymes with this lytic activity

PGH	Sensitive strain
Muramidase	*Oenococcus oeni*, *Clostridium tyrobutyricum*, *Escherichia coli*, *Staphylococcus aureus* *Bacillus subtilis*
Streptococcus agalactiae bacteriophage B30 endolysin	*Streptococcus agalactiae*, *Streptococcus uberis* *Staphylococcus aureus*
PGHs isolated from Pediococcus acidilactici ATCC 8042	*Staphylococcus aureus*

Examples of Recombinant peptidoglycan hydrolases

Cloning of a PGH from *Lactobacillus gasseri* JCM11 31. Two recombinant plasmids, holgaY and lysgaY, were produced. the gene revealed significant homology with hypothetical muramidases from the phage *Lactobacillus* Badh, Lj965, Lj928, LL-H, mv4 and mv1

The AtlL protein from *Staphylococcus lugdunensis* was characterized for the first time and cloned in *E. coli*.

The pET system (pET System, Novagen) was used with *Escherichia coli* strain BL21(DE3) for cloning and expression from *Pediococcus acidilactici* ATCC 8042 .

Application of peptidoglycan hydrolases

The food industry:

- Lysozyme is used in foods such as meats, sausages, fish, vegetables, fruits, wine and milk powder**.**
- Egg lysozyme is listed as a food additive.
- Lysostaphin is an enzyme produced by *Staphylococcus simulant.*

Antimicrobial activity against resistant microorganisms

PGH	Isolated microorganism	Inhibited microorganism	Reference
Acp	*Clostridium perfringens*	*Micrococcus lysodeikticus ATCC4698, Bacillus subtilis, Clostridium difficile and Clostridium perfringens*	Camiade et al.,2010
N-acetylglucosamidase	*Pediococcus acidilactici* 99 kDa	*Streptococcus pyogenes,Enterococcus faecium, Lactobacillus paracasei, Listeria monocytogenes , Pediococcus acidilactici ATCC 8042, Enterococcus faecalis and Staphylococcus aureus ATCC 6538*	García-Cano etal., 2015
AtlD	*Enterococcus faecalis*	*Enterococcus faecium, Listeriamonocytogenes, Enterococcus faecalis, Micrococcus lysodeikticus* ATCC4698, *Enterococcus faecium, Enterococcus faecalis ATCC,Enterococcus faecalis, Listeria innocua, Staphylococcus aureus ATCC 6538*	Serrano-Maldonado et al., 2018.

Conclusions

The overuse of antibiotics is a global public health problem, an alternative to this problem is the use of therapies with lytic enzymes such as PGH produced by BAL.

New bactericidal compounds of natural origin can be designed to replace antibiotics in the health, agricultural and agri-food sectors.

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