Lactoferrin Derived Peptides: Mechanisms of Action and their Perspectives as Antimicrobial and Antitumoral Agents

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Abstract: Antimicrobial peptides, AMPs, exert their function acting mainly at the membrane level. In the wide AMPs panorama a particular position is occupied by lactoferrin derived peptides. They also possess antiviral, antifungal and anti-tumor activities and their parent molecules are available in several mammalian fluids and in dairy industries waste.

Key Words: Antimicrobial peptides, lactoferrin, lactoferricin B, lactoferrampin.

1. INTRODUCTION

1.1. Common Properties of Antimicrobial Peptides

Antimicrobial peptides (AMPs) are produced by almost all species as a component of their immediate non-specific defence against infections. During the past decade they have been isolated from many different organisms, including mammals, insects and amphibians [1]. Unlike antibiotic peptides, that are for the most part synthesized by special metabolic pathways, the amino acid sequence of antimicrobial peptides is naturally encoded in the genetic material of the host organism. Transcription is initiated upon invasion by pathogens, followed by postranslational modifications, that usually include cleavage of a precursor protein, amidation at the C-terminus, and, for about 50% of the currently known AMPs, disulphide bond formation and in rare cases glycosylation [2, 3]. AMPs are an heterogeneous group, varying in primary and secondary structure but sharing some common properties: they are generally short, most of them consisting of less than 45 amino acids, amphipathic and carrying net positive charge(s) [4]. Initially it was observed that antimicrobial peptides are bactericidal but nowadays it has been established that many of them can possess also antiviral [5], antifungal [6, 7], antitumoral [8], and immunomodulatory [9] activities.

It has been shown that AMPs interact directly with the microbial cell membranes rather than with specific membrane proteins, subsequently causing an increase in membrane permeability and cell lysis. The interaction of membrane phospholipids with antimicrobial peptides is also pharmaceutically relevant and it might be the trigger of different effects such as the formation of pores [10], the thinning of the membrane [11], or the destabilization of the bilayer [12]. For example, the b-lactoferricin (bLfcin), an antimicrobial peptide obtained by pepsin cleavage of the basic N-terminal region of bovine lactoferrin (Lf) [13], causes the depolarization of the cytoplasm membrane in susceptible bacteria, but the integrity of the membrane remains intact.

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Despite the focus on bacterial membranes, several antimicrobial peptides have been shown to act versus many other additional intracellular targets such as DNA, RNA and/or proteins [14, 15], with the inhibition of macromolecular biosynthesis [16, 17] and of bacterial enzymes [18].

1.2. AMPs as Antibacterial Agents in Therapeutics

The major motivation for the therapeutic use of AMPs is their diverse potential ways of applications: they can be used as antimicrobials, alone or in combination with other antibiotics with a synergistic effect, or as immunomodulatory and/or endotoxin-neutralizing compounds [19]. AMPs are attractive candidates for clinical development because of their selectivity and potency for broad-spectrum activity, their speed of action and because of the lower resistance developed against them by bacteria compared to other antibiotics already in use. The most potent agents have a broad spectra of activity against Gram-negative and Gram-positive bacteria, and this spectrum can be further extended to fungi and even several viruses. On the other hand, the possible disadvantages include the high cost, the limited stability (especially when composed of L-amino acids), and the unknown toxicology and pharmacokinetics [20]. AMPs were involved in the local response to infection such as topical infections. Some pharmaceutical companies have entered phase I clinical trials for the application of a histatin-derived peptide against oral candidiasis, while some studies have demonstrated that the peptide T-20 [21] reduced the viral load in HIV-infection. Several peptides could be used as antitumoral agents, for example, peptides from the ras-p21 and p53 proteins block proliferation of cancer cell [22].

2. THE ANTIMICROBIAL PEPTIDES

2.1. Classification

More than 800 AMPs have been identified in virtually all living species (see http://www.aps.unmc.edu/AP/main.html), and have been classified, based on their structural characteristics, dividing them in four major groups, namely: group I peptides with a α-helical structure, group II peptides with ß-strands connected by intramolecular disulphide bridges, group III linear peptides having a sequence characterized by the over representation of one or more amino acids and group IV looped peptides (see Table **1**).

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Table 1. Classification and Origin of Some Representative Antimicrobial Peptides

Group	Peptide	Origin
Group I α-helix	Temporin L Temporin B Magainin 2 SMAP29 LL-37 Cecropin A	Rana temporaria (European red frog skin) Rana temporaria (European red frog skin) Xenopus laevis (clawed toad skin) Sheep myeloid Humans, leukocytes, epithelia Hyalophora cecropia (moth)
Group II ß-sheet	Protegrin-1 Tachyplesin-1 Polyphemusin-1 Androctonin Human ß-defensin-1	Porcine leukocytes Tachypleus gigas (Asian horseshoe crab) Limulus polyphemus (Atlantic horseshoe crab) Androctonus australis (scorpion hemolymph Several human tissues
Group III Unusual Composition	Indolicidin Histatin-5 Bactenecin-5 PR-39	Bovine neutrophils Human saliva Bovine neutrophils Pig intestine
Group IV Looped peptide	Bactenecin-1 Ranalexin Thanatin Brevinin 1E Lactoferricin	Bovine neutrophils Rana catesbeiana (bullfrog skin) Insect hemocytes Rana esculenta (European frog skin) Cow and human milk

The abundance of proline-arginine residues and the presence of small ring structures derived from a thioether bond, are some of the distinctive characteristics of peptides that belong to the fourth group. One of the member of this group, nisin, is largely used as antimicrobial agent in food preservation on behalf to its high activity against Gram-positive bacteria [23]. Lfcin is another important member of this group that possesses antiviral, antifungal, antitumoral, and immunomodulatory properties, along with its antibacterial activity.

2.2. Cationic Antimicrobial Peptides' Mechanism of Action

All antimicrobial peptides interact with the bacterial membrane and, on the basis of their mechanism, tend to be divided into two classes: membrane destructive and non-membrane destructive. The peptides possess strong selectivity to membranes and the action responsible for killing bacteria at the minimal effective concentration varies from peptide to peptide and from bacterium to bacterium for a given peptide [24]. The outer membrane of Gram-negative bacteria constitutes a semi-permeable barrier against a variety of substances. The enterobacterial outer membrane bilayer consists of an inner monolayer containing phospholipids and an outer monolayer that is mainly formed by lipopolysaccharides (LPS). In the case of Gram-negative bacteria the LPS, which are localized in the outer leaflet of the outer membrane, are the first target of all antibiotics. The LPS monolayer is a highly ordered quasi crystalline structure with very low fluidity [25] that prevents rapid diffusion of hydrophobic solutes. Since LPS are essential for the survival of Gram-negative bacteria, their release due to antibiotic attack leads to bacterial death. One mechanism of interaction of cationic antimicrobial peptides with the cell envelope of Gram-negative bacteria is reported in detail hereinafter [1, 26]. Passage across the outer membrane is proposed to occur by self-promoted uptake. Unfolded cationic peptides interact with the negatively charged surface of the outer membrane neutralizing the charge of the outer membrane at the site of interaction. Hydrophobic forces promote the formation of a stable α-helical structure, driving the peptides further into the monolayer [27]. This produces fractures through which the peptides can cross the outer membrane (Fig. (**1**) step 1), or actually bind to the divalent cation binding sites on the LPS and disrupt the membrane (step 2). Once the peptides pass through the outer membrane, they will bind to the negatively charged cytoplasmic membrane surface, charge created by the head groups of phosphatidylglycerol (PG) and cardiolipin (CL), and the amphipathic peptides will insert into the membrane interface (the region where the phospholipid headgroups meet the fatty acyl chains of the phospholipid membrane) (step 3).

It is not known at which point of this process the peptide actually folds into its amphipathic structure (i.e. during its passage across the outer membrane or during its insertion into the cytoplasmic membrane). Many peptide molecules will insert into the membrane interface and are proposed to then either aggregate into a micelle-like complex which spans the membrane (step 4) or flip-flop across the membrane under the influence of the large transmembrane electrical potential gradient (approximately 2140 mV) (step 5). The micelle-like aggregates are proposed to be associated with water, and this provides channels for the movement of ions across the membrane and possibly the leakage of larger water-soluble molecules. These aggregates have variable sizes and lifetime and dissociate into monomers that may be disposed at either side of the membrane. The net effect of

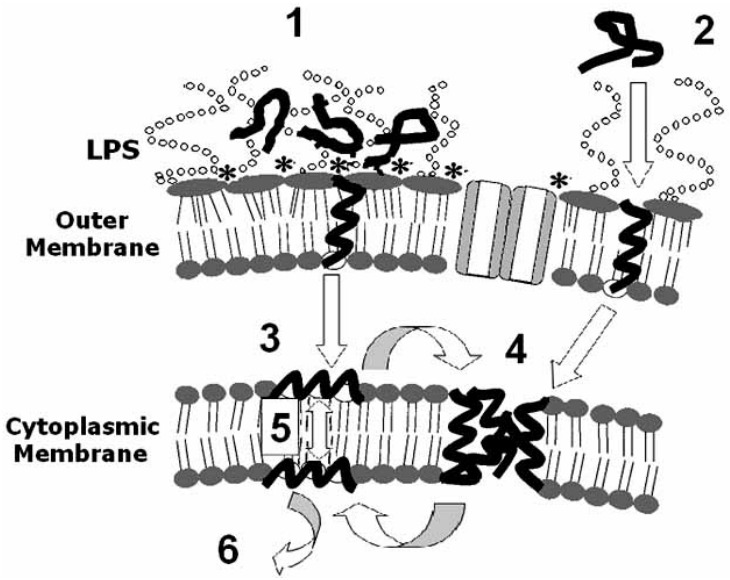

Fig. (1). Cartoon of the major proposed mechanisms of cationic antimicrobial peptides interaction with the cell envelope of gram-negative bacteria. AMPs, randomly structured in solution, adopt a typical - helical structure, upon interaction with target membranes. This produces cracks through which the peptide can cross the outer membrane (step 1), or actually bind to the divalent cation binding sites on the LPS and disrupt the membrane (step 2). Once the peptide has transited the outer membrane, it will bind to the negatively charged surface of the cytoplasmic membrane and the amphipathic peptide will insert into the membrane interface (step 3). Many peptide molecules will insert into the membrane interface and are proposed to then either aggregate into a micelle-like complex which spans the membrane (step 4) or flip-flop across the membrane under the influence of the large transmembrane electrical potential gradient (step 5). The net effect of step 4 and 5 is that some monomers will be translocated into the cytoplasm and can dissociate from the membrane and bind to cellular polyanions such as DNA and RNA (step 6). These mechanisms could be summarized in three models which explain membrane disruptive properties of peptides namely "barrel stave" (1) "micellar aggregate" (4) and "carpet like" (2).

step 4 and 5 is that some monomers will be translocated into the cytoplasm and can dissociate from the membrane and bind to cellular polyanions such as DNA and RNA (step 6). These mechanisms could be summarized in three models which explain the membrane disruptive properties of peptides: the "barrel stave" (1), the "micellar aggregate" (4) and the "carpet like" (2) models, as reported in (Fig. **1**).

3. LACTOFERRIN DERIVED PEPTIDES

3.1. Main Structural Characteristics of Lf

Bovine lactoferrin (bLf) is an iron-binding glycoprotein consisting of 689 amino acids, found in different biological fluids of mammals and in neutrophils. This protein has various biological functions such as antimicrobial, antiviral and anti-inflammatory activity and can regulate the immune system. Lactoferrin is a dominant whey protein in human milk throughout lactation and is able to bind two ferric ions. The transferrin is another iron-binding protein present in milk, even though these two proteins are not always present simultaneously [28]. The affinity constant of Lf for the iron is 300 times higher than that of transferrin, and it can retain iron at a lower pH, in part due to its basic nature [29]. Lactoferrin has been found in the milk of a large number of mammals and its amino acid sequence is known for nine species: human, pig, horse, cow, buffalo, sheep, goat, camel and mouse [30] and it has been also identified in the milk of the African elephant [31]. The three-dimensional structure of Lf from five species are available: human [32], cow [33], buffalo [34], horse [35] and camel [36], and all of them share the same structural organization. Lf is folded into two lobes corresponding in human to residues 1–333 and 345–691, that show sequence homology with each other; they can reversibly bind up to 1.4 mg of iron/g of protein, along with a synergistic anion, usually bicarbonate. These are referred to as the N-lobe and C-lobe and are linked by a short α-helix. In each lobe, two a/b domains, referred to as N1 and N2, or C1 and C2, enclose a deep cleft within which there is the iron binding site. This overall folding for each lobe corresponds to a classic two-domain 'binding protein fold', that is shared by a large family of bacterial periplasmic proteins that transport ions and small molecules, suggesting a common evolutionary origin [37]. Lactoferrin is also a highly basic protein, with a pI of 8-9, probably due to a unique basic region in the N-terminal region of the molecule that is not found in transferring [38]. The structural characteristics described above confer to Lf several biological properties, as shown in (Fig. **2**).

3.2. Content of Lf in Body Fluids

Human milk is particularly rich in Lf, ranging from about 7.0 g/l in colostrum to about 1.0 g/l in mature milk, in which it may rise again at the end of lactation; the Lf content in

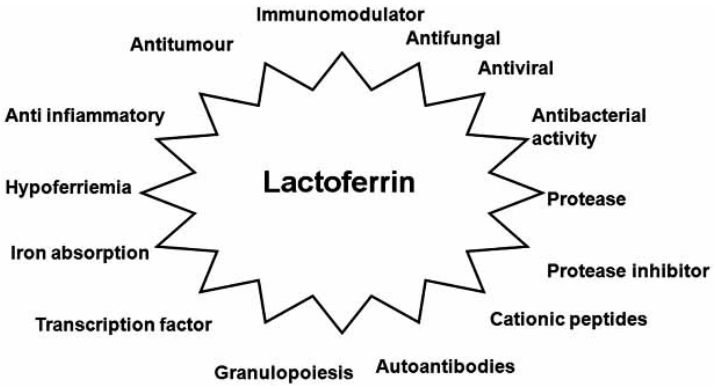

Fig. (2). Main biological properties of lactoferrin.

bovine colostrum and milk are ~1.0 and 0.2 g/l, respectively. This protein may also be found in blood (0.30 μg/ml), derived from the neutrophils whose content in Lf is 0.10 μg/10^6 cells, which degranulate and synthesize Lf during inflammation [39]. This protein is also found in human secretions such as tears, nasal and uterus secretions with a concentration of 0.5-1.5, 0.2 and 0.5-1 mg/ml, respectively. Other human fluids, namely saliva (5-11 μg/ml), amniotic fluid (2-30 μg/ml) and urine (1.5 μg/ml), possess discrete amounts of Lf.

3.3. Antimicrobial Lf Derived Peptides: Structure and Related Mechanism of Action

Some AMPs are derived from larger proteins by proteolytic degradation [40]. It has been thought that the ability of Lf to bind iron prevents microbial growth; however, a bactericidal domain, which is distinct from the iron binding region of the protein, has also been identified and purified. When this protein is digested at acidic pH by proteases such as pepsin, it yields highly active antimicrobial peptides that inhibit the growth of a number of Gram-negative and Gram-positive bacteria, including strains that were resistant to native Lf [41]. Among them, Lfcin, which is released from the basic N-terminal region of Lf, seems to be the most widely studied in literature. It possesses a net charge of + 8 and it is found in various species, such as human lactoferricin (hLfcin) with 47 amino acids corresponding to residues 1 to 47 of hLf and bLfcin containing 25 amino acids corresponding to residues 17 to 41 of bLf, Fig. (**3**).

In vitro studies have shown that bLf has a higher antibacterial activity respect hLf and in a similar way the bLfcin has been shown to be more effective than hLfcin. The antibacterial activity was related to the sequence of residues 17-41 and 18-40, in bLf and hLf, respectively [42]. Both bLfcin and hLfcin express much stronger antibacterial activity respect their parental molecules. It has been suggested that this dramatic increase in potency of Lfcin is related to a change in the secondary and tertiary structure when released from bLf; in particular, it changes from a mixed α- helical and β-strand structure in the intact protein to an amphipathic twisted antiparallel β-sheet in the peptide [43].

The bLfcin has been more extensively investigated respect the hLfcin, because it is most readily available and it has a higher antibacterial activity. The primary sequence of bLfcin contains many hydrophobic and positively charged residues, suggesting that it may interact with biological membranes and in fact membrane blisters have been observed in bacteria exposed to bLfcin. After *E. coli* CL99 1-2 cells were incubated with lactoferricin, a large amount of cell debris was present, and a number of the remaining cells appear to have a clumping or coagulation of cytoplasmic elements, in addition to membrane blistering. The bLfcin contains five arginine and three lysine residues, making it strongly cationic, and lacks detectable carbohydrates; in addition, a number of tryptophane and phenylalanine aromatic residues are present. The two cysteine residues of bLfcin form a disulphide bond, generating an almost completely cyclical peptide, but this disulphide bridge in not required for the antimicrobial potency Fig. (**3**) [44]. Studies focussed on the Trp residues role have shown that they are crucial for the antimicrobial activity [45]. The anchoring properties of Trp, as have been observed in membrane proteins and are believed to be important for the interaction of Trp containing antibacterial peptides with bacterial cell membranes. The aromatic hydrocarbon residues are able to position themselves deeper into the bacterial cell membrane, making the peptide more efficient in disrupting the bacterial cell membrane. A comparison between bLfcin and hLfcin, the last one containing only one Trp instead of two, reveals that there is a "Trp effect", essential in enhancing the antimicrobial effectiveness [46]: it has been reported in fact that a substitution of Trp with Ala dramatically decreases antimicrobial potency [47].

The peptides derived from the N-terminal region of Lf are also reported to have further biological activity. Some of these peptides have been obtained through enzymatic digestion with enzymes, while others have been synthesized. Two peptides (residues 39 to 42 and residues 20 to 37 of human Lf) have antithrombotic properties [48]; while the first 14 N-terminal residues affect the protein hepatic uptake [49]. Fluorescent probes and peptide synthesis have allowed to identify a neutrophil-binding region on the N terminus of human Lf (residues 4 to 52) [50]. These studies highlight the importance of Lf N-terminal region for biological functions which do not involve directly the iron binding. The N1-domain

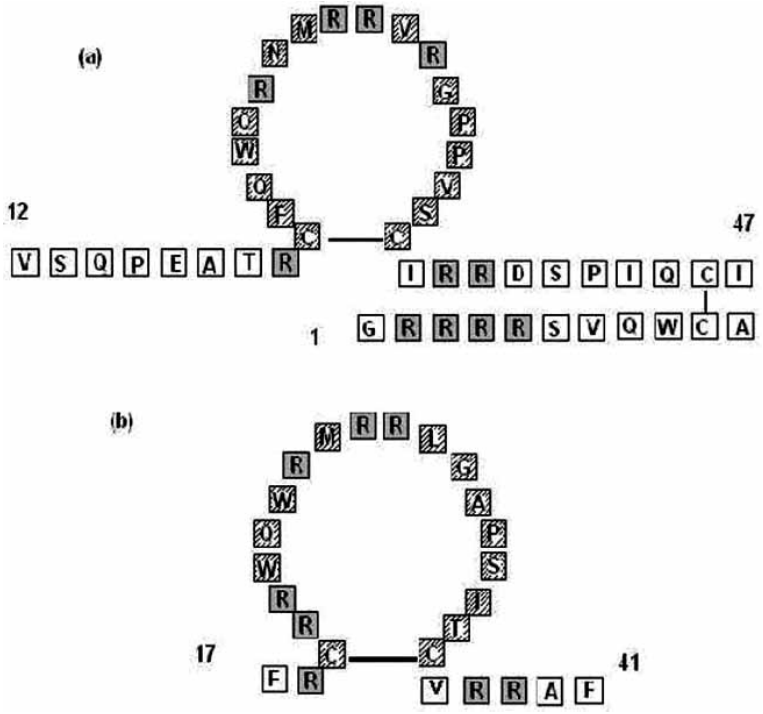

Fig. (3). Human (**a**) and bovin lactoferrin (**b**) sequences (adapted from Brock JH, The physiology of lactoferrin, Biochem. Cell. Biol., 80,1-6, 2002). Human lactoferricin (hLfcin) with 47 amino acids corresponding to residues 1 to 47 of hLf and bovine Lf (bLfcin) containing 25 amino acids corresponding to residues 17 to 41 of bLf. The figure shows the loops and the disulfide bonds (two in the hLfcin and one in bLfcin). The positive residues are in grey; the numbers correspond to the parental mature protein positions.

contains a second stretch, besides lactoferricin, designated lactoferrampin (Lfampin), with some characteristic similar to antimicrobial peptides, i.e. the presence of positively charged residues, as well as an hydrophobic domain which contains tryptophan, a residue that is involved in membrane insertion [51]. Lfampin has no hemolytic activity at antimicrobial working concentrations.

The bactericidal activity of LFampin is different from that of bLfcin 17–30: this probably reflects the fact that both peptides, although sharing amphipathic and cationic features, have a strikingly different amino acid composition and length and therefore their structure differ a lot. Of more importance, physiologically, is the localization of LFampin within the native molecule. The presence of LFampin close to lactoferricin gives bLF two amphipathic and cationic stretches within one domain of the molecule; this domain allows the protein to bind to the membrane interface and might execute its killing activity as a result of a disturbance of the membrane integrity [52].

Several peptides have been synthesized and studied for future clinical trials (Table **2**). For example, kaliocin-1 is a 31-residue synthetic peptide which has shown antimicrobial activity. Moreover, it has been determined the conformation of the octapeptide FSASCVPG by two dimensional NMR spectroscopy [53]. Marieke *et al.* investigated Lfampin 265-284, Lfampin 268–284 and Lfcin 17-30 peptide translocation and ultrastructural effects on the cell membranes of *Candida albicans* and *Escherichia coli*. These peptides were translated across the membrane and they have effects on the plasma membrane integrity; the effects on the *E. coli* membranes showed gradual differences in severity, corresponding to the killing activity; Lfcin 17-30 had the highest effect [54].

3.4. Use of Lf Derived Peptides in the Tumoral Therapy

Because the concentration of Lf in human colostrum is particularly high, it is thought that orally ingested Lf may be able to interact with epithelial cells and immune cells in the mucosa of the intestine: in fact, ingested Lf is reported to stimulate cytokine production [55] and enhance mucosal immunity [56], NK cell and LAK activities [57], neutrophil activity [58, 59], and macrophage cytotoxicity [60]. Previously it has been found that the pro-inflammatory cytokine interleukin-18 (IL-18) is produced by epithelial cells of the small intestine following administration of bLf [56]. IL-18 enhances Th1 type T and NK cell responses and generates CD8+T cells [61].

Lactoferrin inhibits cell proliferation and suppresses tumor growth *in vivo*. One important factor in the control of tumour progression is the cell cycle, controlled by various cyclin proteins, sequential activation of various cyclin-dependent kinases (Cdks) and inhibition of Cdks activity by

Table 2. Some Synthesized Lactoferrin Peptides

Name (Position)	Residues	Sequence	Net Charge	Ref.
Kaliocin-1 (152-182) h*	31	FFSASCVPGADKGQFPNLCRLCAGTGENKCA	+1	[53]
Lfcin (17-30) b**	14	FKCRRWQWRMKKLG	+6	[54]
Lfampin (268-284) b**	17	WKLLSKAQEKFGKNKSR	+5	[52]
Lfampin (265-284) b**	20	DLIWKLLSKAQEKFGKNKSR	+2	[54]
Lfampin (269-285) h*	17	WNLLRQAQEKFGKDKSP	+2	[77]

*; human; **; bovine.

cyclin-dependent kinase inhibitors (CdkI). This cell cycle control system breaks down in tumor cells. Studies *in vitro*, demonstrated that treatment of breast carcinoma cells MDA-MB-231 with human lactoferrin induces growth arrest at the G1 to S transition of the cell cycle. This G1 arrest is associated with a dramatic decrease of Cdk2 and cyclin E protein levels, correlated with an inhibition of the Cdk2 kinase activity. Cdk4 activity is also significantly decreased in treated cells and is accompanied by an increased expression of the Cdk inhibitor p21CIP1 [62].

Wolf J.F. *et al.* demonstrated iron-independent Lf-induced dose-dependent cellular inhibition of squamous cell carcinoma cell lines, associated with decreases in cyclin D1 and increases in P19. The Lf also reduces the cellular production of key proinflammatory and prometastatic cytokines.

By depleting mice of lymphocytes, all tumor inhibition was abrogated suggesting that Lf-induced tumor inhibition is the result of immunomodulation [63].

The Lf is also involved in the cell cycle control through retinoblastoma protein (Rb)-mediated growth arrest in several cell lines. It induces the expression of Rb, a signal mediator of cell cycle control, and most of this Lf-induced Rb persists in a hypophosphorylated form. In addition, the Lf specifically increases the level of a cyclin-dependent kinase inhibitor, p21, but not p27 [64].

Several types of tumoral cells have negative headgroups on the outer leaflet of the membranes, whereas in normal eukaryotic cells the amino phospholipids are present only on the inner leaflet of the membrane. Thus since both bacterial and cancer cells have net negatively charged membranes could offer an explanation for antitumoral properties of Lf and its derived peptides, such as Lfcin. By means of solid-state NMR spectroscopy it has been studied the interaction of bLfcin with acidic phospholipid bilayers as a mimic of cell membrane of *Staphylococcus aureus* and the experimental results suggest the formation of pores in the acidic phospholipid bilayers [65]. The net negative charge that is conferred upon many cancer cells as a result of differential branching and sialic acid content of N-linked glycans associated with transmembrane glycoproteins [66], as well as the elevated cell surface expression of anionic molecules such as phosphatidylserine [67] and *O*-glycosylated mucins [68], is believed to promote electrostatic interactions with bLfcin at the cell surface [13]. bLfcin interacts with various types of tumoral cells as well as the Jurkat T-leukemia cells: it is known that bLfcin binds the Jurkat T-leukemia cell membranes inducing a progressive permeabilization and then causes apoptosis. This peptide enters the cytoplasm of Jurkat T-leukemia cells prior to the onset of mitochondrial depolarization and it was not internalized by endocytosis. The liposome drug delivery systems has played a significant role in formulation of potent drugs to improve therapeutics. Given the evidence that bLfcin disrupted the cell membrane integrity of Jurkat T-leukemia cells and then entered the cytoplasmic compartment, it was of interest to determine whether direct delivery of bLfcin to the cytoplasmic compartment of Jurkat T-leukemia cells in the absence of bLfcin-induced membrane damage would also result in cell death. Collectively, these findings show that intracellular bLfcin is able to induce apoptosis in the absence of damage of the cytoplasmic membrane of neoplastic and untransformed cells [69]. bLfcin is a potent inducer of apoptosis in human cancer cell lines of hematopoietic and epithelial origin, including leukemia and carcinoma of the colon and ovaries [70]. bLfcin-induced apoptosis results from reactive oxygen species and caspase-2-dependent disruption of mitochondrial membrane integrity and the subsequent sequential activation of caspase-9 and caspase-3.

Activation of c-Jun N-terminal kinase/stress activated protein kinase (JNK/SAPK) may also play an important role in bLfcin induced apoptosis in human cancer cells since exposure to pepsin-digested bovine lactoferrin causes JNK/SAPK activation in the human oral squamous cell carcinoma cell line SAS [71]. bLfcin interacts also with the tumor-associated vascular endothelial cells *in vivo* and it interferes with the interaction of the heparin-binding growth factors bFGF and $VEGF_{165}$ with their receptors on the surface of endothelial cells. This peptide decreases the endothelial cell

proliferation and migration and, finally, diminishes the angiogenesis [72]. bLfcin was tested also in a panel of human neuroblastoma cell lines and it induced rapid destabilization of the cytoplasmic membrane and formation of membrane blebs; depolarization of the mitochondria membranes and irreversible changes in the mitochondria morphology were also evident [73]. Moreover it has been found that bLfcin has an high cytotoxic activity against HL-60 cells, in fact it may kill cancer cells by activating an apoptosis-inducing pathway [74].

4. SUMMARY AND CONCLUSIONS

In the wide panorama of AMPs, a prominent position is occupied by lactoferrin derived peptides. This position depends on several factors such as: 1) they derive from easily available parent molecule; 2) the native molecule posses itself the ability to prevent, by iron capture, the bacterial growth; 3) they are produced by enzyme cleavage and 4) they have also antiviral, antifungal and antitumoral activities.

For these reasons, together with the large availability of Lf and thus the possibility to obtain other derivative peptides that may be even more active, these compounds are an attractive model as new antibacterial tools. They also have the advantage, respect conventional antibiotic molecules, since they lack either side effects and/or resistance phenomena, present with conventional drugs induced, for example, by massive antibiotic use in hospital infections [75, 76].

ABBREVIATIONS

AMPs	=	Antimicrobial peptides
bLfcin	=	Bovine-lactoferricin
CL	=	Cardiolipin
hLfcin	=	Human lactoferricin
Lfampin	=	Lactoferrampin
Lf	=	Lactoferrin
LPS	=	Lipopolysaccharide
PG	=	Phosphatidylglycerol.

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