Research News

Recent Advances in Antimicrobial Dendrimers

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Recent progress in antimicrobial dendrimers is reviewed. Both specific interactions and non-specific interactions can be utilized to design multifunctional (polyvalent) antimicrobial agents, which might be more potent than their mono-functional counterparts. Dendrimers or hyperbranched polymers can also be used to design novel drug delivery systems.

1. Introduction

Dendrimers are novel highly-branched three-dimensional macromolecules that emanate from a central core. The advent of dendrimers represents a major breakthrough in synthetic chemistry. Dendrimers can be tailored to generate uniform or discrete functionalities and possess tunable inner cavities, surface moieties, sizes, molecular weights, and solvent interactions. There are many active research programs targeting the synthesis and applications of these novel aesthetic molecules. This article will primarily focus on some of the recent advances in antimicrobial dendrimers. Interested readers can refer to several recent comprehensive reviews on broad issues concerning dendrimers and their applications.

Dendrimers can usually be synthesized by either a convergent or a divergent approach. In the divergent approach, the growth of dendrimers starts from a multi-functional core. Through a series of reaction and purification steps, the dendrimers grow radially outwards. Figure 1 shows a scheme for the divergent approach. At different stages of the synthesis, dendrimers are identified by generations. As the generation increases, the number of functional groups, the size of the dendrimer, and the molecular weight of the dendrimer increase. At a certain stage of the synthesis, steric hindrance prevents one from achieving the perfect structure, where the highest generation is synthesized. Most of the commercially available dendrimers, such as the polyamidoamine (PAMAM) dendrimers from Dendritech Inc. (Midland, MI, USA) and polypropylene imine (PPI) dendrimers from DSM (Geleen, Netherlands) are synthesized by the divergent approach. In the convergent approach, dendrons, as parts of dendrimers, are synthesized according to the convergent approach and these dendrons are then coupled to a multifunctional core. The advantage of the convergent approach is that the chemistry of each dendron can be different and distinct functional groups can be integrated into the dendrimers at precise sites. Due to the repetitive nature of the dendrimer synthesis and excessive purification required to achieve the perfect structure, dendrimers are very expensive and not readily available. Architecturally similar to dendrimers, hyperbranched polymers can be prepared using a one-pot synthesis, so they are typically polydisperse, structurally imperfect, and better positioned for industrial applications.

Because of their compact structure and the availability of many end groups, dendrimers have attracted attention as possible antimicrobial agents. Both specific and nonspecific interaction can be utilized to design novel antimicrobials. If one of the functional groups is able to interact with the target, all the other groups are in such close vicinity that one might hope for synergies or cooperative interactions. If specific interactions are used, the dendritic structure might offer another advantage due to its inherent polyvalent nature. Polyvalent interactions appear frequently throughout biology. For example, the attachment of an influenza virus to a target cell occurs via multiple simultaneous interactions between the hemagglutinin of the virus and the sialic acid
component of the cell wall. The attachment of the virus to
the cell is the first and necessary step for virus invasion. If a
polyvalent inhibitor can be designed to bind to the hemag-
glutinin receptors of the virus, infections might be pre-
vented. The design of antimicrobial dendrimers through
both non-specific interactions (such as quaternary ammoo-
nium based dendrimers and dendrimer–silver nanocompos-
ites) and specific interactions (such as oligosaccharide
based dendrimers) is discussed in this article.

The existence of inner cavities in the dendrimers can be
used to design controlled delivery systems, where drug con-
centrations in the body can be modulated as desired. Dendrimers also offer unique opportunities in these appli-
cations since the structure of the dendrimer can be specifi-
cally tuned to the requirements of the delivery system.
Most drugs are very hydrophobic and not very soluble in
water. Therefore, the interior of the dendrimers needs to
be hydrophobic so that a drug can be loaded. The exterior
of the dendrimer, however, usually needs to be hydrophilic
to increase the circulation time in the body. Some dendi-
rmers can also form stable unimolecular micelles, which
have been commonly used for drug delivery systems. Sever-
al examples of dendrimer drug delivery systems are also re-
viewed.

2. Dendrimers with Antibacterial Functional
Groups

As mentioned during the introduction, dendrimers can
offer a high local concentration of functional groups. If one
can functionalize dendrimers with biologically active
groups, one might expect to see the increased potency asso-
icated with the high local concentration; however, the tar-
get for the antimicrobials must be chosen carefully. For
some instances, bulkier dendrimers might not be able to
penetrate the cell membrane barriers and have difficulty
reaching the target site. Generally speaking, biocides im-
mobilized on dendrimers or hyperbranched polymers will
be more effective if the target sites are cell walls and/or cell
membranes.

2.1. Dendrimers with Quaternary Ammonium Groups

Quaternary ammonium compounds (QACs) have been
widely used as disinfectants. They are effective biocidal
agents when they possess an alkyl chain with at least eight
carbon atoms. Although the exact mechanism of their anti-
microbial action is still unclear, it is mostly attributed to
cell membrane disruption, their ability to increase cell per-
meability, and their possible effects on proteins. Dendri-
mers to include dimethyl dodecyl ammonium groups. Fig-
ure 2 shows the structure of these dendrimer biocides. Bio-
luminescence results (Fig. 3) have confirmed that these
dendrimer biocides with 16 QAC groups on the surfaces
are over two orders of magnitude more potent than the
mono-functional counterparts against the Gram-negative
bacteria, Escherichia coli. These biocides are also very ef-
effective against Gram-positive bacteria such as Staphylo-
coccus aureus, which are usually more susceptible to anti-
microbials due to their less complex structure. One advan-
tage of a QAC based dendrimer is its inherently polycationic
structure. This also facilitates the killing process by speed-
ing up the initial adsorption process, disturbing the cell
membranes, and increasing the permeability of cells toward
foreign molecules. The antimicrobial properties of these
novel biocides depend on the dendrimer generation, the
length of the hydrophobic group, and the counter-ion pres-
ten (unpublished results). One can possibly fine-tune the
biocide structure to design a customer biocide for a specific
strain of bacteria.

2.2. Dendrimers with Oligosaccharides

While one approach to eliminate bacterial/viral infec-
tions is to inhibit the growth and kill the microbes, another
approach is to prevent the initial attachment between bac-
teria/viruses and host cells. Such attachment is usually a
prerequisite for colonization of the bacteria and invasion of
3. Dendrimers That Can Deliver Antimicrobial Agents

While it is promising to incorporate antimicrobial groups on the dendrimers and increase their potency, an alternative way is to design dendrimer-based drug delivery systems. Here two sets of examples are described. The principle of the first set is to design novel drug delivery systems based on the unimolecular micellar structure of dendrimers. The dendrimer nanocomposites, the second example, are hard to classify since these structures and the mechanisms of antimicrobial properties are not fully understood. They share some characteristics of both the incorporation of antimicrobial groups and drug delivery systems.

3.1. Dendritic Boxes and Unimolecular Micelles

Antibiotics has been used for decades to combat bacterial infections. Most of the antibiotics are administered systemically. For some diseases or medical situations, systemic administering might not be the optimal choice. For example, patients who suffer from cystic fibrosis are infected by *Pseudomonas aeruginosa* in their lungs. Controlled release of antibiotics near the lung is considered to be more beneficial than systemic administration because of its low side effects.

Only fairly recently have dendrimers been investigated for drug delivery systems. Most of these systems described here are not specifically designed for biomedical applications, but meet some of the requirements of the delivery systems.

Meijer and coworkers first reported the encapsulation of foreign molecules into dendrimers and coined the term “dendritic box” to describe the inner cavity of a dendrimer.[20] Molecules ranging from *p*-nitrophenol (MW 139) to rose bengal (MW 962) were entrapped within the modified polypropylene imine dendrimer and could be selectively released by the chemical removal of the outer shell. Ulrich and coworkers loaded up to 2 % of lidocaine into water-soluble hyperbranched polymers synthesized in their lab.[21] The drug can then be slowly released.

Some dendrimers form unimolecular micelles with enhanced stability over conventional micelles formed by surfactants.[21,22] Conventional micelles are only thermodynamically stable over the critical micelle concentration and break down in vivo due to dilution, while unimolecular micelles from dendrimers are covalently bound and are very stable.

3.2. Dendrimer Nanocomposites

The versatile chemistry of dendrimers can also include metal atoms. The metal can be either an integral part of the dendrimer, such as in the building block, core, or terminal group, or it can associate with the dendrimer through interactions with branching units. These metals can be metal cations, metal salts, metal oxides or even elemental metal. Newkome and coworkers published a recent comprehensive review on dendrimers with metals (metallodendrimers).[23] Some of the metal salts such as silver have been traditionally used as an antimicrobial. Dendrimer nanocomposites, formed by dendrimers and antimicrobial salts, offer a new way to deliver or enhance the antimicrobial properties of these agents. Balough and coworkers have disclosed dendrimer silver nanocomposites for use as antibacterial agents.[24]

4. Conclusion

Dendrimers have made available new opportunities for creating more potent antimicrobial agents for both industrial and biomedical applications. The unique architecture of dendrimers—which offers: a high local concentration of antibiotics has been used for decades to combat bacterial infections. Most of the antibiotics are administered systemically. For some diseases or medical situations, systemic administering might not be the optimal choice. For example, patients who suffer from cystic fibrosis are infected by *Pseudomonas aeruginosa* in their lungs. Controlled release of antibiotics near the lung is considered to be more beneficial than systemic administration because of its low side effects.

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Dendrimers have made available new opportunities for creating more potent antimicrobial agents for both industrial and biomedical applications. The unique architecture of dendrimers—which offers: a high local concentration of
a given functionality; cooperative effects; polyvalent effects; and sometimes polycationic structure—can be utilized to design both effective antimicrobial agents and efficient biocide delivery systems. These recent advances should warrant further investigations to develop both industrial and biomedical applications.