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Coordination Chemistry Reviews
190–192 (1999) 297–308

COORDINATION CHEMISTRY REVIEWS

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Lanthanides—the future drugs?

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Accepted 17 February 1999

Contents

Abstract

Previous studies on the therapeutical application of lanthanides are critically reviewed. The difference in toxicity/activity between Ln and heavy metals is discussed on the basis of their similarity to calcium ion and deviation from it. Experimental results are summarized to show that the appropriate uses of the regulatory effects of Ln would be useful in therapeutical application. The perforation of cell membrane and apoptosis induced by Ln as well as their influence on ROS mediated oxidative damages and on the assembly and stability of

Abbreviations: CaM, calmodulin; cAMP, cyclic adenosine 3′,5′-monophosphate; cit, citrate; DAG,diacylglycerol; 5DS, 5-doxylstearic methyl ester; IP3, inositol triphosphate; lac, lactate; Ln, lanthanides; MBD, metal based drugs; ROS, reactive oxygen species; GTP, guanosine triphosphate; PDE, phosphodiesterase; PI, phosphatidylinositol; PKA, protein kinase A.

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PII: S0010-8545(99)00072-7

cytoskeleton are discussed as the potential pharmacological action. A perspective of the integrated application of related bioactivities is shown in relation to their uses in anticancer treatment.

Keywords: Lanthanides; Drugs; Pharmacological actions

1. Retrospect of the first round exploration

Exploring the medical use of lanthanides (Ln) once attracted quite a lot of researchers [1,2]. However, the first round exploration was not successful, because of the neglect of the difference in biological behavior between Ln and the heavy metals, such as mercury, gold, platinum, lead, etc. Since most of the previous work merely followed the conventional approach for the study of heavy metal-based-drugs (MBD), they fell into a strategic dilemma.

1.1. The undue emphasis on their toxicity

Generally, the activity/toxicity relation is the inherent contradiction for heavy metals, but the basis of Ln's toxicity is essentially different from that of heavy metals.

Based on an analogy principle [3], the toxicity of a nonessential metal ion, such as Ln^{3+} is determined by its *degree of deviation* from the relevant essential ion as the reference, e.g. Ca^{2+}. The deviation spans the whole range from similarity to dissimilarity with respect to Ca^{2+}. Among the factors determining how far the metal ion deviates from Ca^{2+}, softness, covalence and redox tendency are the most decisive. The high toxicity of most heavy metals is mainly due to a strong deviation in these aspects. Their toxicity is thus inherent and hardly avoided. On the contrary, the lanthanide ions are very close to Ca^{2+} in these aspects. Their adverse effects originate from their deviation in charge, radii and 4f orbital involvement.

These deviations cause minor adverse effects and the effects are related to the effective concentration of Ln^{3+}. Formerly, the growth-dose dependence of a toxic element was described with the right shoulder of the bell-shaped curve for an essential element (Fig. 1(a)).

In this situation a toxic element inhibits growth in the whole concentration range. Later on, radioactivity was found to stimulate the growth in very low dose. Since then, the so-called *hormesis*[1] effect was observed in many toxic compounds. Considering this effect, the growth-dose dependence was better described by curve Fig. 1(b). Recently, the hormesis effect was found in Ln biology [3]. The lanthanides promote growth in very low concentration, but become inhibitory at a higher concentration. Their activity/toxicity can be switched by controlling the effective concentration of Ln^{3+}.

[1] Hormesis: the growth-stimulating effect of the toxic agents in very low dose.

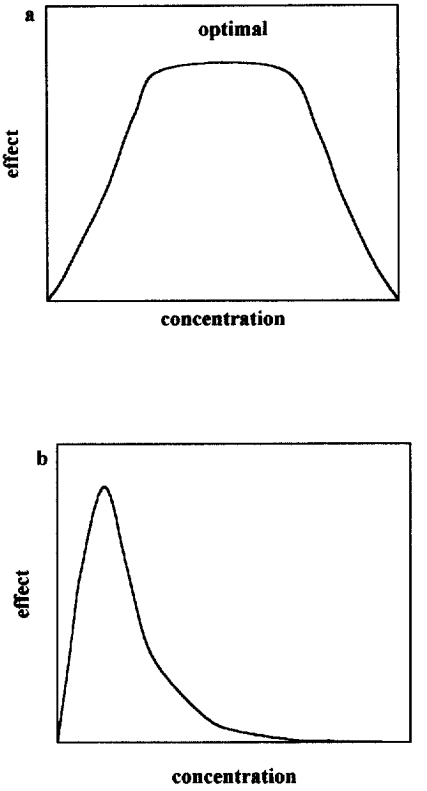


Fig. 1. The growth-dose dependence: (a) essential elements; (b) non-essential or toxic elements.

1.2. Inadequate understanding and utilization of biological effects

Earlier researchers attempted to use the Ln's negative effects to interrupt the biological functions or to kill microbes or cancer cells as they used to do for MBD development. In fact, the outstanding biological effects of Ln are their regulatory

Table 1
Biological effects of medical significance [1,2]

Promoting growth
Stabilizing the oxyhemoglobin and inducing hemolysis
Hormone-like activity
Promoting hydrolysis of nucleic acids
Bacteriostatic effect
Blocking the nervous signal transmission
Influences on lipid peroxidation
Inducing apoptosis
Stabilizing and destabilizing the cytoskeleton

actions, which originate mainly from the Ca^{2+}-analogy (Table 1). It is more rational to use the Ln for regulation, not for killing and damaging.

Furthermore, these regulatory effects are interlinked on the basis of Ca-like activity. It is possible to integrate several effects to a comprehensive pharmacological action.

2. Novel biological effects of medical significance

2.1. Lanthanide induced perforation of the cell membranes

In gene recombination, a critical step is to promote the transformation of the plasmid in bacteria by incubation with $CaCl_2$ [4]. The elevation in permeability induced by Ca^{2+} is discussed in terms of the perforation mechanism. From the standpoint of drug researchers, it will be a desirable way to enhance the across-membrane secretion of endogenous biofactors and the uptake of drug molecules. However, this requires a mM level of Ca^{2+}, which is hardly established in the cellular environment and, even though it could be done, it would be harmful to the host cells. Recently, we found that Ln^{3+} can perforate the membrane in a very low concentration. Huang et al. [5] reported that Y^{3+} and La^{3+} enhance the transformation of plasmid pBR322 and PUC18 in *E. coli* as do the calcium ions. The highest transformation can be achieved by concentrations as low as 10^{-5} M, but a higher concentration will inhibit the plasmid transformation. Canada et al. [6] reported that Tb^{3+} can increase the intracellular accumulation of cisplatin. This fact indirectly supports the permeability increase by Ln^{3+}. To clarify the mechanism of perforation, we followed the outward leaking of hemoglobin from human erythrocytes in the presence of various Ln^{3+}. Firstly, we found that only positively charged species, especially the free Ln^{3+} are effective [7]. The kinetic studies showed that the Ln^{3+}-erythrocyte interaction is a triphasic process. Perforation happens in the second stage, as indicated by the linear increase of hemoglobin concentration outside the cells, but the cells still keep their integrity. This stage is characterized by *sustainable* and *recoverable* hemolysis (Fig. 2), e.g. the hemolysis keeps on after the cells were washed and moved to a Ln-free medium, but EDTA washing can reseal the pores, perhaps by removing the lanthanides [8]. These results indicate that the Ln^{3+} are bound to the cell surface, perhaps by electrostatic interaction, and work there to induce pore formation, but they are easily removed by EDTA.

By means of atomic force microscopy (AFM) [9], we found that the 'pores' actually fall into two categories, *domains* and *crater-shaped pores*, depending on the effective concentration of Ln^{3+}. A concentration of 1.0×10^{-5} M of Gd^{3+} and 30 min incubation resulted in crater-shaped pore formation, while a lower concentration, including the Gd-EDTA or Gd-citrate complex systems, leads to domain structure, as shown in Fig. 3. The domain structure is mainly related to the coexistence of a bilayer phase and a hexagonal phase. A partial phase transition of lipid-bilayer to hexagonal was indicated by ^{31}P-NMR for the liposome [10] and

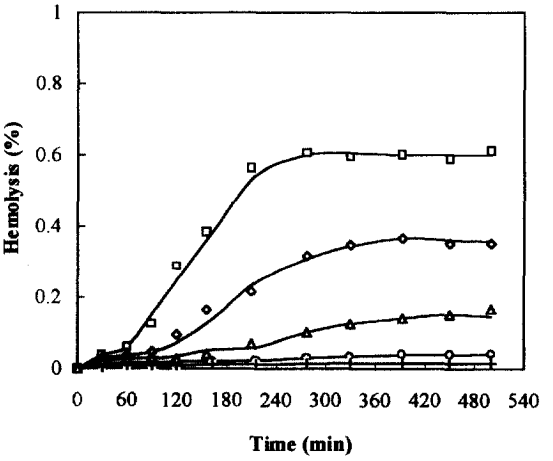


Fig. 2. The effect of Gd^{3+} ions on the hemolysis of erythrocytes as a function of both concentration and incubation time. $GdCl_3$ concentrations: □, 1.0×10^{-4} mol l^{-1}; ◇, 6.0×10^{-5} mol l^{-1}; △, 1.0×10^{-5} mol l^{-1}; ○, 1.0×10^{-6} mol l^{-1}; +, 1×10^{-7} mol l^{-1}).

erythrocyte membrane. Seelig reported that La^{3+} binding to the protein-free lipid bilayer caused a similar domain structure [11]. The crater-shaped pore is likely formed by stacking a number of protein particles ($\sim 10^2$ nm diameter) around a 'hole'. After Ln-binding, the membrane proteins are subject to conformation changes and aggregation, as indicated by FT-IR and fluorescence studies. EDTA treatment can reseal the crater-shaped pores, but the domain structure remained.

In summary, Ln binding and the subsequent phase-transition of lipid bilayer attribute to the domain formation, while the additional conformation changes and aggregation of proteins lead to crater-shaped pore formation. The formation of domains or crater-like pores depends on the effective concentration of Ln^{3+}. Therefore, with a well-designed pM buffer to keep Ln^{3+} in an appropriate concentration, the perforation can be controlled.

2.2. Lanthanide as scavengers of reactive oxygen species (ROS)

ROS, mainly the oxygen-derived free radicals and peroxides are the mediators of a series of degenerative diseases. The ROS scavengers, or *antioxidants*, have been studied as drug candidates to inhibit the development of a series of diseases. The antioxidants of current interest are mostly organic compounds, such as tocopherol, ascorbate, etc. The Ln's antioxidant activity was reported several years ago, but the conclusions are controversial. Wu et al. [12] reported that Ln inhibit the silica induced lipid peroxidation of lung macrophages. Later, $SmCl_3$ and $PrCl_3$ (0.05 mg kg^{-1} body weight, i.p.) were shown to inhibit lipid peroxidation in rat lung, but a higher dose (0.28 mmol kg^{-1} body weight (day, i.p. 3 day) of $LaCl_3$ instead promotes the peroxidation. No significant effect was observed for $TbCl_3$ [13]. We try to clarify the underlying mechanism and interpret the difference in conclusions.

Ln^{3+} binding to peroxides is one of the possible mechanisms. We found that all the Ln^{3+} inhibit H_2O_2-mediated peroxidation of liposome and 'ghosts'. Although the most efficient one is Ce^{3+}, the inhibition cannot be explained on the basis of the redox chemistry of cerium. If *t*-butyl hydroperoxide was used to mediate the peroxidation, light Ln inhibit and heavy Ln promote [14]. Other than this, we found all Ln inhibit H_2O_2-mediated peroxidation when the cells were incubated with Ln^{3+} and H_2O_2, but they enhance the peroxidation if the cells were pretreated with Ln. Therefore, the active species would be the free Ln^{3+}. They lost their

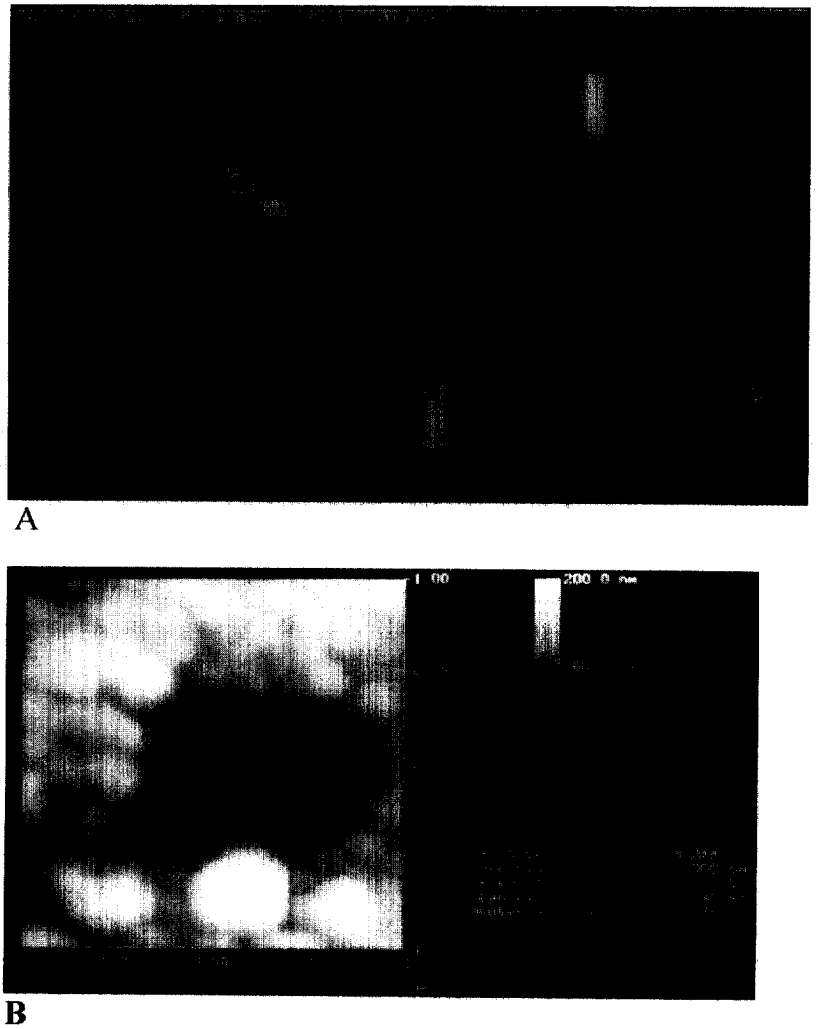
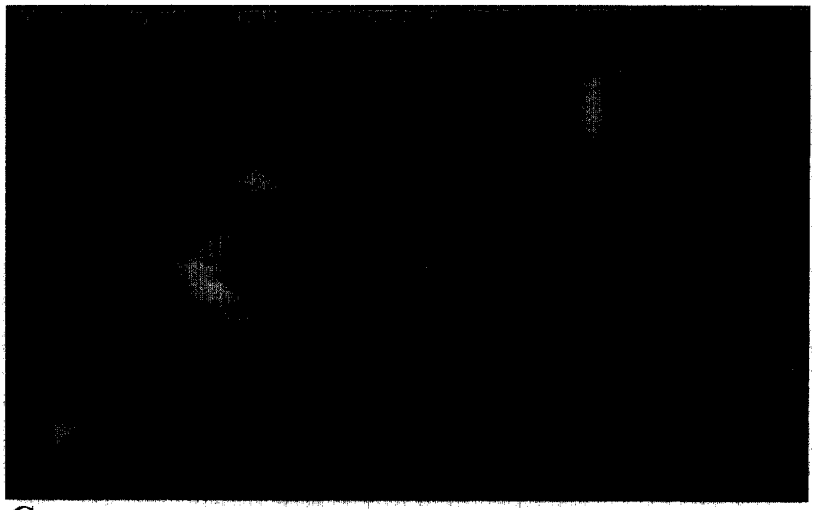


Fig. 3. AFM images of the fine structure of local areas on the surface of rat erythrocytes. Scan-sizes: 1.0×1.0 μm^2; normal erythrocyte (A) and the cells incubated with medium containing 1.0×10^{-5} mol l^{-1} Gd^{3+} (B) and 1.0×10^{-6} mol l^{-1} Gd^{3+} (C).



C

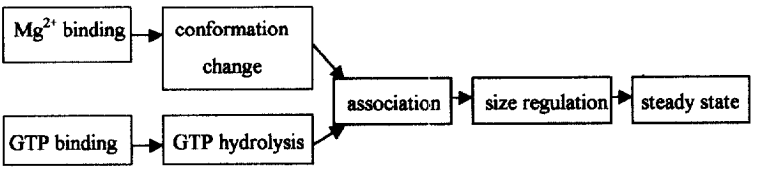
Fig. 3. (*Continued*)

reactivity to peroxides when they are bound to the membrane. In addition, the prior Ln-binding disturbs the orderly assembly of the membrane, which becomes more sensitive to the oxidative attack.

Free radical *masking* might be another mechanism. As reported by Ji et al. [15], Ln^{3+} can depress the EPR signals of $^{\bullet}OH$ and $^{\bullet}O_2^-$, but the mechanism is not clear. The reactions of free radicals with Ln^{3+} have been discussed in terms of the tendencies for coordination (Benelli et al. [16]) and electron transfer (Matko et al. [17]). The results given in Table 2 strongly support the contribution of magnetic interaction. It is noteworthy that Gd^{3+}, Tb^{3+}, Tm^{3+} and Ce^{3+} quench the EPR signals of 5-doxylstearic methyl ester (5DS) effectively, while La^{3+}, Eu^{3+} and Lu^{3+} (as well as Ca^{2+}, Mg^{2+} and Zn^{2+}) cannot affect them significantly within 60 min [18]. Magnetic dipole–dipole interactions are possible as those suggested by Sarna et al for melanin [19]. The magnitude of the quenching constants K_q varies with g_j and μ_{eff}, but Gd^{3+} stands higher than Tb^{3+}. The anomaly shows that the spin-lattice relaxation time plays an important role, as Leigh discussed [20]. Thus we can only assume that the free radical is *masked*, while the contribution of this interaction to Ln's antioxidative activity is not confirmed.

Table 2
The 5DS EPR signal quenching and magnetic parameters of Ln [19]

	La^{3+}	Ce^{3+}	Gd^{3+}	Tb^{3+}	Tm^{3+}
g_j	0	6/7	2	3/2	7/6
μ_{eff}	0	2.54	7.94	9.7	7.6
K_q/M^{-1}	4.27×10^3	3.85×10^4	1.54×10^5	7.81×10^4	5.31×10^4



Scheme 1. Process of microtubule formation.

Ln^{3+} are different in mechanism from existing organic antioxidants. Most of the organic antioxidants scavenge the free radicals by single electron exchange with the radicals and thus are transformed into radicals themselves. For this sake, they are also *prooxidants*. In clinical practice, this property is a potential risk. In this aspect, Ln cations might be one of the distinguished candidates, since they can interact with the free radicals and peroxides but they cannot become radicals. The Ln^{3+} ions are also different from the metal ions undergoing single electron redox reactions, such as Fe^{2+}. The ferrous ion can be regenerated from its oxidized form and increase the electron-transfer turnover, while Ln are not dangerous in this aspect, except Ce^{3+}.

2.3. *Lanthanides influence the stability of microtubules*

A disorganized cytoskeleton, including microtubules and microfilaments etc., is a typical feature of tumor cells and apoptosized cells. The stabilization and repair of microtubules have been known as one of the mechanism of certain anticancer drugs, such as taxol, while the depolymerization of cytoskeleton is one of the events of the apoptosis process (see below). A few but diverse results on the effect of Lns on the cytoskeleton have been reported. According to Xiao et al. [21], mixed lanthanide chlorides increase the amount and orderliness of microtubules in PAMC82 cells. On the other hand, chemical studies showed that different Ln give entirely different results and the difference was interpreted through their analogy to Ca^{2+} or Mg^{2+}. Mg^{2+} stabilizes and Ca^{2+} destabilizes the microtubules. Gd^{3+} and Nd^{3+} destabilize the microtubules, like Ca^{2+} [22], while Tb^{3+}, like Mg^{2+}, stabilizes them [23]. Soto et al. claimed that this difference is due to the difference in their effect on GTPase activities of tubulin [24]. The microtubule formation in the tubulin-GTP-Mg^{2+} system is a multiple step process as shown in Scheme 1. In the process, Mg^{2+} plays an important role by binding to tubulin and modulates the conformation to that required for self-association of tubulin.

For association, GTP binding to tubulin and GTP hydrolysis are essential and the hydrolysis is also under the control of the magnesium ion. After the association begins, a size regulating step proceeds to modulate the size and shape of microtubules. The size regulation takes an oscillatory mode until a steady state is reached. By measuring the turbidity change to follow the whole process, the effect of Ln in each stage can be observed. As shown in Fig. 4 [25], the turbidity-time curve of normal microtubule formation is featured by four steps:

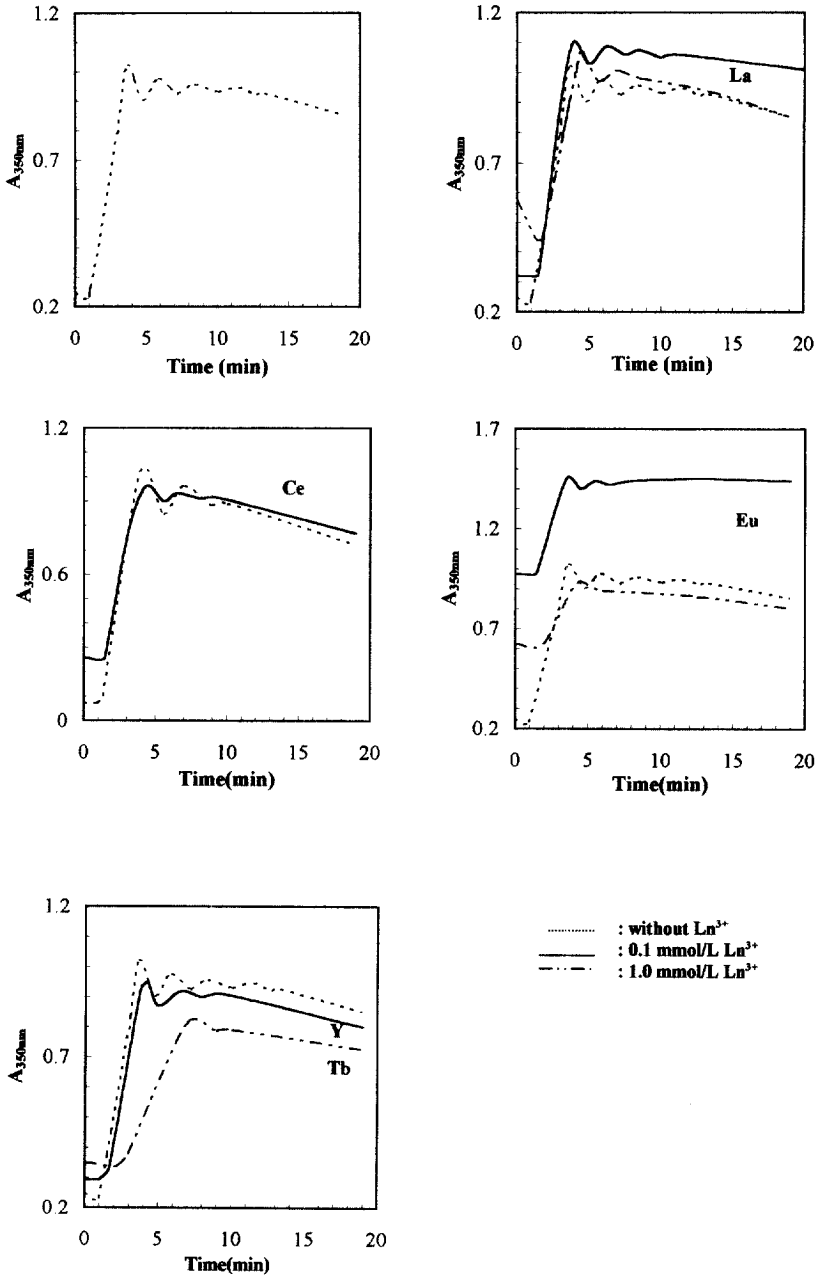


Fig. 4. The oscillation in turbidity during association of tubulin and the influence of lanthanides (La^{3+}, Ce^{3+}, Eu^{3+}, Tb^{3+} and Y^{3+}). The self-association was induced by mixing 300 μl tubulin solution (10 mg ml^{-1}) with polymerizing buffer (pH 8.6) containing GTP and MgCl and switching the temperature from 0 to 37°C. Turbidity was followed by measuring absorbance at 350 nm. Lanthanide chlorides were added to the buffer.

1. *Induction*. This reflects the pre-polymerization states and is characterized by the initial turbidity and the time lag before association starts.
2. *Association*. This rate is characterized by the slope of change in turbidity.
3. *Size regulation*. This is characterized by the turbidity oscillation, its number, period and amplitude.
4. *Disassembly*. This rate is characterized by the negative slope.

From the results given in Fig. 4, La^{3+} supports the whole process in low concentration. Ce^{3+} destabilizes the microtubules, but no effect was displayed on the polymerization. The other Ln^{3+} retard the polymerization and destabilize the microtubule even at low concentration. In higher concentration, all the Ln^{3+} ions cause destabilization. In all cases, high initial and final turbidity values indicate the crosslinking and aggregation and the depressed oscillation indicate the retarded and interfered microtubule assembly.

In summary, in low concentration, several lanthanide ions regulate microtubule formation as does Mg^{2+}. A higher concentration of lanthanides interferes with the assembly by distorting the conformation of protein, crosslinking and destabilizing the polymers.

2.4. Lanthanide induced apoptosis[2]

Anticancer agents kill tumor cells and inhibit tumor growth by two different ways: *necrosis* or *apoptosis*. Earlier studies on the cell level and animal tests indicated that a high dose of Ln^{3+} kills the cells by the cytotoxic behavior or the damaging effect. Recently, Mizgerd reported that Gd^{3+} induces apoptosis of incubated macrophagocytes of rat teeth [26]. By a study on rat skin fibroblasts, Zhang et al. found that $CeCl_3$ and $GdCl_3$ (10^{-5} M) induce apoptosis with a positive dose dependence [27].

The molecular mechanism of apoptosis is not very clear now, but the increased intracellular Ca^{2+} concentration is known to play an important role, because it activate the endonucleases and protein kinases, and mediates DNA cleavage and apoptosis-related gene expressions respectively. The possible pathways leading to Ln induced apoptosis might be summarized as Scheme 2.

Although we cannot lay out the whole picture to describe how a lanthanide ion induces cell apoptosis, there are several links related to Ln actions. Firstly, Ln can increase the intracellular Ca^{2+} level by increasing the Ca influx [28]. They can also promote the hydrolysis of phosphatidylinositol, giving the messengers, diacylglycerol (DAG) and inositol triphosphate (IP_3) [29]. Certain Ln^{3+}, such as Tb^{3+} in higher concentration can also increase the level of the cAMP concentration and then the PKA activity by inhibiting calmodulin and diphosphatase activity [30]. It is now accepted that PKA is an important clue leading to apoptosis. On the other hand, in higher concentration, Ln^{3+} can decrease the concentration of cAMP by promoting the hydrolysis of the cyclic phosphate bond of nucleoside monophos-

[2] Apoptosis: a category of cell death, triggered by exogenous agents, proceeds by a specific program leading to DNA degradation.

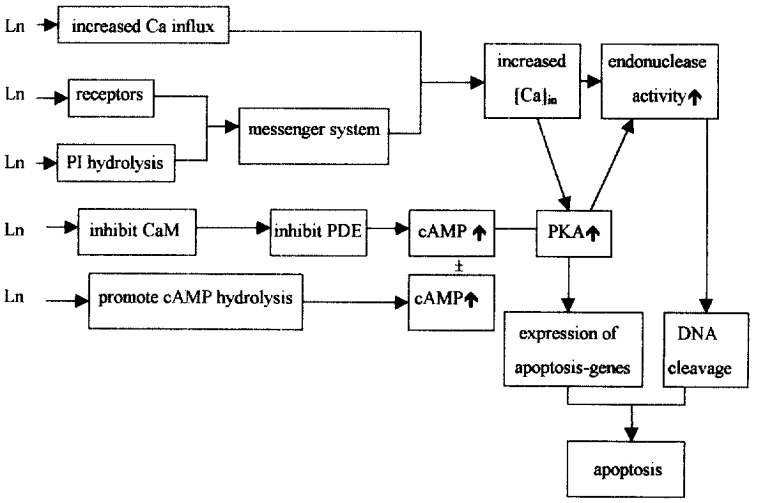
phates [31]. For the Ln induced expression of apoptosis-related genes, Xiao et al. showed that incubation of the PAMC82 cell with $LaCl_3$ or $CeCl_3$ enhanced the expression of p53 as well as of p16 (MTS1) and p21 (WAF1) [21].

3. The perspective for integrated pharmacological activities of Ln

The cells respond to the attacking metal ions as a multiple-target system, in which various reactions with various targets are organized to a sequence of events. The ultimate biological effect is actually the integrated effect of these events.

The events that happen when Ln ions attack a cancer cell and finally induce apoptosis might be considered as the core of their potential anticancer activity. Along with the apoptosis, there are several synergic related effects: ROS scavenging, cell protection, cytoskeleton stabilization and also immunologic enhancement. It is, perhaps, unique that the lanthanide affects the cancer cells by an integrated mode. Especially, the working concentration is very low.

Nonetheless, researchers worried about the risk in this idea. Since it was well established that the Ln strongly promote cell proliferation, could the Ln promote tumor growth? Indeed, are the Ln harmful to the normal cells while they kill the cancer cells or induce their apoptosis? It has long been known that the Ln selectively accumulate in the tumor tissues, but it does not mean that they can selectively affect the cancer cells. Nie [32] and Ji [33] found with different cell lines, an appropriate dose may inhibit the cancer cells without significant influence on the normal cells. Other than this, $CeCl_3$ and $NdCl_3$ incubation decreases the CaM level in the cancer cell K562, but increases that in the normal human FL [33]. We cannot say that there is any selectivity to cancer cells, but it is possible.



Scheme 2. The possible pathways leading to Ln induced apoptosis.

Acknowledgements

This work has been supported by State Commission of Science and Technology and National Natural Science Foundation of China. We thank Professors J.Z. Ni and Y.X. Nie for their suggestions and comments.

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