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MiniReview

Interaction of viral proteins with metal ions: role in maintaining the structure and functions of viruses

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Abstract

Metal ions are integral part of some viral proteins and play an important role in their survival and pathogenesis. Zinc, magnesium and copper are the commonest metal ion that binds with viral proteins. Metal ions participate in maturation of genomic RNA, activation and catalytic mechanisms, reverse transcription, initial integration process and protection of newly synthesized DNA, inhibition of proton translocation (M2 protein), minus- and plus-strand transfer, enhance nucleic acid annealing, activation of transcription, integration of viral DNA into specific sites and act as a chaperone of nucleic acid. Metal ions are also required for nucleocapsid protein-transactivation response (TAR)–RNA interactions. In certain situations more than one metal ion is required e.g. RNA cleavage by RNase H. This review underscores the importance of metal ions in the survival and pathogenesis of a large group of viruses and studies on structural basis for metal binding should prove useful in the early design and development of viral inhibitors.

Keywords: Viral protein; Virus; Nucleoprotein; Metal; Metalloprotein; Zinc

1. Introduction

Among the many roles of metal ions in biological processes are bridging distant residues or domains of proteins, mediating interactions between proteins and ligands, and serving in the active site as a nucleophilic catalyst and in transfer of electron. Biological processes are often metal ion specific, although more than one metal ion can play each of these roles. For example the coagulation cascade is Ca^{2+} specific, protein biosynthesis is primarily Mg^{2+} specific, several enzymes are Zn^{2+} ion specific and oxidative processes are often iron specific. The conformational changes induced by binding a metal ion are remarkable. Residue side chains, which are greater than 20 Å apart in the metal ion-free structure, may become constituents of the metal ion-binding site [1,2]. A number of trace metals are essential micronutrients and their deficiency and infectious diseases often coexist and exhibit complex interactions. Several trace metals such as zinc, copper and manganese, etc. influence the susceptibility to, the course and the outcome of a variety of viral infections. Deficiency of trace metals is known to alter the genome of the viruses and the grave consequences of this may be the emergence of new infections [3]. On the other hand some metals like hexavalent chromium may have toxic effects [4,5]. Metals are integral part of several viruses and are known to play an important role in their survival and pathogenesis. This paper briefly reviews the consequences of the interactions of various metal ions with proteins of different viruses. Due to constraint of space only a limited number of studies have been cited.

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1.1. Composition of virion

Viruses are the smallest infectious agents containing only one type of nucleic acid (DNA or RNA) covered by a protein coat, which may be surrounded by a lipid-containing membrane. A virion is composed of viral proteins, nucleic acid, lipids and carbohydrates. The structural proteins of viruses protect the viral genome, participate in attachment of virus to a susceptible cell, facilitate transfer of viral nucleic acid from one host cell to another and are antigenic determinants of the virus. Viral envelopes contain lipids and glycoproteins (gp), the lipids are derived from the host cell while the glycoproteins are virus-encoded. Surface glycoproteins attach the virus to a target cell and are important viral antigens. Viral proteins coded by nonstructural genes are known as nonstructural proteins (NS). Present in the virus-infected cells, these proteins appear to have regulatory roles during replication. To give a few examples, the hepatitis C virus (HCV) genes code for NS2, NS3, NS4A, NS4B, NS5A, and NS5B nonstructural proteins. The mature structural proteins are C, E1 and E2 [6].

1.2. Protein–metal interactions

An interaction between a protein and a metal ion is of different types. Metalloprotein is a generic term for a protein that also contains a metal cofactor. One-third of all proteins are ''metalloproteins''. The metal ions in metalloproteins are critical to the protein's function, structure, or stability and numerous essential biological functions [7]. Understanding and ultimately controlling the binding and activity of protein metal sites are of great biological and medical importance. The functions of metalloproteins having metals that bind with different viral proteins are presented in Table 1.

Three proteins have been identified in mammals, GLABROUS1 (GLI), GLI2, and GLI3, having a highly conserved zinc finger (ZF) domain and function as transcription factors in the vertebrate sonic hedgehog-patched signaling pathway [7]. During evolution some proteins have chosen Mg^{2+} as a natural cofactor. Mg-binding sites appear to be weak and can be replaced by other divalent metals like Zn^{2+}, and in some cases, inhibit enzymatic activity thereby. Therefore, it seems that the cell machinery governs the process of metal binding by regulating appropriate concentrations of Mg^{2+} and Zn^{2+}, etc. in various biological compartments. Zn^{2+} has a higher affinity for a protein ligand and strongly prefers a tetrahedral geometry. Consequently, rigid Zn^{2+}-binding sites appear to be more selective than Mg^{2+}-binding sites, and a protein can generally select Zn^{2+} against the background of a much higher Mg^{2+} concentration [8]. The commonest metal to bind with a virus-protein is zinc. Zinc is the second most abundant trace metal found in eukaryotic organisms, second only to iron. Zinc is required for essential catalytic functions in more than 300 enzymes, stabilization and induction of the folding of protein subdomains. The latter functions include the essential role of zinc in the folding of the DNA-binding domains of eukaryotic transcription factors, including the ZF transcription factors [9]. ZF are small protein domains in which zinc plays a structural role contributing to the stability of the domain and are small DNA-binding peptide motifs. The cysteine-rich zinc-binding motifs known as the RING and B-box are found in several unrelated proteins. ZF are structurally diverse and are present among proteins that perform a broad range of functions in various cellular processes, such as replication and repair, transcription and translation, metabolism and signaling, cell proliferation and apoptosis. ZF typically function as interaction modules and bind to a wide variety of compounds, such as nucleic acids, proteins and small molecules. Three of these fold groups comprise the majority of zinc fingers, namely, C2H2-like finger, treble clef finger and the zinc ribbon [10].

1.3. Binding of metal ions with different virion proteins

Bindings of metal ions with viral proteins and its consequences have been investigated with a number of the

Table 1
Functions of metalloproteins

Metals	Enzyme and protein	
	Classes	Example
Zinc	Transferases, hydrolases, lyases, isomerases, ligases, oxidoreductases, transcription factor	RNA polymerases, alcohol dehydrogenases, glucocorticoid receptor
Copper	Oxidoreductases	Superoxide dismutase, ferroxidase (ceruloplasmin)
Iron	Oxidoreductases	Cytochrome oxodase
Cobalt	Transferases	Haemocysteine methyl-transferases
Manganisium	Oxidoreductases, methyltransferase,	Superoxide dismutase, protoporphyrin
Selenium[a]	Oxidoreductases, transferases	Glutathione peroxidase
Nickel	Oxidoreductases, hydrolases	Urease

Modified from Chaturvedi et al. [3].
[a] It is not a true metal.