Immunoglobulin-like domains on bacteriophage: weapons of modest damage?

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Recent work has shown that Immunoglobulin-like (Ig-like) domains occur frequently on the surface of tailed dsDNA bacteriophages. Several of these Ig-like domains are added to bacteriophage structural proteins via programmed ribosomal frameshifts, and their evolutionary patterns suggest that they can be exchanged by horizontal transfer, independently of the protein to which they are attached. We propose that Ig-like domains on phages interact with carbohydrates on the cell surface and facilitate phage adsorption. Furthermore, Ig-like domains appear to be one of a number of conserved domains displayed on phage surfaces that serve to increase infectivity by binding to or degrading polysaccharides.

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Introduction

The analysis of many bacteriophage genomes has shown that they are highly mosaic because of rampant horizontal transfer of genes between diverse phages infecting a wide variety of bacteria [1,2]. It is becoming clear that the overall mosaicity of phage genomes is often mirrored in individual phage proteins, which may contain multiple horizontally transferred domains. These domains are prevalent in virion proteins in tailed dsDNA phages (*Caudovirales*) and are frequently involved in cell surface carbohydrate binding or degradation. We recently discovered that Ig-like domains are present on the surface of approximately 25% of the members of this class of phage [3••]. These domains, the function of which has not yet been proven, present an excellent case study of how related domains can multiply within diverse phage genomes and attach themselves to proteins possessing a wide range of functions. Phage Ig-like domains, along with the lectin-like domains of *Bordetella* bacteriophage ([4,5] and review in this issue), are demonstrations of an emerging trend in bacteriophage genomics: bacteriophages use novel genetic strategies to increase the structural diversity of their surface proteins to aid in infection. In this paper, we review the current knowledge of phage-borne Ig-like domains and place these domains into the context of other conserved domains found in *Caudovirales* structural proteins. We also offer speculation on the function and evolution of these domains.

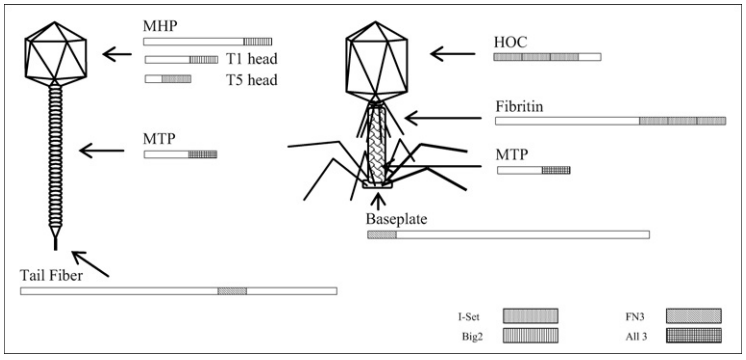
Ig-like domains: a frequent phage surface feature

Although the presence of an Ig-like domain in the phage T4 Hoc protein was first noted in 1996 [6], the widespread occurrence of these domains in the structural proteins of tailed dsDNA phages was not appreciated until our recent study [3••]. The positioning of Ig-like domains in exposed positions on phage surfaces has been demonstrated by several structural studies. For example, the Ig-like domain-containing Hoc protein is highly exposed on the head of phage T4 [7•], and the density corresponding to the C-terminal Ig-like domain of the phi29 Major Head Protein (MHP) was clearly observed to be positioned on the capsid surface of this phage by cryo-electron microscopy [8]. In addition, the C-terminal Ig-like domain of the phage λ Major Tail Protein (MTP) protrudes from the tail tube [9], and the additional domains attached to the C-terminus of this protein can be bound in phage display experiments [10–12]. Particularly intriguing was the recent identification, on the basis of its positioning in the head structure, of a Hoc-like protein on the surface of phage T5 [13•]. This protein, identified as pb10, contains an Ig-like domain 43% identical to T4 Hoc even though there is no sequence similarity between the other regions of these proteins [3••]. Ironically, its possession of an Ig-like domain similar to that found in some tail proteins has led pb10 to be misannotated as a tail protein [3••].

The case for horizontal transfer

Ig-like domains have not been found in any other class of phage except the *Caudovirales* where three distinct families of Ig-like domains (Big2, I-set, and FN3) have been identified. They are found in MHPs, MTPs, and tail fiber proteins in members of the *Siphoviridae* (non-contractile tail) and *Podoviridae* (short tail) families (Figure 1). In *Myoviridae* (contractile tail) they are found in HOC, fibritin, and baseplate proteins. Supporting the hypothesis that these domains have been horizontally transferred, similar Ig-like domains are found in proteins that are unrelated outside the Ig-like domain and that come from completely unrelated phages. For example, the I-Set family Ig-like

Figure 1



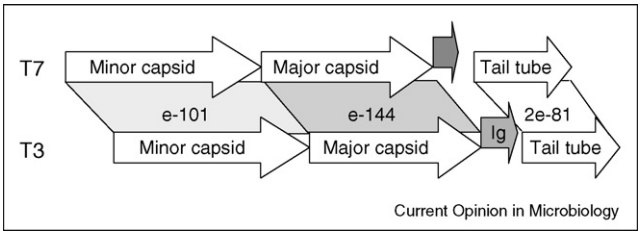
Bacteriophage Ig-like domains are found on a variety of virion proteins. Schematic diagrams of a *Siphovirida* (left) and a *Myovirida* (right) are shown, and the locations of various Ig-like domain-containing proteins are indicated. Ig-like domains are shaded according to their class. Some proteins groups (e.g. MTPs) are found with all three classes of Ig-like domain and this is also indicated.

domain of the *Siphoviridae* phage T5 head protein, pb10, is 46% identical to an Ig-like domain of the *Myoviridae* phage RB43 Fibritin, and 43% identical to the HK97 MTP. In another example, the T7-like *Podoviridae* phiYeO3-12 possesses a Big2 family Ig-like on its MHP that is 43% identical to a Big2 domain in the MHP of the *Siphoviridae* ul36. In this case, similar domains have been transferred to two phages of different classes that infect Gram-negative (*Yersinia enterocolitica*) and Gram-positive (*Lactococcus lactis*) bacteria, respectively. On the contrary, there are also examples of pairs of closely related proteins in which only one has an Ig-like domain. For example, fibritin proteins, which form the 'collar whiskers' required for proper positioning of the long tail fibers during virion morphogenesis of T4-like phages, have similar N-terminal domains but variable C-terminal domains. Phage T4 fibritin has a 30 residue C-terminal domain that is required for assembly and folding of the fibril protein, phage 42 lacks this domain completely, and phages RB42 and RB43 contain three tandem repeats of Ig-like domains instead [14]. It is difficult to explain these patterns of appearance of Ig-like domains except by horizontal transfer. Amazingly, these transfers cross the classes of phages and diverse species of bacteria. We have even been able to identify Ig-like domains in phage infecting photosynthetic marine bacteria, showing their dispersal in diverse environments ([15], JSF, unpublished results). A similar broad and sporadic distribution of FN3 domains in bacterial glycohydrolases has also been attributed to horizontal transfers and domain shuffling [16] (Figure 2).

Frameshifts: Ig-optional

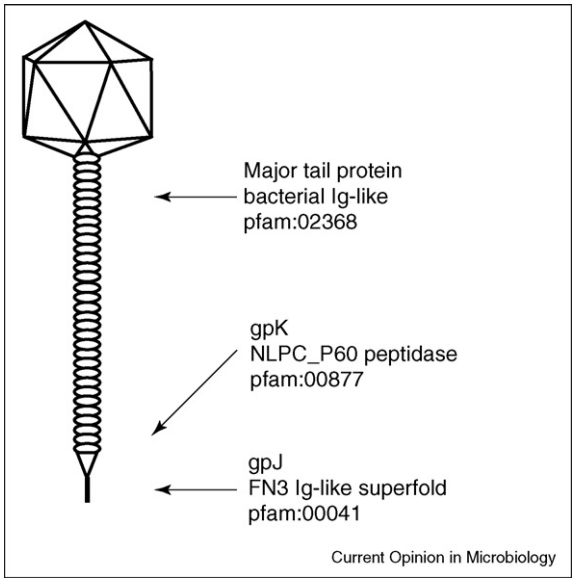
An intriguing and complicating feature of phage Ig-like domains is that a number of them are added to the C-termini of morphogenetic proteins by programmed ribosomal frameshifts. Programmed ribosomal frameshifts occur when the ribosome is forced to switch to an overlapping reading frame and continue translating. Bacteriophage mRNA-bacterial ribosome frameshifts are thought to require slippery sequences of repetitive rare-codon mRNA and downstream mRNA secondary structure elements [17]. Upstream Shine-Dalgarno sequences have also been implicated in prokaryotic frameshifting through ribosome stalling [18]. All three classes of phage Ig-like domains have been identified in frameshifted structural proteins. Five experimentally verified frameshifts are readily identifiable as Ig-like fusions to capsid or tail proteins ([19–22] and Tavares, personal communication) and an additional six Ig-like domains have been proposed to be fused to capsid or tail structural proteins [3••]. The presence of frameshifted and non-frameshifted protein has been shown to be crucial for phage infectivity in some cases. For example, the *Lactobacillus* phage A2 frameshifts a C-terminal Ig-like domain on its MHP, and prophages expressing only the N-terminal domain (head-short) or the frameshift fusion (head-long) are unable to support infection [21]. Interestingly, the MTP of A2 also contains a frameshifted Ig-like domain that shares 42% identity

Figure 2



Genetic organization of the T7 and T3 capsid region. Significant sequence similarity is detected between genes encoding the capsid, major capsid, and tail tube proteins (*E*-values shown in red connecting shading). However, no similarity is detected in the frameshifted region that has fused C-terminal to the major capsid protein. The T7 frameshifted region is 35 amino acids shorter than the T3 region. The tail tube gene starts 66 base pairs away from the end of the fusion protein in T7 and 204 base pairs away from the end of the fusion protein in T3. This raises the possibility that the frameshifted regions may be exchanged independently from the surrounding genes.

Figure 3



Conserved carbohydrate binding or degrading domains on bacteriophage λ.

with the one contained in the MHP, but the functional importance of this domain has not been determined [20]. The phage T3 and T7 MHPs each possesses a domain that is appended by frameshifting. Remarkably, an Ig-like domain is added to the T3 MHP while a different unrelated domain is added to the T7 protein. Aside from the frameshifted areas, the MHPs of these phages are more than 70% identical in amino acid sequence (Figure 3). These data again emphasize the sporadic appearance of Ig-like domains in related phage proteins.

Putative role of Ig-like domains in cell surface binding

The ubiquity of Ig-like domains on the surface of tailed dsDNA phages implies that they provide some selective advantage. However, none of the identified Ig-like domains in phage has yet had a specific function ascribed to it. Indeed, the sporadic occurrence of Ig-like domains on proteins with identical functions suggests that these domains may be dispensable in many cases. The ability of phages λ and T3 to replicate normally in the absence of Ig-like domains in their MTP and MHP, respectively, supports this idea [9,22]. On the contrary, the Ig-like domain in the MHP of phage A2 is essential for growth [21]. We believe that Ig-like domains generally play an accessory role in the infection process, probably by binding to carbohydrates. The support for this hypothesis is as follows: first, Ig-like domains appear to be always on the surface of phage particles, second, Ig-like domains in eukaryotic and prokaryotic cells are most commonly involved in extracellular adhesion processes [16,23,24], and finally, the most closely related bacterial Ig-like domains to those in phage are found in bacterial glycohydrolases, such as chitinases and cellulases. We imagine that Ig-like domains could help to maintain the phage in the vicinity of cell surface by mediating weak, possibly non-specific interactions with carbohydrates on the cell surface, until the correct receptor is contacted. Thus, it would not matter which protein on the cell surface carried

Table 1

Some conserved polysaccharide binding or degrading domains found in phage virion proteins

Domain name	ID[a]	Number[b]	Examples[c]	Known functions[d]
NLPC_P60	PF00877	20	λ gpK phiADH TMP T1 putative minor tail	Cell wall peptidase; peptidoglycan hydrolysis [39]
CHAP	PF05257	63	md2 TMP Sfi21 TMP	Amidase function, proposed to be involved in peptidoglycan hydrolysis [40,41]
SLT	PF01464	52	Sfi19 TMP T7 gp16 head internal scaffold phi 12 tail fiber	Peptidoglycan lytic transglycosylase [42]
Peptidase_M23	PF01551	22	ul36 structural protein phig1e minor capsid tuc2009 structural protein	Endopeptidase
Glucosaminidase	PF01832	25	Sfi11 putative minor structural protein	Hydrolyses peptidoglycan
Galactose-binding like	IPR008979	Not available	Q54 receptor-binding protein bIL170 putative accessory fiber λ gpM	Carbohydrate binding [29]

[a] Identification numbers are taken from the Pfam (PF) or Interpro (IPR) database.
[b] Number of occurrences of this domain in tailed dsDNA phages. Most of the proteins are unannotated, so it is not known how many are structural proteins.
[c] These are examples of annotated structural proteins that contain the domain.
[d] Domain functions are from the indicated publications or from the Pfam database REF.

the domain. Supporting our model of Ig-like domain function, the necessity for some phages to bind both a carbohydrate and protein component on the cell surface has been demonstrated for certain lactococcal phages [25,26]. The three-dimensional structures of two different receptor-binding proteins of two other lactococcal phages have shown that each displays a modular structure with one domain being responsible for saccharide binding [27,28]. In a possible parallel to MTPs possessing C-terminal Ig-like domains, the MTP of lactococcal phage Q54 displays a C-terminal domain added by a translational frameshifting mechanism [29••]. This frameshifted domain comprises the receptor-binding domain and possesses a galactose-binding domain that is conserved in many different proteins (Table 1).

Other polysaccharide binding and hydrolyzing domains on phages

Phages are in an evolutionary arms race against their bacterial hosts [30]. Given that the attachment of a phage or phage tail to the surface of a cell even in the absence of DNA injection and further replication can be lethal [31,32], the armaments stockpiled by cells and phage may lie predominantly on their surfaces. A growing number of conserved domains are being recognized on phage structural proteins that probably play roles in attachment to host cells through sugar binding or degradation of the polysaccharides on the cell surface. Table 1 shows a brief list of conserved domains associated with polysaccharide binding or degradation that occurs in multiple phage structural proteins and may play roles in the infection process. We identified these domains in the literature or through browsing the Pfam database [33]. They are also found in many bacterial proteins and eukaryotic proteins. The frequent location of polysaccharide degrading domains in Tape Measure Proteins (TMPs) is provocative and bolsters the notion that these proteins interact with the cell before the DNA is injected [34]. Supporting this point, the TMPs of several mycobacteriophages contain domains that mediate peptidoglycan degradation and play an essential role when these phages infect cells in the stationary phase [35••]. One of the domains associated with this peptidoglycan-degrading activity has been found in a variety of bacterial and fungal proteins [36]. The necessity of the peptidoglycan-degrading activity of these TMPs only under certain conditions raises an important point about these structural protein accessory domains. In seeking a phenotype caused by their deletion, it may be necessary to assess phage growth under a variety of conditions. The lack of an identified function for Ig-like domains on the surface of phages λ and T3 may be the result of not finding the conditions where these domains are required. Alternately, some domains may only be required for the infection of particular bacterial strains.

In Figure 3, it can be seen that the tail of one phage, in this case phage λ, can possess multiple domains with possible polysaccharide binding or hydrolyzing activities. Phages appear to gain a selective advantage by adding multiple types of these domains to their virion surfaces through horizontal transfer processes. Bacteria also seem to gain evolutionary advantage in a similar manner. A systematic study has shown that one of the three most common locations for the products of horizontally transferred genes in bacteria is on the cell surface [37]. Thus, both bacteria and phages go to great lengths to fortify their surfaces by recruiting proteins or parts of proteins from a variety of non-homologous sources.

Conclusions

The common occurrence of Ig-like and other conserved domains in the structural proteins of tailed dsDNA bacteriophages is a source of both insight and confusion. Since Ig-like domains are found in proteins of diverse functions, their presence in some phage proteins has led to functional misannotation [3••]. Conversely, the knowledge that Ig-like domains appear to only occur in structural proteins can aid in identifying these proteins in phage genomes. For example, in *Staphylococcal* Bacteriophage K, there is a gene, ORF 96, encoding an Ig-like domain-containing protein that does not lie near most of the other morphogenetic genes. However, a recent proteomic study has shown that this protein is indeed a virion protein, though it is not the MTP as stated by its current Ig-like domain-based misannotation [38]. This type of example emphasizes that a full understanding of the function of proteins comprising phage particles will require a thorough investigation of the panoply of conserved domains appearing in these proteins. Future bioinformatic studies to identify all conserved domains found in phage structural proteins will be essential. Since many of these domains may play accessory functions in the adsorption process, growth of phage under normal laboratory conditions may not be affected by their removal. Thus, functional analyses may be challenging in some cases. However, further investigation will allow other fascinating questions to be addressed. Why are these domains often added by translational frameshifting? Are conserved domains frequently found in other classes of phages besides the *Caudovirales*? What are the mechanisms by which phages acquire these domains? We look forward to future studies in these areas.

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