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13. Selected baculovirus genes without orthologs in the AcMNPV genome: Conservation and function

Below is a non-inclusive list of baculovirus genes that are not present in the AcMNPV genome, but that either have homology with well-characterized genes from other organisms, or that have been investigated in baculoviruses. Following this list is a summary of investigations on each gene.

- Apsup
- CIDE domain protein
- Collagenase
- DNA ligase
- dUTPase
- Enhancin
- Eukaryotic translation initiation factor 5
- G protein-coupled receptor
- Helicase-2
- HOAR
- Iap-3
- Metalloproteinase
- Nicotinamide riboside kinase 1
- PARP
- Phosphotransferase
- PTP-2
- Photolyase
- Ribonucleotide reductase Large subunit
- Ribonucleotide reductase Small Subunit
- Serpin
- SWI/SNF Chromatin remodelers
- Thymidylate kinase
- Trypsin-like
- V-TREX

Apsup: a third baculovirus antiapoptotic gene family

The apoptotic suppressor (*apsup*) was discovered in the genome of the *Lymantria dispar* MNPV. It encodes a protein with a predicted mass 39.3 kDa and does not appear to be related to other proteins in the database. It blocks initiator caspases. Homologs were identified in *Lymantria xylina* MNPV and also in AcMNPV

(Ac112/113). Ac112/113 shows about 30% amino acid sequence identity to APSUP, but is truncated and lacks 79 amino acids at its C-terminus and also lacks anti apoptotic activity (1-3).

CIDE domain proteins. The cell death-inducing DFF45-like effector (CIDE) domain is usually present near the N-terminus of a DNAse that is activated by caspase cleavage and is associated with the degradation of DNA during apoptosis and lipid homeostasis (4). CIDE_N domains have been identified (ORF38) of the Mythimna unipuncta GV (MyunGV)) (5) and in a Group I NPV Choristoneura fumiferana def (CfdefMNPV) (orf142). MyunGV orf38 is related to orfs from 5 other GVs. In contrast, CfdefMNPV orf142 is most closely related to an orf from another Group I NPV (*Neophasia* sp – the pine butterfly – NespNPV. Both lineages showed structural relatedness to CIDE domains from Mus musculus and Drosophila melanogaster with a probability of almost 100% by Hhpred (6). The predicted CIDE domain proteins from the NPVs and GVs are only distantly related suggesting that this protein may have been incorporated into baculovirus genomes on two independent occasions.

Collagenase. Most group II alphabaculoviruses encode proteins of over 800 amino acids related to collagenases from Clostridium. In Clostridium these are extracellular enzymes (reviewed in (7)).

DNA Ligase. A DNA ligase would be involved in the ligation of Okazaki fragments during lagging strand synthesis. Homologs of DNA ligase are present in all sequenced granulovirus genomes and at least two NPV genomes (LdMNPV and MacoNPV-B). The GV ligases are similar to ligase I, whereas the LdMNPV is similar to ligase III (8). Vaccinia also encodes an ortholog of ligase III (9). The DNA ligase of LdMNPV was characterized and found to be capable of ligating double-stranded synthetic DNA substrates containing a single nick (10). A striking feature of the baculovirus ligase homologs is that they are always (except MacoNPV-B) accompanied with a helicase homolog that is not found in any of the genomes lacking ligase. This helicase is related to the PIF1 family (10) (note: this is not a per os infectivity factor). Members of this family have a preference for RNA-DNA hybrids and could be involved in the maturation of Okazaki fragments (11). This may involve displacement of the RNA primer, producing an RNA flap that would then be cleaved by a flap endonuclease (FEN) (12) or digested by a 5' to 3' exonuclease. DNA polymerase would then fill in the gap by extending the Okazaki fragment, and the ligase could join the fragments.

dUTPase. Deoxyuridine triphosphate (dUTP) can be mutagenic if incorporated into DNA. The enzyme dUTPase dephosphorylates dUTP to dUMP, which is a substrate for thymidine biosynthesis. Homologs of dUTPase are present in many NPVs (most in Group II) and a few GV genomes (13). Baculoviruses may have incorporated this gene to either supplement or substitute for the host gene. The viruses that encode a *dutpase* homolog also normally encode both subunits of ribonucleotide reductase (RR) (see below). The presence of RR may have selected for the incorporation of *dutpase* in order to mitigate the production of the dUTP mutagen by ribonucleotide reductase. In one study of an NPV, dUTPase first appeared in cell nuclei, but late in the infection it appeared to be excluded from the nucleus, but was diffusely located in the cytoplasm (14). An orf in *Perigonia lusca* single nucleopolyhedrovirus (PeluSNPV), (*pelu112)* was predicted to encode a fusion of *dUTP and thymidylate kinase* (*tmk*) (15).

Enhancin. Metalloproteinases are endopeptidases that contain divalent cations as integral components of their structure (16). Enhancins are members of this proteinase group and are encoded by a few lepidopteran NPVs and GVs. In one study of TnGV, enhancin was estimated to comprise up to 5% of the mass of occlusion bodies (17). In LdMNPV, enhancin was found to be associated with ODV (18). Enhancin genes are often present in multiple copies, e.g., the XecnGV genome has four copies (19). In LdMNPV, which encodes two enhancins, deletion of either results in a 2- to 3-fold reduction in potency, whereas deletion of both caused a 12-fold reduction (20). Enhancin is thought to facilitate baculovirus infection by digesting the peritrophic membrane (PM). The PM forms a barrier in insect guts that prevents the ready access of pathogens to the epithelial cells. The PM is rich in chitin and insect intestinal mucin, and enhancins appear to target the degradation of intestinal mucin, thereby facilitating access of virions to the underlying cells (21) (22). Enhancins show sequence

homology with high levels of significance (e.g., E = 3e-29) to predicted proteins of some pathogenic bacteria, e.g., *Clostridium botulinum*, and a variety of *Bacillus* (e.g., *B. anthracis*) and *Yersinia* (e.g., *Y. pestis*) species. To investigate their function, enhancins from *B. cereus*, *Y. pseudotuberculosis*, or TnGV were cloned into a construct of AcMNPV that yielded occluded viruses. Although the LD50 of these constructs was found to be about half of wt, only the construct expressing the TnGV enhancin caused a reduction in survival time. In addition, the bacterial enhancins failed to degrade insect intestinal mucin. It was suggested that the bacterial enhancins may have evolved an activity distinct from their viral homologs (23).

Eukaryotic translation initiation factor 5. Orthologs of eukaryotic translation initiation factor 5 have been found in at least two baculoviruses including *Choristoneura rosaceana* NPV (ChroNPV) and *Choristoneura occidentalis* GV (ChocGV). They are closely related (72% sequence identity) and are members of a lepidopteran lineage indicating that the gene was likely captured from a host insect and subsequently one virus obtained it from the other during a co-infection (24) (25).

G protein-coupled receptor (*GPCR*). A predicted G protein-coupled receptor (GPCR) was found in the Diatraea saccharalis *GV (DisaGV-Disa-038) genome. It has not been reported in other baculoviruses, but orthologs have been identified in a number of entompox viruses. The DisaGV GPCR was most closely related to those from Lepidoptera (26). The DisaGV GPCR was predicted to encode a signal peptide and 7 trans membrane domains suggesting that it belongs to the Secretin family of GPCRs (27).* A human herpesvirus (Epstein-Barr virus) encodes a GPCR that hijacks the signaling pathways of the cell (28).

Helicase-2. A second helicase homolog has been found in many GV and a few NPV genomes (13). The homology to one of the NPVs, from *Spodoptera littoralis* (SpliNPV)-ORF 40, is minimal. The *hel-2* gene from LdMNPV (29) is related to a yeast helicase that is important in recombination and repair of mitochondrial DNA. It had no effect on DNA replication in a transient replication assay and could not substitute for helicase-p143 (10). With one exception, *Mamestra configurata* NPV (MacoNPV-B) (and the limited homology of SpliNPV-ORF40 described above), the *hel-2* and *DNA ligase* genes (see above) are found in the same genomes (predominantly GVs), suggesting that they may participate in the same metabolic pathway in these viruses (see Chapter 5). In one GV genome, the hel-2 gene was fused to the alkaline exonuclease gene (30), suggesting that the fused gene may encode a protein involved in the separating and digestion of the RNA primer component of Okazaki fragments during lagging strand synthesis. A closely related ortholog of *hel-2* is also present in ascoviruses.

HOAR. According to Prof. David Tribe the name is derived as follows: 'H refers to Heliothis, O open reading frame and Hoar sounds like the given second name of the student Hoa (TH Le) who determined the sequence.' HOAR is predicted to contain a RING-finger domain and the gene appears to be somewhat unstable and shows a high degree of variation in a repeated region (31). Based on Hhpred it has a 96% probability of being a ubiquitin ligase. It is found in many group II alphabaculoviruses

Iap-3. Inhibitor of apoptosis-3. Although 6 lineages of *iap* genes have been identified in baculoviruses, the *iap-3* lineage is the most well-characterized and is a powerful inhibitor of apoptosis in certain cell lines. It is not found in the AcMNPV genome, although related *iap* genes are present. This lack of *iap-3* is likely compensated by the presence of *p35*, another apoptotic inhibitor. Members of the *iap*-3 lineage are found in Group I, II, GVs and hymenopteran NPVs. *Iap-3* genes are closely related to *iap* genes of insects. OpMNPV IAP-3 is 57% identical to IAP from *B. mori,* indicating that the *iap* gene was likely captured by viruses on one or more occasions. In addition, *iap* from *S. frugiperda* has similar properties to IAP-3 in terms of its structure and function (32). For additional information, see Chapter 7.

Metalloproteinase. As described above, metalloproteinases are endopeptidases that contain divalent cations. Baculoviruses encode three distinct metalloproteinases, cathepsin, enhancin, and a stromelysin1-like metalloproteinase. Although cathepsin homologs are found most lepidopteran group I and II NPVs, they are

only found in four GV genomes and are not present in the hymenopteran and dipteran viruses. However, there are other enzymes encoded in GVs that might compensate for the lack of cathepsin. One such enzyme is a metalloproteinase that has homologs in all sequenced GV genomes, but is not present in NPV genomes. They have about 30% amino acid sequence identity to a catalytic domain in a stromelysin1 metalloproteinase of humans and sea urchins. The GV enzyme lacks a signal peptide and a cysteine switch that maintains the other enzymes in an inactive form. The stromelysin1-like metalloproteinase from XcGV was characterized and found be capable of digesting proteins and was inhibited by metalloproteinase inhibitors (33). It is possible that the universal presence of metalloproteinase homologs in the GV genomes is involved in assisting in their viral transmission by facilitating the disintegration of cells after the GV replicative cycle is complete.

Nicotinamide riboside kinase 1 (NRK1). Orthologs of NRK1 are found in most group II NPVs and in some GVs. It plays a role in nicotinamide adenine dinucleotide (NAD+) synthesis. It phosphorylates nicotinamide riboside yielding nicotinate mononucleotide (34). Since PARG reverses the ADP-ribosylation of proteins by PARP and NRK1 is part of the nicotinamide adenine dinucleotide pathway, it is possible that the presence of PARG and NRK1 in many group II baculoviruses is indicative of their ability to manipulate these processes.

PARP. A homolog of poly (ADP-ribose) polymerases (PARP) has only been reported in a single baculovirus genome, *Anticarsia gemmatalis* (AgMNPV), Ag31 (35) (36). PARP is an enzyme found in nuclei. It is activated by DNA strand breaks and signals enzymatic pathways involved in DNA repair. Upon detecting a single strand break, it binds to the DNA and uses NAD+ as a substrate to synthesize polymers of ADP-ribose on acceptor proteins that in turn act as signals for recruiting enzymes involved in DNA repair. It is also involved in telomere elongation, chromatin structure, and the transcription of a variety of genes involved in immunity, stress resistance, hormone responses, and the possible silencing of retroelements (37) (38). It may also be involved in the regulation of a mitochondrial protein that induces apoptosis (39). PARP is a caspase-3 substrate and its cleavage is used as a measure of apoptosis.

Phosphotransferase. Homologs to RNA 2′-phosphotransferase are found in all three of the sequenced gammabaculovirus genomes (40). The substrates of this enzyme are [[2'-phospho-[ligated tRNA]]] and NAD+ and yields mature tRNA.

Protein tyrosine phosphatase-2. All group Group I alphabaculoviruses encode an ortholog of protein tyrosine phosphatase. The Group I viruses are divided into two major lineages and most of the viruses in one of these lineages encode another ptp gene called ptp-2. In addition, most Group II baculoviruses and at least two betabaculoviruses (GVs) also encode orthologs to ptp-2 (41). In OpMNPV, ptp-1 (op10) shows 60% aa sequence identity to AcMNPV PTP-1, but only ~20% identity to Op9 (PTP-2). PTP-2 is more closely related to a vaccinia and a human PTP with sequence identity of ~27% (42). The PTP2 of Spodoptera exigua multiple nucleopolyhedrovirus (SeMNPV) was found to induce mild apoptosis when transiently expressed in *Spodoptera frugiperda* (Sf) 21 cells and the larvae infected. Deletion of ptp2 from SeMNPV resulted in a reduced yield of viral inclusion bodies (43). The crystal structure of ptp-2 from Cydia pomonella virus (CpGV) has been reported and it was found to contain a similar fold and active site structure to other phosphatases. It also contains a C-terminal extension in a region that corresponds to the interface of poxvirus dimeric phosphates that belong to the Tyr-Ser homology group(44).

Photolyase. Homologs of photolyase genes have been found in the genomes of Group II baculovirus that are members of a lineage that infects insects of the subfamily Plusiinae of the family Noctuidae (45-47). Orthologs are also found in some poxviruses (48) including entomopox viruses (49). They have also been observed to be associated with mitotic structures (50). Photolyases are involved in the repair of DNA damage caused by ultraviolet light. *Chrysodeixis chalcites* NPV (ChchNPV) encodes two photolyase genes that are predicted to encode proteins with 45% amino acid sequence identity. When both were tested, only one copy showed photoreactivating activity (51). Transfection of egfp fusions of photolyase genes into *T. ni* cells resulted in fluorescence localized to chromosomes and spindles and other structures associated with mitosis. Baculovirus

infection of the transfected cells caused fluorescence to localize to the virogenic stroma (50). It was observed that one of the ChchNPV binds a CLOCK protein and represses CLOCK/BMAL1- transcription affected the oscillation of embryonic mouse fibroblasts indicating that it may be involved in circadian clock regulation (52). The incorporation of an algal virus photolyase gene as a means to cause resistance to UV inactivation of AcMNPV has been described. However, although BV survival was increased after exposure to UV light, occluded virion survival was not affected (53).

Ribonucleotide reductase. Ribonucleotide reductase is a heterodimer composed of large and small subunits (RR1 and RR2, respectively). It is involved in the catalysis of ribonucleotides to deoxyribonucleotides as a pathway for providing nucleotides for DNA synthesis. Well-documented RR1 and RR2 genes have been reported in the genomes of a few GVs, many Group II NPVs, and at least one Group I NPV (OpMNPV) (13). Two different RR2 genes have been reported for LdMNPV (29). Based on the phylogeny of baculovirus RR1 genes, it has been postulated that two different capture events resulted in baculoviruses obtaining this gene (8). One source was from a bacterium for the OpMNPV and LdMNPV RR1 gene lineage, whereas the other lineage (e.g., *Spodoptera exigua* MNPV (SeMNPV)) appears to have been derived from eukaryotes, most likely insects. The two RR2 genes from LdMNPV appear to be derived independently, one from each different source, rather than via gene duplication.

Serpin. Serpins, (serine protease inhibitors), were named because of their ability to inhibit chymotrypsin-like serine proteases. A sequence related to lepidopteran serpins was found in the genome of a baculovirus of Hemileuca sp., a member of the Saturniidae. It shows about 34% amino acid sequence identity to serpins from *Manduca sexta* and *Bombyx mori* suggesting that it was captured from a host insect (54). No other baculoviruses have been reported to encode this gene. Expression of the HespNPV serpin in AcMNPV increased the virulence of infection by four fold in T. ni larvae (55). It was found that in *Helicoverpa armigera* inhibition of melanization by serpin-9 and -5 elevated the levels of baculovirus infection (56).

SWI/SNF Chromatin remodelers. Blast analysis indicates that *Lonomia obliqua* NPV (LoobMNPV) (57) encodes a protein (loob035) closely related to Transcription termination factor 2 (TTF2)(57). Hhpred (6) analysis of this same orf predicts with about 100% probability that it is related to the SWI/SNF family of chromatin remodelers.

Thymidylate kinase. A gene encoding an ortholog of Thymidylate kinase was observed in the genome of a GV pathogenic for *Epinotia aporema* (30). Thymidylate kinase is involved in adding a phosphate to thymidine 5' monophosphate and converting it to thymidine 5' diphosphate. It is important for the production of dTTP for DNA synthesis. An orf in *Perigonia lusca* single nucleopolyhedrovirus (PeluSNPV), (*pelu112)* was predicted to encode a fusion of *dUTP and thymidylate kinase* (*tmk*) (15).

Transcription termination factor 2. See WI/SNF Chromatin remodelers above.

Trypsin-like. Although hymenopteran lack homologs of chitinase and cathepsin, they all encode a trypsin-like protein (e.g., Nese7) (58) that shows high levels of aa sequence identity (e.g., 50%) to insect trypsin-like homologs. It is possible that the presence of this enzyme compensates for the absence of chitinase and cathepsin and facilitates the release of virus from infected gut cells into the environment and to provide inoculum for the re-infection of other gut cells.

V-TREX (Viral three-prime repair exonuclease). A gene with homology to 3' to 5' exonucleases from other systems has been identified in three Group I NPVs, AgMNPV, CfMNPV and AnpeNPV. The enzyme from both AgMNPV and CfMNPV demonstrated to 3' to 5' exonucleolytic activity. It is thought that they may be involved in DNA repair (59, 60).

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