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Review

Stress granules (SG) and processing bodies (PB) in viral infections

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During reaction to stress caused by viral infection, RNA granules are formed in order to protect mRNA. Stress granules (SG) and processing bodies (PB) provide cell homeostasis and mRNA stability. They are formed, for example, during polio virus and MRV (mammalian orthoreovirus) infections. Some viruses, such as influenza virus and HTLV-1 (Human T-lymphotropic virus 1), block the formation of granules. In addition, there are viruses like West Nile Virus, Hepatitis C Virus (HCV) or human Herpes viruses, which influence the functioning of the granules.

Key word: stress granules, processing bodies, viral infection

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INTRODUCTION

Post-transcription processes occurring in eukaryotic cells, such as modification of mRNA particles, play an important role in the regulation of gene expression, and affect the expression level of a major part of transcriptome (Wilusz & Wilusz, 2004; Eulalio *et al*., 2007). The processes occur through cellular enzymes, and are related to protein complexes, including mRNP (messenger ribonucleoprotein) which when translationally silenced, can organise itself into RNA granules present in the cytoplasm, namely stress granules (SG) and processing bodies (PB) (Reineke & Lloyd, 2013). At present, apart from SG and PB granules, there are also reports on exosomal granules, granules caused by UV radiation, and glucose depletion granules (EGP) (Hoyle *et al*., 2007; Gaillard & Aguilera, 2008; Robbins & Morelli, 2014), whose role in infections, including viral infections, is still unknown.

CHARACTERISTICS OF STRESS GRANULES (SG) AND PROCESSING BODIES (PB)

Stress granules (SG) are dynamically formed in the cells structures, for example as a result of a viral infection (V-SG, viral SG), heat shock (HS-SG, heat shock SG) or impact of chemical agents (e.g. Ars-SG, arsenite SG) (Reineke & Lloyd, 2013; Niedźwiedzka-Rystwej, 2015). Such structures affect mRNA stability in cells, block apoptosis and condition cell homeostasis (Niedźwiedzka-Rystwej, 2015). SG are a differentiated group, including: proteins binding and regulating RNA, e.g. Caprin-1 (Cell cycle associated protein 1), G3BP (Ras-GTPase-activating protein Sh3-domain-binding protein 1) and ZBP1(Z-DNA-binding protein 1), as well as elements related to translation silencing or mRNA stability, e.g. proteins from TIA1 (T cell restricted intracellular antigen-1), TIAR (TIA-1-related protein), Pum1 (Pumilio RNA-binding family member 1), Smaug and HuR/ELAVL1 (Hu antigen R/ELAV-like RNA-binding protein 1) and also enzymes HDAC6 (Histone deacetylase 6) and ADAR (Adenosine deaminase, RNA-specific), as well as universal components for such granules, namely PABP-1(PolyA-binding protein 1) and mRNA transcripts: eIF3 (Eukaryotic translation initiation factor 3) and Phospo-eIF2α (Eukaryotic translation initiation factor 2A), and small ribosomal subunits (40S) (Table 1) (Kedersha *et al*., 1999; Kimball *et al*., 2003; Tourriere *et al*., 2003; Baez & Boccacio, 2005; Kedersha *et al*., 2005; Deigendesh *et al*., 2006; Kwon *et al*., 2007; Weissbach & Scadden, 2007; Morris *et al*., 2008; Anderson & Kedersh, 2008; Onomoto, 2014; Valiente-Echevierria, 2012; Kedrsha *et al*., 2012; Katoh *et al*., 2013; White & Lloyd, 2014;). Under normal conditions, elements forming SG are dispersed exclusively in the nucleus, while under the conditions of stress caused e.g. by a viral infection, they aggregate in the cytoplasm (Onomoto *et al*., 2014). It was evidenced that such components as G3BP, as well as TIA1 and TIAR, play a key role in formation and stabilization of granules (Anderson & Kedersha 2008; Onomoto *et al*., 2014). During stress, cells most probably shut off synthesis of cellular proteins, after which SG are formed, which most probably occurs as a result of eIF2α phosphorylation caused by HRI(eIF2αKI), PKR(eIF2αK2), PERK/PEK(eIF2αK3) and GCN2(eIF2αK4) kinases. It was evidenced that HRI kinase is activated during haem deficiency and oxidation stress, PKR during a viral infection, PERK/PEK during

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Abbreviations: ADAR, adenosine deaminase; RNA-specific; APOBEC3G, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; Caprin-1, cell cycle associated protein 1; CNOT6/CCR4, CCR4-NOT transcription complex, subunit 6; DCP1a, DCP2a, decapping mRNA 1a i 2a; EDC4/GE-1/Heldis, enhancer of mRNA decapping 4; eIF3, eukaryotic translation initiation factor 3; FAST, Fas-activated Ser/Thr kinase; FMRP, the fragile X protein; G3BP, Ras-GTPase-activating protein Sh3-domain-binding protein 1; EGP, glucose depletion granules; HDAC6, histone deacetylase 6; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HuR/ELAVL1, Hu antigen R/ELAV-like RNA-binding protein 1; HTLV-1, human T-lymphotropic virus 1; mRNP, messenger ribonucleoprotein; MRV, mammalian orthoreovirus; PABP-1, PolyA-binding protein 1; Pan3, PAB-dependent poly(A)-specific ribonuclease subunit PAN3; Phospo-eIF2α, eukaryotic translation initiation factor 2A; PB, processing bodies; Pum1, Pumilio RNA-binding family member 1; RAP55, RNA-associated protein 55; RSV, respiratory syncytial virus; SFV, Semliki forest virus; SG, stress granules; TIA1, T cell restricted intracellular antigen-1; TIAR, TIA-1-related protein; TMEV, Theiler's murine encephalomyelitis virus; Xrn1, 5′-3′ exoribonuclease 1; ZBP1, Z-DNA-binding protein 1

Table 1. Elements of stress granules (SG), processing bodies (PB) and common components for SG and PB

Full name	Abbreviation	Function
SG components		
Cell cycle associated protein 1	Caprin - 1	RNA regulation, cell growth
Ras-GTPase-activating protein Sh3-domain-binding protein 1	G3BP	RNA regulation, Ras signalling
Z-DNA-binding protein 1	ZBP1	Translation silencing, mRNA stability
T cell restricted intracellular antygen-1	TIA1	Translation silencing, mRNA stability
TIA-1-related protein	TIAR	Translation silencing, mRNA stability
Pumilio RNA-binding family member 1	Pum1	Translation silencing, mRNA stability
Smaug	Smg	Translation silencing, mRNA stability
Hu antigen R/ELAV-like RNA-binding protein 1	HuR/ELAVL1	Translation regulation, mRNA stability
Histone deacetylase 6	HDAC6	Translation regulation
Adenosine deaminase, RNA-specific	ADAR	Translation regulation
PolyA-binding protein 1	PABP1	Translation regulation, mRNA stability
Eukaryotic translation initiation factor 3	eIF3	Translation regulation
Eukaryotic translation initiation factor 2A	Phospo-eIF2á	Translation initiation
Eukaryotic small ribosomal subunit	40S	Translation regulation
PB components		
CCR4-NOT transcription complex, subunit 6	CNOT6/CCR4	mRNA regulation
Decapping mRNA 1a	DCP1a	mRNA processing
Decapping mRNA 2a	DCP2a	mRNA processing
Enhancer mRNA decapping 4	EDC4 / GE-1 / Hedls	mRNA processing
Lsm1, U6 small nuclear RNA associated	Lsm1	mRNA processing
5′-3′ exoribonuclease 1	Xrn1	mRNA processing, translation regulation
PAB-dependent poly(A)-specific ribonuclease subunit PAN3	Pan3	mRNA processing
SG and PB components		
Apolipoprotein B mRNA-ending enzyme catalytic polypeptide-like 3G	APOBEC3G	Participation in antiviral response
Eukaryotic translation initiation factor 4E	eIF4E	Translation
The fragile X protein	FMRP	Translation, mRNA stability
Fas-activated Ser/Thr kinase	FAST	Translation, mRNA stability
RNA-associated protein 55	Rap55	mRNA silencing

References: Kedersha *et al*. 2002; Tourriere *et al*., 2003; Antar *et al*., 2005; Andrei *et al*., 2005; Yu *et al*., 2005; Deigendesh *et al*., 2006; Wichroski *et al*., 2006; Yang *et al*. 2006; Kwon *et al*., 2007; Weissbach *et al*., 2007; Beckham & Parker, 2008; Kimball *et al*. 2008; Morris *et al*., 2008; Anderson & Kedesha, 2008; Dougherty *et al*. 2011; Valiente-Echevierria *et al*., 2012; White & Lloyd, 2012; Katoh *et al*., 2013; Reineke & Lloyd, 2013; Otomoto *et al*., 2014

protein processing in endoplasmic reticulum, while GCN2 kinase is activated in the case of amino acid deficiency and UV radiation (Valiente-Echevierria *et al*., 2012; Onomoto *et al*., 2014). Each of such kinases, while phosphorylating subunit α of eIF2 factor, leads to translation blockage and to formation of the SG granules.

In the case of processing bodies (PB), it was evidenced that, contrary to SG stress granules, they are permanently present in the cytoplasm of an eukaryotic cell, although their formation was also noted for e.g. as a result of glucose deficiency (Lui *et al*., 2011). It was reported that, similarly to SG granules, PB bodies contain many elements, although they have not been fully identified. Nevertheless, it was recorded that they included such components as: CNOT6/CCR4 (CCR4-NOT transcription complex, subunit 6), DCP1a, DCP2a (decapping mRNA 1a i 2a), EDC4/GE-1/Heldis (enhancer of mRNA decapping 4), Lsm1 (Lsm1, U6 small nuclear RNA associated), Xrn1 (5'-3' exoribonuclease 1) and Pan3 (PAB-dependent poly(A)-specific ribonuclease subunit PAN3), which are responsible for, among others, mRNA processing, as well as for its control, including

Table 2. Viruses affecting SG granules

Virus type	Virus family	Viral Genome
SG formation		
Mammalian Orthoreovirus (MRV)	Reoviridae	dsRNA
Respiratory Syncytial Virus (RSV)	Flaviviridae	ssRNA (-)
Polio Virus	Picornaviridae	ssRNA (+)
Semliki Forest Virus (SFV)	Togaviridae	ssRNA (+)
SG blocking		
Measles Virus	Paramyxoviridae	ssRNA(-)
Flu Virus	Orthomyxoviridae	ssRNA (-)
Mengovirus	Picornaviridae	ssRNA(+)
Theiler's Murine Encephalomyelitis Virus (TMEV)	Picornaviridae	ssRNA(+)
Human T-lymphotropic virus 1 (HTLV-1)	Retroviridae	ssRNA
Rotaviruses	Reoviridae	dsRNA
SG modulation		
Western Nile Virus	Flaviviridae	ssRNA (+)
Hepatitis C Virus (HCV)	Flaviviridae	ssRNA (+)
Dengue Virus	Flaviviridae	ssRNA (+)
Sindbis Virus	Togaviridae	ssRNA (+)
HIV Virus	Retroviridae	ssRNA
Human Herpes Viruses	Herpesviridae	dsRNA

References: McInerney *et al*. 2005;Berlanga *et al*., 2006; Emara & Brinton, 2007; Eulalio *et al*., 2007; Montero *et al*. 2008; Qin *et al*., 2009; Toroney *et al*., 2010; Borghese & Michiels, 2011; Linquist *et al*., 2011; Khaperskyy *et al*., 2012; Valiente-Echevierria *et al*., 2012; Lindquist *et al*., 2013; Reineke & Lloyd, 2013; Okonski & Samuel, 2013; Onomoto *et al*., 2014; Khapersky *et al*., 2014; Niedźwiedzka- Rystwej *et al*., 2015

silencing (Table 1) (Kedersha *et al*., 2005; Andrei *et al*., 2005; Yu *et al*., 2005; Dougherty *et al*., 2011; Reineke & Lloyd, 2013; Onomoto *et al*., 2014). It was stated that the molecular mechanism of PB formation is related to concentration of RNA and mRNA-binding proteins, hence their processing occurs as a result of RNases (Reineke & Lloyd, 2013).

Among components occurring both in SG granules and in processing bodies (PB), one must point to APOBEC3G (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) which participates in antiviral immunity and mRNA transcripts, e.g. eIF4E (Eukaryotic translation initiation factor 4E), or protein components related to mRNA translation and stability, as well as silencing, namely: FMRP (The fragile X protein), FAST (Fas-activated Ser/Thr kinase) and Rap55 (RNA-associated protein 55) (Table 1) (Kedersha *et al*., 2005; Antar *et al*., 2005; Wichroski *et al*., 2006; Yang *et al*. 2006; Onomoto *et al*., 2014).

SG AND PB IN VIRAL INFECTIONS

Viral infections may lead to inhibition of cellular protein synthesis by affecting and activating the SG component eIF2α, although it was also reported that proteins of some viruses, for e.g. mammalian orthoreovirus (MRV) or respiratory syncytial virus (RSV), can also lead to shut off of cellular protein synthesis by binding the eIF4A translation factor (Onomoto *et al*., 2014), and causing formation of stress granules (SG). This was described for MRV virus (Table 2), which causes mild respiratory tract diseases (Linquist *et al*., 20011; Onomoto *et al*., 2014) and in early stages of the infection leads to increased phosphorylation of eIF2α kinase, causing SG formation. It was, however, evidenced that PKR kinase and other eIF2α kinases, are not necessary for SG induction, which confirms that the virus induces SG formation by activation *via* eIF2α (Linquist *et al*., 2010; Reineke & Lloyd, 2013). In the case of RSV virus (Table 2) infecting primarily young mammals, including infants as well as children with reduced immunity, it induces SG formation. This was evidenced (Linquist *et al*., 2010) by stating a correlation between higher level of M2-1 and M2-2 proteins of RSV, and the occurrence of SGs, that an infection with RSV not only causes eIF2α phosphorylation, but also PKR activation (Linquist *et al*., 2010). Also, in the case of Polio virus (Table 2), which causes palsy in children, it was reported that regardless of eIF2 kinase activation, stress granules are induced already in an early phase of the viral infection (Table 2), as granules containing G3BP and eIF4GI are formed as early as in 2–3 hours post-infection, while during the further course of infection their formation decreased. It was also recorded that SG granules are separated through the impact of 3C proteinase of the virus, the consequence of which is the inhibition of mRNA translation initiation factors, as well as mRNA-binding proteins in such

granules (White & Lloyd, 2012). In turn, SFV (Semliki forest virus) (Table 2), causing mortal encephalitis in rodents, was originally characterised as a factor modulating cellular response to stress (McInerney *et al.*, 2005). It was finally adopted that infections with such virus induce eIF2α kinase phosphorylation and SG formation in fibroblasts of mice embryos. It was also stated that despite shutting off cellular protein synthesis, SFV still affects the translation process of its own mRNA. In the case of infection with Rubella virus, causing a contagious disease in children, reports include formation in the cytoplasm of G3BP-1 protein clusters, yet these are atypical SGs, because they lack such proteins as PABP or TIA-1 (White & Lloyd, 2012).

In the case of some viruses, it was stated that in order to assure their survival, they have found a way to avoid an unfriendly environment by inhibiting SG formation. This was described in the case of infections with the Measles virus (Table 2), which causes a rash disease in children, and type A flu virus — causing respiratory system diseases, stating that they do not induce stress granules, but contribute to blocking their formation. In the case of Measles virus (Table 2), it was evidenced that its inhibiting impact on SG formation in cells is probably a result of the viral C protein (Okonski & Samuel, 2013; Onomoto *et al.*, 2014). On the other hand, in the case of type A flu virus, inhibition of SG formation is caused by its viral non-structural protein 1 (NS1) which blocks PKR kinase activation by inhibiting eIF2α kinase phosphorylation and leads to inhibition of SG formation (Khaspersky *et al.*, 2012; Onomoto *et al.*, 2014; Khaspersky *et al.*, 2014). Other infections inhibiting SG formation are those due to mengovirus and Theiler's Murine Encephalomyelitis Virus (TMEV) (Table 2) (Onomoto *et al.*, 2014; Borghese & Michiels, 2014). It was evidenced that inhibition of such granules is most probably caused by impact of non-structural Leader protein – L-protein of such viruses, yet the mechanism of SG inhibition is still unknown (Onomoto *et al.*, 2014). Also, Human T-lymphotropic Virus (HTLV-1) (Table 2) causing acute leukaemia as a result of impact from viral regulatory protein Tax, inhibits SG formation. It was also proven that, in response to environmental stress, the protein is transferred from the nucleus to cytoplasm, and by interacting with histone deacetylase 6 (HDAC6), blocks the stress granule formation (Valiente-Echevierria *et al.*, 2012; White & Lloyd, 2012; Onomoto *et al.*, 2014). As to the etiological factors of acute diarrhoea in young mammals — rotaviruses, it was stated that they cause SG inhibition as a result of containing VP2, NSP2 and NSP5 proteins (Montero *et al.*, 2008; Niedźwiedzka-Rystwej *et al.*, 2015).

Apart from the aforementioned viruses inducing and inhibiting SG formation in mammalian macro-organisms, a third group of viruses was described which modulates such granules (Table 2). This group includes Western Nile Virus, Hepatitis C Virus, Dengue Virus, Sindbis Virus, HIV, and human herpesviruses (White & Lloyd, 2012; Reineke & Lloyd, 2013; Onomoto *et al.*, 2014; Niedźwiedzka-Rystwej *et al.*, 2015). In the case of Western Nile Virus causing meningitis in horses and humans, and carrying a lifecycle between mosquitos and birds, but also able to infect amphibians and reptiles (Valiente-Echevierria *et al.*, 2012; Niedźwiedzka-Rystwej *et al.*, 2015), it was evidenced that it suppresses the translation process by inhibiting eIF2α kinase phosphorylation (Niedźwiedzka-Rystwej *et al.*, 2015). It was also stated that by interacting with TIA-1 and TIAR components of SGs, its genome causes reduced viral replication in infected cells (Li *et al.*, 2002; Valiente-Echevierria *et al.*, 2012). In the infection with HCV, it was determined that it does not only induce SG formation, but also, as a result of external stress factors, may cause the inhibition. However, additional observations point to strong activation of PKR kinase by the virus to form SGs, while GADD34 (growth arrest DNA damage-inducible 34 factor) and protein phosphatase 1 (PP1) component, causes SG inhibition by leading to dephosphorylation of eIF2α kinase (Onomoto *et al.*, 2014; White & Lloyd, 2012). In the case of Dengue virus, it was stated that it affects translation of genetic material or replication of its RNA by binding to G3BP protein of SG granules. In the case of Sindbis Virus, it was reported that its RNA-dependent RNA polymerase — nsP4 cooperates with G3BP1 and G3BP2 markers of stress granules (SG), facilitating access of cellular mRNA into SGs (Niedźwiedzka-Rystwej *et al.*, 2015). In turn, HIV affects various stages of SG formation, probably by inactivation of the Staufen 1 protein. In the case of human herpesviruses it is suggested that SGs are regulated by modulation of Pbp1 expression (Niedźwiedzka-Rystwej *et al.*, 2015).

Table 3. Viruses affecting PB granules

Virus type	Virus family	Viral genome
PB inhibition		
Polio Virus	Picornaviridae	ssRNA (+)
Coxsackie Virus	Picornaeviridae	ssRNA (+)
PB formation		
Flu Virus	Orthomyxoviridae	ssRNA (–)
Human Papilloma Virus (HPV)	Papillomaviridae	dsDNA
HIV Virus	Retroviridae	ssRNA

References: Hebner *et al.*, 2006; Beckham & Parker, 2008; Balagopol & Parker, 2009; Dougherty *et al.*, 2011; Niedźwiedzka-Rystwej *et al.*, 2015

While discussing the characteristics of SGs, it must be stated that the knowledge on processing bodies is much more limited, including viral infections, as it is still unknown how PBs interact with viruses. It is suspected that the mechanism involves dispersing these structures and their components (Beckham & Parker, 2008; Balagopol & Parker, 2009; Niedźwiedzka-Rystwej *et al.*, 2015). It was evidenced for e.g. that infections with Polio and Coxsackie viruses (Table 3) distorts PB formation in the middle of their replication cycle. It was additionally observed that PB dispersal occurs by processing of enzymes: Xrn1, Pan3 or Dcp1, as a result of their degradation by 3C protease of such viruses (Dougherty *et al.*, 2011). In turn, the mechanism of PB formation described for type A flu virus (Table 3) is a result of interaction between viral NS1 protein and an inhibitor protein of PB — Rap55 (Dougherty *et al.*, 2011). Such observations reveal that processing bodies can also participate in an antiviral response, for example PKR protein kinase which is activated by dsRNA of the virus and contributes to antiviral protection by gathering in PBs. This was also reported for the infection with Human Papilloma Virus (HPV) (Table 3) (Hebner *et al.* 2006). Moreover, antiviral role of PBs can be related to the presence of APOBEC3G and 3F proteins in such granules, as APOBEC belongs to cytidine deaminases that carry out cytidine deamination processes in the genomes

of various viruses, including retrotransposons (Beckham & Parker, 2008). APOBEC3G was also reported to be included in HIV-1 virions (Table 3), and it can inhibit replication of transcriptors of such viruses by cytidine deamination, which finally leads to turning guanosine into adenosine in the positive strand of cDNA of the virus. Other retroviruses (Beckham & Parker, 2008), produce proteins inhibiting APOBEC functions, e.g. *vif* proteins of HIV bind to APOBEC3G, which leads to its degradation (Beckham & Parker, 2008).

CONCLUSION

Maintaining the homeostasis of a macro-organism's cells is a major challenge for living organisms, including response to various factors, e.g. a viral infection. Such a condition causes macro-organism's cells to induce many reactions assuring their stability, including formation of SG and PB granules. However, it must be stated that the data regarding such granules, including their interaction with viruses, still raise many questions; answering them would allow to explain the impact of viruses on the macro-organism's cells and to reduce such impact.

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