Technical Brief

Re-mining serum proteomics data reveals extensive post-translational modifications upon Zika and dengue infection

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Abstract

Zika virus (ZIKV) and dengue virus (DENV) are two closely related flaviviruses with similar symptoms; understanding differences in their molecular impact on the host is therefore of high interest. Viruses interact with the host’s post-translational modifications, inducing changes visible in serum. As modifications are diverse and of low abundance, they typically require additional sample processing which is not feasible for large cohort studies. Therefore, we tested the potential of next-generation proteomics data in its ability to prioritize specific modifications for later targeted analysis. We re-mined published mass spectra from 122 unenriched serum samples from ZIKV and DENV patients for the presence of phosphorylated, methylated, oxidized, glycosylated/glycated, sulfated, and carboxylated peptides. We identified 272 modified peptides with significantly differential abundance in ZIKV and DENV patients. Amongst these, methionine-oxidized peptides from apolipoproteins and glycosylated peptides from immunoglobulin proteins were more abundant in ZIKV patient serum and generate hypotheses on the potential roles of the modification in the infection. The results demonstrate how data-independent acquisition techniques can help prioritize future analyses of peptide modifications.
**Introduction**

Zika virus (ZIKV) and dengue virus (DENV) belong to the Flavivirus genus of the Flaviviridae family and are closely related. ZIKV and DENV cause a similar immune response in the host. While most infections are asymptomatic, symptoms can range from mild body pain to life-threatening fever (CDC 2020; Wen et al. 2017; Ngono and Shresta 2019). They overlap in their geographical distributions and can be transmitted by the same types of mosquitoes, *Aedes aegypti* and *Aedes albopictus* (CDC 2019; Ngono and Shresta 2019; CDC 2014). While the 2015 to 2017 outbreak in the Americas has waned, Zika cases have been surging in other places of the world such as India (Pierson and Diamond 2020; Sharma 2021; Bhargavi and Moa 2020). DENV infections are similarly widespread, resulting in ~96 million symptomatic cases per year (World Health Organization 2020).

Viruses frequently interact with the cellular system of post-translational modifications (PTMs), changing host and viral proteins that may directly support the infection or modulate the antiviral response (Hu et al. 2020; Kumar et al. 2020). For example, DENV and ZIKV prevent STAT2 phosphorylation, which is required for the antiviral interferon response (Mazzon et al. 2009). Host proteins involved in the regulation of modifications can be potential drug targets that limit viral replication (Kumar et al. 2020). Common modifications in blood proteins are N- and O-glycosylation, phosphorylation, acetylation/alkylation (e.g. acetylation, formylation, methylation, and pyroglutamylation), sulfation, hydroxylation, carboxylation, disulfide bridges, and proteolytic processing such as N- or C-terminal truncation (Schaller et al. 2008). Blood PTM signatures are emerging as biomarkers in clinical settings, e.g. for glycated hemoglobin, which is elevated in diabetes patients, and the phosphorylation status of vasodilator stimulated phosphoprotein to assess platelet reactivity (Mnatsakanyan et al. 2018).

However, modifications are challenging to analyze as they are highly diverse, with >400 known modifications (Aebersold et al. 2018), and typically of low abundance. Techniques for PTM-specific enrichment are cost and labor intensive (Doll and Burlingame 2015) which is often prohibitive for large sample numbers. Therefore, we tested the ability of existing data to help with prioritization of highly promising modifications for future analyses. Specifically, we examined a published mass spectrometry data set from 62 dengue and Zika patient serum samples (Allgoewer et al. 2021) (Figure 1A) which had been acquired in data-independent acquisition (DIA) mode for protein abundance analysis. DIA methods are well suited for such an analysis as they generate fragmentation spectra for all ions captured in the full scan and contain all their ion chromatograms, providing the quantification abilities of targeted analyses with an expanded coverage of proteins and enabling the re-mining of existing data (Rosenberger et al. 2014; Faria et al. 2017). In addition, DIA has been shown to detect and quantify modifications reproducibly without prior enrichment (Goetze et al. 2020). Testing six PTM-specific libraries, we identified >1,800 modification events across eight different types of modifications of which methionine-oxidation, methylation, and glycosylation/glycation were most abundant and tested their differential abundance in the Zika and dengue patient serum samples.

**Methods and Materials**

**Data and analysis:** We obtained the RAW files from Allgoewer et al. (2021). The data had been collected in data-independent acquisition mode, comprising 124 patient and 20 quality control samples. RAW files were converted into the Spectronaut file format HTRMS (MS1/MS2 to centroid). All samples were analyzed using Spectronaut 14 against the project-specific spectral libraries with template fragments being used as the preferred fragment source for decoy generation. The remaining analysis settings remained in default. Two samples failed in their data acquisition and were removed from the analysis. False discovery rate (FDR), based on mProphet (Reiter et al. 2011), was calculated run-wise at the peptide precursor and experiment-wide at the protein group level and filtered for 1% on both levels. Modified peptides were extracted pooling different charge states.

**Spectral library generation:** We prepared spectral libraries based on data acquired in data-dependent acquisition mode from pooled and fractionated serum samples of Zika and dengue patients (Allgoewer et al. 2021) using the Pulsar search engine within Spectronaut 14. Settings included Trypsin/P digest, peptide length of 7 to 52 amino acids and up to two missed cleavages. The FASTA file (human) was downloaded from UniProt (02/15/2018) and contained 93,798 entries including protein isoforms. Spectral libraries allowed for the following variable modifications: carboxylation, formylation, glycosylation (monohexose, dihexose, hexosamine, acetylhexosamine), methylation (monomethylation, dimethylation), phosphorylation, and sulfation (Table S1). In addition, acetylation (N-term) and oxidation (methionine) were set as variable modifications in each library. Carbamidomethylation of cysteine was set as fixed modification. Pulsar performs by default an internal mass calibration with optimized mass tolerance prediction.
for precursor and fragment ions. The FDR was calculated by Pulsar for peptide-spectrum matches, peptides, and protein groups and filtered for 1% at all three levels.

**Extraction of differentially abundant modified peptides:** To identify differentially abundant modifications in serum of Zika and dengue patients, differential abundance was tested for modified peptides using the feature in Spectronaut 14 (two-sample t-test). We further processed the results to normalize for the abundance of the corresponding unmodified peptides. To do so, we subtracted the log base 2 fold change of the unmodified peptide from the log base 2 fold changes of modified peptide. We calculated q-values using the normalized log base 2 fold changes, the standard errors, and degrees of freedom (Benjamini and Hochberg 1995). Modified peptides without corresponding unmodified identifications were removed. Volcano plots were generated in R using the EnhancedVolcano() function.

**Protein function enrichment:** Protein function information was retrieved from the PANTHER Classification System using the category “PANTHER protein class” (Mi et al. 2019; Mi et al. 2021). Actin-related proteins and non-motor actin binding proteins were summarized under the protein class parent "Cytoskeletal Protein". Serine Proteases, Metalloproteases, and Proteases were summarized under the protein class parent "Protease". Marimekko charts (mosaic plots) were generated in R using the ggplot() function. The size of each segment represents the number of unique modified peptides in each protein class and category. P-values for under- or overrepresentation were calculated using the UCLA Graeber Lab hypergeometric calculator (Graeber Lab 2009).

**Results**

Using our workflow (Figure 1A), we generated spectral libraries specific to 12 different types of modifications (Figure S1A) and identified 1,652 modified peptides containing 1,806 different modifications (Table 1, Table S5, Figure S1B). The most common modification category was methionine-oxidation, followed by methylation, glycosylation/glycation, carboxylation, phosphorylation, sulfation, and acetylation (Figure 1B, Figure S1C, Table S4).

The distribution of modifications amongst amino acid residues (Figure S1C, Table S4) was consistent with the literature, except for glycosylation: 37% of modifications were located on lysine and arginine, which are most common for glycation, which is often non-enzymatic (Baldensperger et al. 2020). We observed a surprising dominance of O-linked glycosylation events on serine, threonine, and tyrosine (47%), as serum proteins are reportedly predominantly N-linked glycosylated (Sun et al. 2018). C-linked glycosylation was generally rare, and we observed 11 peptides with this modification. Five of these contained the Trp-X-X-Trp consensus sequence (Krieg et al. 1998; Chauhan et al. 2013) and comprised several components of the Complement system which have been previously described as C-mannosylated (Hofsteenge et al. 1999) (Table S3).

Figure 1C shows the 272 modified peptides which differed significantly in their abundance between DENV and ZIKV patients (q-value ≤0.05) (Table S6). We observed more peptide oxidation, methylation, phosphorylation, and carboxylation in DENV than in ZIKV patients and more glycosylation/glycation and sulfation in ZIKV patients than in DENV patients. We identified no significant differences for acetylation and formylation.

**Methionine oxidation**

We identified 148 methionine-oxidized peptides with significantly different abundance (q ≤ 0.05, Table 1, Figure S2A). While methionine-oxidation can result from sample preparation (Potgieter et al. 1997; Liu et al. 2013), all samples were processed similarly and evidence from literature supports the validity of the observed modification events.

For example, methionine oxidized peptides that were more abundant in ZIKV patients were significantly enriched for apolipoproteins (p = 0.0002, hypergeometric test, Figure 2A/B). The oxidation sites in the peptides from APOA1 (residue 136) and APOA2 (residue 49) have been described elsewhere (Pankhurst et al. 2003). In APOA1, methionine oxidation may affect structure and stability as well as impair the transport of cholesterol by inducing amyloid fibril formation. In the formation of infectious viral particles, host apolipoproteins play a role similar to Flaviviridae secretory proteins Erns and NS1 (Fukuhara et al. 2017), while APOE may be a target of the DENV capsid protein (Faustino et al. 2014).

Further, six methionine oxidized fibrinogen peptides were more abundant in ZIKV patients. Methionine oxidation in fibrinogen can change protein structure and impair aggregation and coagulation (Weigandt et al. 2012; White et al,
Molecular weight form, Kininogen also has proinflammatory functions, and was shown to be downregulated in dengue infection sites observed in our data, impacting the proinflammatory function of neutrophils (Schenten et al. 2018). In its high molecular weight form, Kininogen also has proinflammatory functions, and was shown to be downregulated in dengue infection sites observed in our data, impacting the proinflammatory function of neutrophils (Schenten et al. 2018).

Phosphorylation plays a significant role in modulating the function of various proteins. In our study, we identified phosphorylated peptides that differed significantly in their abundance between dengue and Zika virus (ZIKV) patients (q-value ≤ 0.05, Table 1, Figure 2C/D). The phosphorylated peptides were enriched in transfer/carrier proteins and immunoglobulins (p-value ≤ 0.05). All three modified peptides belonging to immunoglobulin class G were significantly more abundant in DENV patients. In addition, we found extensive methylation of Serum Albumin. While most protein methylation events have been described for histone proteins (Liu et al. 2013), Arginine monomethylation was found to be one of the most abundant modifications in the serum of cancer patients (Gu et al. 2016). Gu et al. (2016) speculate that Arginine methylation could either be catalyzed in the bloodstream or be released from intracellular compartments, since various Arginine methyltransferases can occur in plasma (Liu et al. 2007; Sennels et al. 2007). Key platelet proteins are known to be Arginine methylated, which may promote aggregation in response to thrombin and collagen (Marsden et al. 2021). In mouse brain tissue, Arginine methylation has been detected in transporters and vesicle proteins as well as in ion channels and receptors, all of which are involved in synaptic transmission (Guo et al. 2014).

Glycosylation and glycation

The third most frequently identified modification was glycation, where two thirds of the modified peptides were more abundant in ZIKV patients (q-value ≤ 0.05, Table 1, Figure 2E/F). The 46 modifications included 41 monohexoses, 4 hexosamines, and one acetylhexosamine. Immunoglobulins were significantly overrepresented among peptides that are modified in ZIKV patients (p-value ≤ 0.05). We observed 23 modifications on Lys/Arg residues, rendering them more likely to be glycations (Baldensperger et al. 2020). Three of the remaining 23 modification sites were N-linked glycosylations; 20 were O-linked of which many were more abundant in ZIKV patients (Figure S3A).

A large number of glycosylated/glycated peptides derived from serum albumin (27) and immunoglobulin components (11) (Figures S3B/C). Glycation of serum albumin influences its conformation and function and leads to a shorter half-life, with the primary glycation site being Lys-525 (Jones et al. 1983; Shaklai et al. 1984). We observed this modification in two of the identified peptides. Glycation of immunoglobulins can occur in vitro and in vivo: while no impact on function could be detected in human antibodies (Goetze et al. 2012), activity loss through glycation has been reported in some studies on therapeutic antibodies (Wei et al. 2017). All three glycosylation/glycation events that were detected on IgG peptides were more abundant in ZIKV patients. Alterations in immunoglobulin glycosylations are also associated with aging, disease, and inflammation (Gudelj et al. 2018; Karsten et al. 2012). Afucosylation of maternal anti-DENV IgGs has been shown to influence susceptibility of infants to symptomatic disease (Thulin et al. 2020). Finally, we observed a modified haptoglobin peptide, i.e. a glycation event (Lys, monohexose) that was significantly less abundant in ZIKV patients. This specific modification (glycated Lys-141) has been described as a potential biomarker for the early diagnosis of type 2 diabetes (Spiller et al. 2017).

Other modifications

We identified phosphorylated peptides that differed significantly in their abundance between dengue and Zika virus patients (q-value ≤ 0.05). Phosphoproteins and phosphorylated sites are known to be upregulated in DENV infected cells compared to controls (Miao et al. 2019). The phosphorylated sites included residues in serum albumin, Fibronectin, S100-A9, and in Kininogen. Phosphorylated Fibronectin has been shown to enhance cell attachment (Yalak et al. 2019), and fibronecrint was reported to be elevated in the serum of pregnant ZIKV patients (Foo et al. 2017). Altered expression of the inflammatory protein S100-A9 is associated with recurrent pregnancy loss (Nair et al. 2013). Both its intracellular and extracellular function was shown to be regulated by its phosphorylation in the specific site observed in our data, impacting the proinflammatory function of neutrophils (Schen ten et al. 2018). In its high molecular weight form, Kininogen also has proinflammatory functions, and was shown to be downregulated in dengue infection sites observed in our data, impacting the proinflammatory function of neutrophils (Schenten et al. 2018).

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patients (Oehmcke-Hecht and Köhler 2018; Ray et al. 2012). We also identified phosphorylation in Fibrinogen Alpha. Phosphorylation of fibrinogen has been suggested to alter its function, increase fiber diameters, and potentially prevent bleeding (Martin et al. 1992; de Vries et al. 2020).

We further identified 7 carboxylated peptides which differed significantly in their abundance between DENV and ZIKV patients (q-value ≤ 0.05, Table 1, Figure S4C). Carboxylation most commonly occurs on Glu residues and is associated with blood clotting, extraosseous calcification, and bone growth (Lee et al. 2011). Lys carboxylation has been shown to modulate the activity of enzymes (Li et al. 2010; Jimenez-Morales et al. 2013). In human blood cells, increased protein carboxylation has been observed after treatment with catechol (Bukowska et al. 2015).

We observed two sulfation events in different immunoglobulin regions (IGKC and IGHV4-34) which are more abundant in ZIKV patients. Both sulfation modifications are located on Tyr residues, which has been shown to alter immunoglobulin potency and contributes to the diversity of the humoral immune response (Choe et al. 2003).

Finally, we observed N-terminally acetylated and N-terminally formylated peptides, but without significant differences in abundance between ZIKV and DENV patients (Table 1). Acetylation is the second most frequent intracellular modification (Khoury et al. 2011). The low number of identifications in our data, may indicate the need for special enrichment methods, which are often deemed essential for the analysis of N-terminal modifications (Yeom et al. 2017; Chang et al. 2021). The acetylated peptides belong to Haptoglobin-Related Protein, immunoglobulin fragment IGHV3OR16-9, Peptidyl-Prolyl Cis-Trans Isomerase A, Hemoglobin Subunit Alpha 1, and Hemoglobin Subunit Beta. Altered protein acetylation may play a role in certain diseases such as rheumatoid arthritis (Arito et al. 2015).

Discussion

Analysis of protein modifications typically requires selective enrichment of modified peptides (Larsen et al. 2006) - which can be labor and cost intensive if conducted at a large scale and is not possible for all types of modifications. Therefore, we tested the potential of re-mining DIA data to identify modifications in a cohort of serum samples without prior enrichment. We identified >1,800 modification events across data from Zika and dengue patients (Table S5), 272 of which were significantly different between the two types of infection (Table S6). Literature supports the validity of the results in their potential to generate new hypotheses.

Future work might investigate methionine oxidation: the 148 oxidized peptides with significantly differential abundances in serum from Zika and dengue patients suggest true biological relevance. As non-enzymatic reactions during sample preparation can affect the results (Potgieter et al. 1997; Morand et al. 1993), future experiments would require oxidation of all methionine with isotopically labeled hydrogen peroxide to distinguish between true and false positive oxidation events (Liu et al. 2013).

Specifically, we observed an enrichment in methionine-oxidation on apolipoproteins with higher abundance in Zika samples. Host apolipoproteins play a role in Flaviviridae infection (Fukuhtara et al. 2017); for example, Apolipoprotein E (APOE) interacts with the DENV capsid protein (Faustino et al. 2014). Some APOE genotypes are associated with microcephaly and neurocognitive disorders (Oria et al. 2005; Geflin et al. 2017; Braga et al. 2010; Kuroda et al. 2007). Further, methionine oxidation of Apolipoprotein A-I can induce amyloid fibril formation, impairing transport of cholesterol (Wong et al. 2010; Shao et al. 2008). Host cholesterol levels, in turn, support virus replicative complex formation, virus assembly and egress (Li et al. 2013; Li et al. 2013; Osuna-Ramos et al. 2018). Finally, hepatitis C virus oxidizes APOB, resulting in degradation by the 20S proteasome (Wang et al. 2021).

While phosphorylation is typically the most abundant PTM in eukaryotic cells (Khouri et al. 2011), it is less abundant in the extracellular space (Chen et al. 2017). Highly active phosphatases in blood further challenge identification. The fact that we still detected 9 significantly different phosphorylation events suggests that phosphorylation is another modification worth exploring in future experiments. However, enrichment and the use of phosphatase inhibitors during sample preparation will be essential (Chen et al. 2017).

Another modification with highly promising results in our data was glycosylation/glycation, for which we observed 45 modified peptides, in particular from immunoglobulin proteins, with significant abundance differences between Zika and dengue patient serum. Glycosylations in immunoglobulin components are associated with aging, disease, inflammation, pathophysiology and immune suppression (Gudelj et al. 2018; Karsten et al. 2012; Bovenkamp et al. 2016). Changes in glycosylation patterns of IgG have been observed in patients with autoimmune disease such as rheumatoid arthritis (Parekh et al. 1985; Maverakis et al. 2015). Consistent with our observations, specific subclasses
of neutralizing antibodies from ZIKV patients require glycosylation for binding to ZIKV envelope proteins (Henderson et al. 2020) - generating hypotheses on the role of this modification in this infection.

Further, we observed substantial glycation, in particular of serum albumin. Glycation of serum albumin, however, is known to cause a shorter half-life (Jones et al. 1983; Shaklai et al. 1984) - and our data contained the primary glycation site responsible for this effect. Serum albumin glycation is a biomarker for diabetes mellitus and a potential predictor for renal, cerebro- and cardio-metabolic diseases (Giglio et al. 2020). Our results therefore motivate the future analysis of the structure and function of glycoforms, e.g. by hydrophilic interaction liquid chromatography with fluorescence detection (de Haan et al. 2020).

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Figure 1: Re-mining serum proteomic data for modified peptides

A) We analyzed 122 serum samples from 62 patients from Trinidad, diagnosed with dengue and Zika as published in Allgoewer (2021). B) Most peptides observed and with significant expression differences had one modification, but some had more. C) Number of modified peptides with significant differential abundance between dengue and ZIKV patients. Modified peptides with significantly higher abundance (q-value ≤ 0.05, un-paired t-test) in dengue and ZIKV patients are shown in yellow and green, respectively. No acetylated and formylated peptides with significant differential abundance were identified.
Figure 2: Function enrichment and abundance of the three most common modification types

Panels show results for oxidation (OX), methylation (MET), and glycosylation/glycation (GLY) in A/B, C/D, and E/F, respectively. Panels A, C, and E show the function enrichment obtained from the PANTHER classification system. Apolipoproteins and immunoglobulins are significantly overrepresented amongst methylated peptides (A) and glycosylated peptides (E), respectively (p-value ≤ 0.05). Panels B, D, and F show the volcano plots of fold-change (Zika/dengue) and q-value as a significance measure. q-value ≤ 0.05 (blue), absolute fold change (FC) ≥ 1.5 (green), beyond both thresholds (red), below both thresholds (grey). Panel B highlights apolipoproteins which were significantly overrepresented amongst methionine-oxidized peptides that are more abundant in serum from ZIKV patients.
Table 1. Identified modifications.

We identified 1,652 modified peptides containing 1,806 modifications. Modified residues are indicated using the one-letter amino acid code. For 1,122 modified peptides, the corresponding unmodified peptide could be identified, and fold changes were adjusted accordingly. We observed 272 modified peptides with significant differential abundance, with 117 and 155 being more abundant in Zika and dengue patients, respectively (Table S6).

<table>
<thead>
<tr>
<th>Modification</th>
<th>Modifications identified across all samples</th>
<th>Modified residues</th>
<th>Identified across all samples</th>
<th>With unmodified counterpart</th>
<th>ZIKV patients</th>
<th>Dengue patients</th>
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<tbody>
<tr>
<td>Oxidation</td>
<td>860</td>
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<tr>
<td>Phosphorylation</td>
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<td></td>
<td>1652</td>
<td>1122</td>
<td>117</td>
<td>155</td>
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References


Burk, R.F., Hill, K.E., Motley, A.K., Winfrey, V.P., Kurokawa, S., Mitchell, S.L. & Zhang, W. (2014) Selenoprotein P and apolipoprotein E receptor-2 interact at the blood-brain barrier and also within the brain to maintain an essential


A) 62 patients with Dengue and 122 samples of Zika virus. The samples were analyzed using mass spectrometry with data-independent acquisition, leading to the identification of modified peptides.

B) The graph shows the fraction of peptides with different numbers of modifications per peptide. The black bars represent all peptides (n=1,652), and the red bars represent significant peptides (n=272).

C) The bar graph illustrates the number of modified peptides with significant expression differences. The green bars indicate peptides enriched in Zika patient samples, while the yellow bars indicate peptides enriched in dengue patient samples. The modifications include oxidation, methylation, glycosylation, carboxylation, phosphorylation, and sulfation.