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| **Supplementary Table 4.**Summaryofstudiesusingbiosystemsapproachanditsmainfindings |
| **Author(year)** | **Aim** | **Celltype** | **Molecularanalyses** | **Systembiologytools** | **Molecularresults** | **Applicationofsystembiologyanalyses** | **Relationshipofmolecularresultsandneurologicaloutcomes** |
| Aguiar *et al.* (2020)1 | To perform a multiomics analysis in postmortem brains of neonates with CZS  | Postmortem brains | ExomeTranscriptomeProteome | NetworkAnalyst, STRING, and Cytoscape | Reduced expression (RNA and protein) of collagen genes and upregulation of cell adhesion genes | To integrate the exome, transcriptome and proteome findings | Collagen genes have been previously associated to arthrogryposis and cell adhesion factors to neuronal migration and axon guidance  |
| Anderson *et al.* (2020)2 | To determine whether ZIKV modulates host cell epigenetic profiles *in vivo* | Blood cells | Genome-wide DNA methylation profiling | Packages in R | Altered host methylation patterns, especially at *RABGAP1L* - important in brain development -, at viral host immunity genes *MX1* and *ISG15*, and in an epigenetic module containing the causal microcephaly gene *MCPH1* | To identify differentially regulated modules of genes that may be contributing to the microcephaly phenotype | Given the importance of the affected genes to brain development and antiviral response, their altered methylation could the clinical signs of CZS |
| Park *et al*.(2020)4 | TodescribemolecularalterationsduetheZIKVinfection *in vitro* | hPNs,hNCCs,mDCs | Transcriptome | PPIinSTRING,Cytoscape | ThederegulatedgeneswererelatedtoDNArepairandprolactinsignalingaswellastheinterferonsignaling,neuroinflammation,andcellcyclepathways | Toperformaprotein-proteininteractionanalysisoftheDGEgenesidentifiedinRNA-seq | Neuronalcelldamageoccurredthroughup-regulationofneuroinflammationanddown-regulationoftheDNArepairsystem |
| Saade *et al.* (2020)5 | To investigate the interaction between ZikV-NS5 protein with the interactome of hNPCs | hNPCs | Zika-host proteome interaction | PPI network, Gene Ontology enrichment | Enrichment of cytoskeleton, especially microtubule, host proteins that interact with ZikV-NS5 | To identify the Gene Ontologies of the human proteins that interact with ZikV-NS5, according to the human fetal brain library | The identification of these proteins might help to understand how ZIKV impacts neurogenesis |
| Souza *et al*.(2020)6 | *In silico* protocol:keygenesandpathwaysforemergingvirusdiseasepathogenesis | Human neuralcellsinfectedwithZIKV | Transcriptome | PPInetwork:Gephi,STRING,Cytoscape | 30DEGs(24upand6down)associatedtoendoplasmicreticulumstressandDNAreplication.Neurogenesisand/orapoptosis | Integrativeanalysisoftheupanddownregulatedgenes | Downregulationof *CENPF*, *MCM2, MCM4, MCM6* genes(DNAreplicationonneocortex)possiblyrelatedtomicrocephaly |
| Tabari *et al.* (2020)7 | To profile the host transcriptome after ZIKV infection | hNSC infected with ZIKV Uganda and French Polinesia strains | Transcriptome and miRnome | Reactome signaling pathways and networks | Upregulation of genes included in antiviral infection signaling, ER stress, and unfolded proteins pathways. Downregulation of signal transduction, cell cycle, and gene expression related pathways. | To identify the signaling pathways the perturbed genes are associated with | *ASNS*, a gene previously associated to microcephaly,was perturbed by both strains |
| Beys-da-Silva *et al*.(2019)8 | TodescribeproteomealterationsduetheZIKVinfection *in vitro* | hMSC | Shotgunproteomics | PPIinSTRING,Cytoscape | Reprogrammingofthemetabolicmachineryandpotentialinhibitionofautophagy,neurogenesis,andimmuneresponse;ProteinsrelatedtoAlzheimer’sdisease,autismspectrumdisorder,amyotrophiclateralsclerosis,andParkinson’sdisease,hadtheirexpressionalteredduetoZIKV | Toassociatederegulatedgeneswithhumanbraindiseases | ThemolecularpathwaysaffectedbyZIKVinhMSCarerelatedtobraindiseases |
| Dang *et al*.(2019)9 | RoleofmiRNAsinZIKVpathogenesisandmicrocephaly | hNSCs | mRNAandmiRNAtranscriptomes | miRNA-mRNAinteractionsCytoscape, | UpregulationofsomemiRNA(e.g.let-7candmiR-124–3p),repressorscellcycle,stemcellmaintenance,andneurogenesisgenes | To analyzemiRNA-mRNAinteractionsinhNSCinfectedcells | ZIKVupregulatedmiR124–3panddownregulatedthetransferrinreceptor(*TFRC*)inZIKV-infectedhNSCs-NSCmaintenancedysregulated |
| Lima *et al*.(2019)10 | TranscriptionalchangesinducedbyZIKVinfection *in vitro* | hiNPCs | Transcriptome | PPIinSTRING,Cytoscape | Inductionoftype-Iinterferons(IFN-I)IFN-Isstimulatedgenes(ISGs):cytokinesandpro-apoptoticchemokinesCXCL9andCXCL10 | To identify specificnetworksinducedbyZIKVininfectedhiNPCs | UnbalancedandchroniclocalinflammatoryresponseelicitedbyZIKVinfection,whichcontributestodamagetothefetalbrain |
| Brahma *et al*.(2018)11 | Tohaveasystems-levelunderstandingofbiologicalprocessaffectedbyZIKVinfetalbrain | HumanfetalNSCs | Transcriptome | PPIinSTRING,Cytoscape | 613downregulatedgenes:defenseresponsetovirus,receptorbinding,lamininbinding,extracellularmatrixandendoplasmicreticulum.471upregulated:translationinitiation,RNAbinding | ToidentifycandidategenesassociatedtoZIKVinfectionthroughanetwork-basedanalysis,assemblingPPInetworks | Pathwayssuchassystemiclupuserythematosus,defenseresponsestovirus,ribosomestructure,chromosome,andplateletscouldbeallinvolvedinZIKVmicrocephaly |
| Caires-Júnior *et al*.(2018)12 | GeneexpressionofcellsfromCZS-affectedandCZS-unaffectedtwins | hNPCsderived | Transcriptome | NetworksofenrichedGOinMetascape | 64DEGsassociatedwithregionalization,embryonicmorphogenesis,embryodevelopmentandcentralnervoussystemdevelopmentontologies | To evaluateinteractionsbetweenenrichedgeneontologies | Differentialexpressionofneuraldevelopmentgenes(e.g. *DDIT4L*)maycontributetothedifferentsusceptibilitiestotheZIKVBRinfection |
| Janssens *et al*.(2018)13 | ZIKVinfectionintheneuralDNAmethylation | Human NPCs,astrocytes,differentiatedneurons | Methylome | *psygenetR* package(Rlanguage) | ZIKValtersDNAmethylationatspecificgenelociimplicatedinthepathogenesisofbraindisorders,especiallyneuropsychiatricdisorders | Networkassociatinggenesdifferentiallymethylatedandneuropsychiatricdisorders | ZIKV-inducedmethylationchangessuggestthatinfectionduringfetaldevelopmentcouldleadtoaspectrumoflate-onsetneuropsychiatricdisorders |
| Garcez *et al*.(2017)14 | TodescribemolecularalterationsduetheZIKVinfectioninvitro | HumanneurospheresderivedfromiPS | Transcriptomeandproteome | PPIinSTRING | Upregulationofresponsetoviralreplication,DNAdamage,cellcyclearrestandapoptosispathways,downregulationofneuronaldifferentiation | To create a interactomemapofproteinsandgenesalteredbyZIKVinfection | ZIKVdownregulatestheneurogenesisandincreasescelldeathinprogenitorcells,whichcouldberelatedtotheZIKVcongenitalsyndrome |
| Moni *et al*.(2017)15 | TounderstandthemechanismofZika-associateddisordersthroughinfectomeanddiseasomeanalysesofZIKVinfection | hiPSCsandhNPCs | Transcriptome | Cytoscape | 341genesupregulated:ProteinprocessinginendoplasmicreticulumandtransferRNAbiosynthesissignalingpathways;588genesdownregulated:Cellcycle,DNAreplication,andFanconianemiapathways | To analyze a networkcontainingdatarelatedtoZIKVinfectome,diseasomeandassociatedcomorbidities | InterlinkedgenesbetweenZIKVinfectionandotherdiseasesindicatesthatmetabolic,neurological,andcancerdiseasecategoriesarepossiblyimplicatedinZIKVinfectionandmalformations |
| Rolfe *et al*.(2016)16 | ToanalyzedthetranscriptionalchangesinducedbyZIKVinfection *in vitro* | hNPCs | Transcriptome | Cytoscape,ClueGOapp | Upregulatedgenesrelatedtonucleicacidmetabolismregulationpathway.Enrichmentofnumerouspro-inflammatorypathways.Downregulatedgenesrelatedtochromosomesegregation. | ToprovideanetworkofthebiologicalprocessesassociatedtoZIKVinfection | Enrichmentofpro-inflammatorypathwayscausesCNScytotoxicpro-inflammatoryenvironmentthatcouldinducecelldeath.DGEassociationwithneurologicalclinicalphenotypes,suchasmicrocephaly,epilepsy |
| Zhang *et al*.(2016)17 | TodescribemolecularalterationsduetheZIKVinfectioninvitro | hNPCs | Transcriptome | Gene-geneinteractionnetworksGeneMania | TheAsianZIKVinduceddysregulationofDNAreplicationandrepairgenes(e.g. *TP53*),andtheupregulationofviralresponsegenes,TypeIIinterferonsignaling,Toll-likereceptorsignalingandTNFsignalingpathways | To evaluate gene-geneinteractionsthatcouldbeconsideredmolecularsignaturesfortheinfectionofdifferentZIKVstrains | Thep53upregulationcouldplayapivotalroleintheapoptosisinhNPCs |
| PPI:Protein-proteininteraction;String:Stringdatabase;Cytoscape:Cytoscapesoftware;Gephi:Gephisoftware;ClueGO:ClueGOapp;GO:Geneontology;hiNPCs:Humaninducedneuroprogenitorcells;CZS: Congenital Zika Syndrome; NPCs:Neuroprogenitorcells;hNPCs:Humanneuroprogenitorcells;iPS:inducedpluripotentstem;hPNs:Peripheralneurons,hNCCs:neuralcrestcells;mDCs:myeloiddendriticcells;hMSC:Humanmesenchymalstemcells;DGE:differentialgeneexpressed. |

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