2022 Joint Usage and Research Report

<table>
<tr><td colspan="2">Title of Research Project</td><td colspan="3">Elucidation of the role of SKIV2L in innate immunity.</td></tr>
<tr><td rowspan="2">Applicant</td><td>Institution</td><td>University of Chittagong, Bangladesh.</td><td>Under40
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<tr><td>Job title
and Name</td><td>Associate Professor
Sunanda Baidya</td><td>○</td><td></td></tr>
<tr><td rowspan="4">Research
collaborators
(Please add lines as
appropriate)</td><td>Institution</td><td></td><td></td><td></td></tr>
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and Name</td><td></td><td></td><td></td></tr>
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and Name</td><td></td><td></td><td></td></tr>
<tr><td colspan="2">Host researcher at IGM</td><td colspan="3">Professor Akinori Takaoka</td></tr>
<tr><td colspan="2">Purpose of the Research Project
(approx. 250 words)</td><td colspan="3">It has been reported previously that mutation in SKIV2L, a component of RNA exosome is responsible for a rare congenital bowel disorder trichohepatoenteric syndrome (THES) [Fabre A, et al, Am J Hum Genet. 2012; 90:689-692]. SKIV2L is a negative regulator of RIG-I-like receptors, which trigger innate immune responses against viral infection, and loss of SKIV2L function can result in type I interferon overproduction. Moreover, human patients with SKIV2L deficiency have a potent IFN signature in their peripheral blood cells [Eckard SC, et al, Nat Immunol. 2014;15:839-845]. However, the role of SKIV2L in constitutive weak interferon signal is not fully understand yet. Thus, the purpose of the study is to investigate the role of SKIV2L in innate immunity.</td></tr>
<tr><td colspan="2">Development of the Research Project and Results
(approx.. 850 words)
*Enter the number of web meetings.</td><td colspan="3">To elucidate the role of SKIV2L in innate immunity we had successfully generated HEK293T SKIV2L KO cells and found elevated IFNβ and IFNλ mRNA expressions in KO cells than wild type HEK 293T cells by qRT-PCR. Next, we transfect SKIV2L plasmid DNA through Lipofactamine 2000 to the SKIV2L KO cells and we found elevated IFNβ and IFNλ responses had been reduced by the re-expression of SKIV2L in KO cells. Furthermore, we investigated which innate sensing pathway is responsible for the upregulated IFN response in SKIV2L KO cells by the knockdown experiment of different innate immune sensors retinoic acid-inducible gene I (RIG-I), mitochondrial antiviral-signaling protein (MAVS) and Melanoma Differentiation-Associated gene 5 (MDA5). Knockdown</td></tr>
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	experiment of innate immune sensors reflected upregulation of IFNβ and IFNλ in SKIV2L KO cells mediated by RIG I pathway. Afterward to confirm the role of SKIV2L in maintaining constitutive weak IFN response, we transfected WT and KO cells RNA into THP-1 cells. Introduction of SKIV2L KO RNA in THP-1 cells enhanced both IFNβ and IFNλ mRNA expressions significantly. Stimulations of SKIV2L KO cells RNA also induced pro-inflammatory cytokines IL-6, TNF-α, and IP-10 in THP-1 cells. We also found knockdown of SKIV2L enhanced IFNβ and IL-29 expression in THP-1 cells. Moreover, we compared the IFN-β, IFNλ, and NFκB gene promoters activity between HEK-293T WT and HEK293T SKIV2L KO cells by stimulating thapsigargin at different concentration to ensure the role of SKIV2L in innate immunity. Thapsigargin is an inhibitor of sarco endoplasmic reticulum Ca^{2+}–ATPase (SERCA), depletes Ca2+ store in the ER and thereby causes ER stress, leads to the accumulation of unfolded proteins in the ER. Stimulation of thapsigargin induced IFN-β, IFN-λ, and NFκB gene activation more significantly in a dose dependent manner in KO cells than the WT cells. It had been reported that an organogermanium compound 3-(trihydroxygermyl) propanoic acid (THGP), can inhibit RIG-I mediated IFN induction [Baidya S. et al, Viruses 2021, 13(9), 1674], in consistent with the previous reports, we had found THGP can restrain the elevated IFN response in SKIV2L KO cells. In future we will find out whether increased ISG signature would also be found in SKIV2L KO cell through transcriptome analysis. We are looking for THES patients in Bangladesh, as THES is very rare genetic disorder, we could not find any THES patient yet. We hope if we get THES patients samples that would be a great resource to execute our future joint research plan. In the long run we will try to elucidate the mechanism of regulation of constitutive weak IFN response by SKIV2L. Moreover, Bangladesh has several patients diagnosed with Idiopathic Granulomatous Mastitis (IGM), which is a rare chronic inflammatory lesion of the breast that can clinically and radiographically mimic breast carcinoma. There is no evidence of SKIV2L deficiency or mutation in IGM patients. We are planning to do the genetic analysis of SKIV2L in IGM patients and if we get any positive result, that will help us to explain inflammatory symptoms of IGM patients and we would also be able to step

	forward to identify the role of SKIV2L in innate immunity. If so, that will show us a way to find out a suitable agonist of SKIV2L, which could be a possible therapeutic agent to reduce enhanced IFN response not only in SKIV2L deficient patients but also in different autoimmune disease patients caused by the hyperactivation of type I IFN response.
Publication *Enter the information of conference or journal (vol. page. Year.) where the above work was presented.	【Conference, symposium, workshop etc.】 Not presented yet
	【Journals】 Not published yet