

# A REVIEW ON ANTI-INFLAMMATORY PEPTIDES AND ITS ACTIVITIES

Smt. Shilpa A.S and Satish Kumar Murari

Department of Chemistry, PES College of Engineering, Mandya -571401, Karnataka, India

## ABSTRACT

All living organisms contain anti-inflammatory peptides. These peptides show anti-inflammatory properties because they contain hydrophobic and positively charged amino acids. It is an effective immunomodulator and interferes with signal transduction pathways involved in inflammatory cytokine expression, and chemotactic. These peptides can exert health-beneficial properties and are considered as a development of nutraceuticals or functional foods.

**Key Words:** Anti-inflammatory peptides, Inflammation, Synthesis, Activities.

## INTRODUCTION

The health diseases namely gastric problems, ulcers, bleeding problems, thrombosis, and related diseases are treated by using anti-inflammatory peptides. These peptides are immune modulators and decrease the creation of pro-inflammatory cytokines. Therefore, anti-inflammatory peptides are used to cure acute or chronic related infectious and other diseases. Cyclic peptides as a promising anti-inflammatory agent. Some natural cyclopeptides occur in plants or marine organisms and show anti-inflammatory activity.

Some of the peptides occur from natural sources and others are synthetic compounds. The peptide sequence exhibits anti-inflammatory activities. We have studied some related papers below.

Anneta Smyrniotou, Marula G- Kokotou<sup>1</sup> Employed 2-Oxoamides is a dipeptide that is more inhibitor of GVIA iPLA2. The calcium-independent phospholipase A2 is a medical target. The known poly fluoro ketones are inhibitors of GVIA iPLA2. 2-oxoamides that prevent the activity of human GVIA iPLA2 and their choosiness over the major intracellular GIVA CPLA2 and secreted GVSPLA2. Structure and their activity enlighten the 2 – oxoamide (GK317) is an effective inhibition of GVIA iPLA2.

Sara La Manna, natale, Floria<sup>2</sup> converses the anti-inflammatory bioactivity of peptides. Some of the peptides, SOCSs are very active in brand-new fatal inflammatory disease, auto-immune cephalitis, and cancer processes. The pro-inflammatory action of macrophages is inhibited by Chromo fungin peptide and suppresses the receptor of IL-15 and cyclotide (T20K) Kalata B1, and blocks the immune-competent cells proliferation. Anti-inflammatory agents are used for the treatment of different diseases.

Peng wang, Yongtao Li<sup>3</sup> explains the systematic scheme of the preparation of peptides from different aspects like protein docking and redocking, molecular dynamics simulation, and

binding affinity of the PLA2. Lastly, he found the PLA2 inhibitory peptides from different methods.

The mutation energy map is used to guide peptide structure optimization. Then we have to study the dynamic and reserve of a few considered peptides versus HsPLA2.

LLAYK & AVFRS suppress the enzymatic activity lastly structure examination gives the designed peptides intensive nonpolar networks of Vander Waals associates and aquaphobic interaction with PLA2, considering the steadiness and attraction of the composite system.

Woo Seok yang, and Young–Jin Son<sup>4</sup> developed nano-fibers that are widely used in drug delivery as a nanomedicine platform & self-assembling peptide. S5 peptide reduces the production of PGE2 & TNF- $\alpha$  and also regulates DNA promotor activity. This peptide decreases the transcriptional activity of MYD88 & PMA. S5 peptide prevents the phosphorylation of MKK3/6 & TAK1. This peptide prevents AP-1 signaling peptide K5 is suppressing the TNF –  $\alpha$  production in RAW 264.7 cells. S5 and K5 peptides show non-immunogenic and non-invasive properties. It exerts a synergetic effect. S5 peptide is used for drug delivery system and with therapeutic use and synergize with provocative molecules. S5 peptide blocks the nuclear translocation of C-jun & reduces the making of PGE2 & TNF- $\alpha$  in macrophages and down-regulates the COX-2, TNF- $\alpha$ , and IL-1 $\beta$  expression by C-Jun. So, the S5 peptide shows anti-inflammatory activity by preventing the C-Jun/p38 signaling pathway.

From preserved egg white we have to extract peptides are SR-7, MF-7, DR-10 and ML-7(SGD-PEW), it shows the anti-inflammatory effects on Caco – 2 cells and mouse model of blocked the DSS-induced colitis and prevents the phosphorylation of NK-KB and Mapk signalling pathway in caco-2cells. These peptides effectively alleviated in the medical symptoms of DSS-induced mice inflammatory bowel disease like body changes, diarrhoea, blood signs, irritation, histological changes, disease activity index (DAI).

Anti-inflammatory peptides prevent the secretion of pro-inflammatory cytokines in colon and reduces the emission of some factors and measuring m-RNA appearance including INF- $\nu$  and MCP-1

The elevated level of IL-10 is used in inflammatory bowel diseases and DSS- induced colitis mice. MF-7 shows good result of improving DSS- made colitis. They are used in the treatment of chronic intestinal inflammatory diseases. These peptide shows cellular antioxidant and anti-inflammatory activity. This defeats the pro-inflammatory factors in CaCo-2 and HT-29 cells.  $\nu$ -glutamyl -peptides displays solid anti-inflammatory action in CaCo-2 cells than in HT-29 cells and involved the peptide transporter PepT1.

In Rheumatoid arthritis (RA) some enzymes are involved, mainly secretory phospholipase A2 (SPLA2) and matrix metalloproteinases (MMPS) and these enzymes are modulated for potential therapeutic field. Designed, synthesized multimeric peptide are modulated and inhibit the SPLA2. These multimeric peptides 10f (PIP-18) effects on SPLA2 (IC<sub>50</sub> 1.19 $\mu$ m) based on the CD-spectra, 10f (PIP-18) having stable secondary structure and  $\beta$  -sheet conformation in solution phase. NMR and molecular modelling indicate the peptides 10f (PIP-18) having  $\beta$  -leaf structure with aquaphobic surface. These peptides supress SPLA2 activity and different matrix metalloproteinases in RASF. Since both SPLA2 and MMPs shows an important character in Rheumatoid arthritis, these peptides are very active and valuable for cure the Rheumatoid arthritis.

Chengye Zhan, Shusheng Li, Qiang Zhong<sup>5</sup> describe the phospholipase A2 in an enzyme having calcium dependent, di-sulphide linked,  $\alpha$ - helical proteins and it shows pro-inflammatory activity to the arthritis since it releases arachidonic acid. It possesses an open active pocket in a physiochemically compatible having substrata and peptide preventors. Large number of peptides developed for target the PLA2 proteins originated from plants and animals. Only few were found to have inhibitory potency against hsPLA2.

Synthesis of artificial HSPLA2- peptides from snake PLA2 in apo hsPLA2 having transmutation and optimisation properties. The inhibitory effects of FLVYK, FLSFK, and FISYR peptides on hsPLA2. and defeat the enzymatic movement by ALSYK, LVFYA and KGAILGFM peptides. The FLVYK was used for the interact with PLA2.

Guilherme D. Brand, Marcelo H. S Ramada<sup>6</sup> Studied the how HSO<sub>2</sub> affecting on marine macrophages aware in Lipopolysaccharide. Lipopolysaccharide- neutralising activity is observed in several AMPs. The Lipopolysaccharide in AMPs which decreases the TLR4 activity in HsO<sub>2</sub> and avoid the cytokine issues at peptides concentration as  $\leq 0.1\mu\text{m}$ . From NMR and CD spectra results shows that the HsO<sub>2</sub> peptides having secondary structure of helical conformation. HSIAPs prevents the development of micro-organism at absorptions  $\leq 1\mu\text{m}$ . HSO<sub>2</sub>, it hinders the TNF –  $\alpha$  in LPS.

Vikas Chandra, Jayashankar, Punit Kaur<sup>7</sup> studied, Phospholipase A2 from *Daboia russelli pulchella* (DPLA2) occurs in both solution and crystalline forms (molecule A &B). The enzymes of from snake – venom origin, PLA2 is extracted. This prevents important changes in the alignments of Trp 31 of these two molecules.

Membrane phospholipids dissociates the two molecules at the boundary and make a suitable conformity in the visible site previously required it.so it clearly indicates that DPLA2 have minor action and sophisticated stability compare to other PLA2 enzyme.

Designing of the peptide LAIYS (Leu-Ala-Ile-Tyr-Ser) works on the basis of Lock and Key – principle. The membrane phospholipids induce of conformity of Trp31 in the enzyme. So, it can be included that LAIYS has a large attraction for the PLA2. Then peptide LAIYA appears as an excellent inhibitor for PLA2s.

Bingjun Qian<sup>8</sup> examined, pepsin, trypsin and maxi pro PSP enzymes involved in the reaction at oyster soft tissues, gives a 4 aquaphobic peptides likes PEP-1, PEP-2, TRYP -2 and MIX-2. These peptides down regulated the emission of TNF- $\alpha$  & m-RNA activities in RAW 264.7 cells. So, this TRYP-2 peptide is a source for normal anti-inflammatory molecule.

Sara Aviles- Gaxiolo, Josefina, Yazmin<sup>9</sup> explain the MO leaves protein hydrolysate (MOPH) shows anti-inflammatory activity. It occurs in moringa oleifera leaves It is used in intestinal enzymes for enlightening social healthiness and for curing inflammatory diseases. MOPH is used as an antioxidant and anti-inflammatory peptides.

Yuhuan chen, Hua Zhaug<sup>10</sup> employed the 2  $\nu$ - glutamyl peptides occurs in beans. These peptides having anti-inflammatory activity. The beans probiotic bacterium fermentation bounces nutritious values and suggestion to novel food crops to advantage the primary producers, the food manufacturing and consumers.

CaSR (Calcium Sensing receptor) elaborate the intracellular signal transduction and stated on intestinal tract. Agonists and CaSR shows to anti-inflammatory activity.

Subhadeep Chakrabarti, Forough<sup>11</sup> Studies the bioactive peptides activity on the human body for curing the inflammatory diseases. And also prevents the pro-inflammatory factors. these peptides are used in food and nutritional field & it gives the pro-inflammatory signalling kinases. These are used for treating chronic disease.

Fatiha Tabet<sup>12</sup> employed the both 5A peptide & apoA-I shows anti-inflammatory and anti-oxidant properties in acute invitro and invivo models. invitro 5A peptides reduces atherosclerosis and the cholesterol content of cells. apoA-1 peptides used as a clinical agent. The 5A-PLPC complex prevent nuclear factor-KB activation. ApoA-I. rHDL and 5A/PLPC prevents the adhesive molecules, O<sub>2</sub><sup>-</sup> invention, neutrophils to carotid intima.

Edwin Enique<sup>13</sup> explains the chronic disease is a diabetes, these disease causes a large number of other inflammatory diseases such as tumour, kidney problems, heart disease, stroke, dementia, and eye problems. These diabetes is cured & prohibited by using the biopeptides. These diabetes disease has an obvious concentration for pro-inflammatory cytokines. The biopeptides are used for nutritional treatment for diabetes.

Sudheer gupta, Ashok K. Sharma<sup>14</sup> studied how amino acids and their sequences are experimentally validated in examining anti-inflammatory epitopes (AIEs) and non-anti-inflammatory epitopes (NAIEs). A machine learning classification technique and its features to determine the anti-inflammatory peptides and proteins also. It also focuses on anti-inflammatory cytokine and therapeutic uses. The designed computational work focus on the academic usage of anti-inflammatory peptides.

welina Zielinsk<sup>15</sup> explores the relationship between edible insects and bioactive peptides. The relationship indicates anti-inflammatory peptides and antioxidant properties of peptides occur in the gastrointestinal digestion process and absorption process. Entomophagy proved to be preventing civilization diseases.

Young Ran Park, YunjoSoh<sup>16</sup> suggests that NCW peptide occurs in clam worms, HPLC is used to purify & extract the peptide. The mass spectrometry shows NCW peptide have molecular weight of 1757.56 K Da. In RAW 264.7 cell. NCW peptide shows antioxidant, anti-inflammatory activity & prevents the making of some enzymatic hydrolysates. NCW peptide is very useful for human healthiness because of its clinical uses.

Fatemeh Bambad, Scongee bark<sup>17</sup> employed the BLG was hydrolysed using HHP-EH method a large proportion of small peptides were obtained.  $\beta$ -lactoglobulin activities is increased by hydrostatic pressure.  $\beta$ -lactoglobulin hydrolysates decreases the nitric oxide level NO after pre-incubation, the cells are treated by HHP-BLG-Alc hydrolysates it reduces the appearance of pro-inflammatory cytokines. In macrophage cells, BLG-HHP-Alc shows anti-inflammatory properties. peptide sequence of BLG-HHP-Alc is aquaphobic and aromatic in nature.

Lin Lu, Ya Nan Wang<sup>18</sup> studied chromogranin A (CgA) containing Vasostatin-1 and Vaso statin-2, these are protein molecules, some enzymatic hydrolysis gives bioactive peptides, vasostatin-2 maintains vascular homeostasis and decreased in patients with coronary artery diseases, the vasostatin -2 also controlled the TNF- $\alpha$ , AngII and some adhesive molecules

and weakened the monocytes to endothelial cells. In coronary artery diseases, the serum vasostatin-2 levels reduce. It is independent risk factor for CAD. Inflammation is increases the vasostatin -2 level should be decreases & it shows the anti-inflammatory properties.

Bala Chandra manavalan<sup>19</sup> employed the AIP pred performed popular benchmarking and independent data sets. AIP pred is determined by random forest (RF) method. Anti-Inflam, ERT, KNN and SVM achieved the AIP pred, AIP pred ranges 0.801value in area under the curve (AUC), So, anti-inflammatory peptides are expected by AIP pred& used in medical field.

Mst.Shamima Khatun<sup>20</sup> investigated the silico predictors is formed from in vitro method, it is having anti-inflammatory activity, so it is called as PreAIP. These peptides having different structural features is found out by random forest method. So, anti-inflammatory peptides are expected by preAIP & used in medical field.

Fatemeh Bamdad, Seulki Shin<sup>21</sup> developed the casein-derived peptides possess anti-inflammatory activity. From enzymatic hydrolysis the casein hydrolysates (CH) produced, it is a cyto-compatible. It decreases the nitric oxide level pre-incubation method; CH shows the repressive effect of the hydrolysates in inflammation. In chemical and cellular models CH gives the information about degree of hydrolysis (DH), molecular weight spreading and anti-inflammatory properties. HHP-Fla-CH composed of valine and leucine so, it gives the anti-inflammatory properties in stimulated RAW 264.7 macrophage cells. These peptides are used as a therapeutc agents & aiming to treat chronic diseases.

Yu Fu Wang, Xiang Xu<sup>22</sup> discover a AIP6, it is a pentapeptide molecule, AIP6(RLRWR) avoids the binding of NF-KB with KB elements & it binds with P65. It decreases the Zymosan or TPA. From in vitro and in-vivo methods, AIP6 shows an essential and strong cell- penetrating property. Local administration and AIP6 inhibits inflammation induced by zymosan in mice. So AIP6 changes the NF-KB inhibitors as an anti-inflammatory agent.

Lin Wei, Li Dong<sup>23</sup> studied the anntoxin is occurs from the tree frog, it is a neurotoxin. Tetrodotoxin-sensitive (TTX-S) & voltage-gated sodium channel (VGSC) is inhibited by anntoxin. R-anntoxin is an inhibitor of the COX-2 and TNF- $\alpha$  levels. It reduces the oedematous epidermis induced by carrageenan.

Matthew K REnne, Ya – Ching Shen<sup>24</sup> developed a three new cyclic heptapeptides cyclomarins A-C. This is extracted from SanDiego CA. It is a cytotoxic in vitro towards cancer cells and it is having anti-inflammatory properties. Cyclomarins is a novel cyclic heptapeptides containing four unusual amino acids. CA structural information obtained from the ID,2D NMR and X-ray crystallographic methods.

Richard Houghten<sup>25</sup> described how the peptides are synthesised and purified by solid phase synthesis method using ELISA- type assay. The different peptides are obtained by resin and solvent systems, it involves the different steps for synthesis of peptides, The peptides HA1 is synthesised and characterised. It containing aspartic acid at 101 site, Aspartic acid & alanine is very important to binding interaction.

Mario Delgado and Doina Gance<sup>26</sup> describe Neuropeptides are the anti-inflammatory agents, it is an endogenous molecule that contribute to the resolution of inflammation, vasoactive

intestinal peptide, urocortin, adrenomedullin these are neuropeptides and hormones such as melanocyte stimulating hormone, ghrelin and cortistatin, these are autoimmune model. Neuropeptides prevents the antigen – specific TH1 and generate regulatory T-cells. These peptides give G-proteins in immune cells.

Afef Dellai, Igor Maricic, Cipin Kumar<sup>27</sup> explained the Cyclosquamosin D(A1) and met-cherimolacyclopeptide D(B) are the cyclic peptides, occurs from the Annona squamosa seeds. these peptides decrease the manufacturing of pro-inflammatory cytokines in J774A% macrophage cells and it shows the anti- inflammatory properties, the excretion of IL-6 and TNF-  $\alpha$  is decreased by the cyclosquamosin D(A1).

Nithin Kumar, Nakegawa P, Janic B, RomesroCA<sup>28</sup> was studied the AC-SDKP is occurs from the In-vitro thymosin  $\beta$ 4 & oligopeptidase, it is a tetra-peptide & it shows the anti-inflammatory activity. peptidase enzyme hydrolysis the Thymosin $\beta$ 4 gives amino terminal middle peptides. AC- SDKP is also occurs in rat kidney. plasma concentration of these peptide increased by captopril in In-vivo method.

Hui-Min Qian, Guo- Feng Pan<sup>29</sup> studied the cordymin is an anti- inflammatory and anti-nociceptive peptide. medicinal mushroom cordyceps sinensis is used to sanitized the cordymin. The cordymin reduces the tumour-necrosis-factor- $\alpha$ , IL-1 $\beta$  and anti- oxidant status. It prevents the stomach problems; these are tested by hot plate test for the calculation of the essential antinociceptive effect. Compare to cordymin & neurolysin, cordymin is very stronger than neurolysin. These are used as an anti-inflammatory and analgesic medicine.

Jae-Dong Lee, Su-young Kim<sup>30</sup> Study the designing of the BV in murine type II collagen – induced arthritis (CIA) model. Bovine type II collagen is experimentally identified by using male mice, it causes the arthritis and swelling problems. BV suppress the cytokines and production of TNF- $\alpha$ . BV acupuncture therapy, decreases the arthritis and immune reply in type II collagen made arthritis.

Wuyang Huang, Subhadeep Chakrabarti, majumder<sup>31</sup> demonstrated that IRW diminish the TNF- $\alpha$ -level and oxidative tension in endothelial cells. The IRW avoiding cardiovascular diseases. IRW occurs from egg protein with changing the enzyme inhibitory activity of angiotensin. it decreases the superoxide ions in the presence and absence of TNF- $\alpha$ . IRW obstructs the TNF- $\alpha$  induced rises of VCAM -1, ICAM -1 and MCP-1 creation in a concentration-dependent manner.

**The below table shows the different anti-inflammatory peptides from previous research done by scholars and their activity light thrown to draw the research inferences**

Peptides	Activities	References
2-Oxoamides	Inhibition of GVIA iPLA2	Anneta Smyrniotou maroula G- Kokotou
Chromofungin	Suppress the activities of macro phages	Sara La Manna, natale, Floria
S <sub>5</sub> -peptide	Decreases the creation of pro-inflammatory mediators.	Woo & Son

DR-10, MF-7, SR-7 & ML-7	Inhibiting phosphorylation of the NK-KB and Mapk signalling pathway	Yuhuan Chena,b, Hua Zhangb, Ronghua Liub
10f (PIP-18)	Supresses mRNA expression	Maung Maung Thwin, † Seetharama D
FLSFK, FLVYK, & FISYR.	Repressing the activity of hsPLA2	Chengy & Qiang
HSO2	Inhibits the release of TNF – $\alpha$	Guilherme D. Brand
LAIYA	Inhibitor for PLA2s.	Vikas Chandra, Jayashankar
PEP-1, PEP-2, TRYP - 2, MIX-2	Down regulated secretion of TNF- $\alpha$ and m-RNA expressions	Bingjun Qian
CaSR	TNF- $\alpha$ stimulated signalling pathway.	Yuhuan chen, Hua Zhaug
5A peptide	Reduces atherosclerosis and cholesterol content of the cells. prevent TNF $\alpha$ -induced NF-KB activation.	Fatiha Tabet
NCW peptide	Prevent the excess manufacture of pro-inflammatory cytokines	Young Ran Park, YunjoSoh
HHP-Fla-CH	Defeat the pro-inflammatory cytokines in lipopolysaccharide	Fatemeh Bamdad, Seulki Shin
AIP6	Suppressed Zymosan	Yu Fu Wang, Xiang Xu
Anntoxin	Inhibitor of tetrodotoxin-sensitive (TTX-S) voltage	Lin Wei, Li Dong
cyclosquamosin D(A1)	Suppress the secretion of IL-6	Afef Dellai, Igor Maricic, Cipin Kumar
Cordymin	Inhibits the acetic- acid induced abdominal constrictions	Hui-Min Qian, Guo- Feng Pan
IRW	It prevents TNF- $\alpha$ .	Wuyang Huang, Subhadeep Chakrabarti

**CONCLUSION:**

The present study emphasis various studies conducted on anti-oxidative, anti-hypersensitive, anti-inflammatory peptides various research scholars and unique findings and contributions. This study helps to insight about anti-inflammatory peptides and results drawn to identify the research gap and analyse the future scope of work and the table indicates the anti-inflammatory peptides and its activities. so that These peptides are used in medicinal field. It also suggest the previous work done on peptides research areas and research outcomes in medicinal field.

**REFERENCES**

1. Annetta Smyrniotou a , Maroula G. Kokotou b,c , Varnavas D. Mouchlis c , Efrosini Barbayianni b , George Kokotos b , Edward A. Dennis c,† , Violetta Constantinou-Kokotou a
2. Sara La Manna \*, Concetta Di Natale \*, Daniele Florio and Daniela Marasco
3. Peng Wang<sup>1</sup> \*, Yongtao Li<sup>2</sup> \*, Qiuping Shao<sup>1</sup> , Wenqin Zhou<sup>1</sup> , and Kuifeng Wang
4. Woo Seok Yang,<sup>1</sup> Young-Jin Son,<sup>2</sup> Mi-Yeon Kim,<sup>3</sup> Soochan Kim,<sup>3</sup> Jong-Hoon Kim,<sup>4</sup> and Jae Youl Cho
5. Yuhuan Chena,b , Hua Zhangb , Ronghua Liub , Lili Matsb , Honghui Zhub , K. Peter Paulsc , Zeyuan Denga,\* , Rong Tsaob,\*
6. Maung Maung Thwin,† Seetharama D. Satyanarayanajois,‡ Latha M. Nagarajarao,† Kazuki Sato,§ Pachiappan Arjunan,† Satish L. Ramapatna,| Prem V Kumar,⊥ and Ponnampalam Gopalakrishnakone†,
7. Chengye Zhan, Shusheng Li, Qiang Zhong, Daixing Zhou
8. Vikas Chandra,a Jayasankar Jasti,a Punit Kaur,a Sharmistha Dey,a A. Srinivasan,a Ch. Betzelb and T. P. Singha
9. Bingjun Qian<sup>1</sup> | Xin Zhao<sup>2</sup> | Ye Yang<sup>1</sup> | Chongchong Tian<sup>1</sup>
10. Sara Aviles-Gaxiola a , Josefina Leon-F elix a , Yazmín B. Jimenez-Nev arez a , Miguel A. Angulo-Escalantea , Rosalio Ramos-Payan b , Juventino Colado-Velazquez III c , J. Basilio Herediaa, \*
11. Chakrabarti, Forough Jahandideh, and Jianping Wu
12. Fatiha Tabet, Alan T. Remaley, Aude I. Segaliny, Jonathan Millet, Ling Yan, Shirley Nakhla, Philip J. Barter, Kerry-Anne Rye, Gilles Lambert.
13. Edwin Enrique Martínez Leoa , Juan José Acevedo Fernándezb , Maira Rubi Segura Camposa, \*



14. Sudheer Gupta† , Ashok K. Sharma† , Vibhuti Shastri, Midhun K. Madhu and Vineet K. Sharma\*
15. Ewelina Zielińska \*, Barbara Baraniak and Monika Kara
16. Young Ran Park<sup>1</sup>, Chan-Il Park<sup>2</sup>, Yunjo Soh<sup>1,3\*</sup>
17. Søren Drud Nielsen, Robert L. Beverly, Yunyao Qua, and David C. Dallasa,\*
18. Nosratola D. Vaziri<sup>1</sup> , Hamid Moradi<sup>1</sup> , Madeleine V. Pahl<sup>1</sup> , Alan M. Fogelman<sup>2</sup> and Mohamad Navab
19. Lei Zhao a,b,\* , Xuan Wang a,b , Xiao-Lei Zhang a,b , Qiao-Fei Xie a,b
20. Yong Hai Nan<sup>1</sup> , Ka Hyon Park<sup>1</sup> , Yoonkyung Park<sup>2</sup> , Young Jin Jeon<sup>3</sup> , Yangmee Kim<sup>4</sup> , Il-Seon Park<sup>1</sup> , Kyung-Soo Hahm<sup>1</sup> & Song Yub Shin<sup>1</sup> Kyung-Soo Hahm<sup>1</sup> & Song Yub Shin<sup>1</sup>
21. Mei-Li Chenga , Hsuan-Chi Wang a , Kuo-Chiang Hsub and Jyh-Sheng Hwanga \*
22. Yu-Pei Chen<sup>1,2</sup> • Chia-Hua Liang<sup>3</sup> • Hong-Tan Wu<sup>1,2</sup> • Hai-Yue Pang<sup>1,2</sup> • Chuan Chen<sup>4</sup> • Guey-Horng Wang<sup>1,2</sup> • Leong-Perng Chan<sup>5</sup>
23. Lin Lu<sup>1,2†</sup> , Ya Nan Wang<sup>1†</sup>, Ming Chun Li<sup>2</sup>, Hai Bo Wang<sup>2</sup>, Li Jin Pu<sup>2</sup>, Wen Quan Niu<sup>2</sup>, Hua Meng<sup>2</sup>, Er Li Yang<sup>2</sup>, Rui Yan Zhang<sup>1</sup>, Qi Zhang<sup>1</sup>, Qiang Zhao<sup>3</sup>, Qiu Jing Chen<sup>2</sup>, Raffaele De Caterina<sup>4\*</sup>, and Wei Feng Shen<sup>1,2\*</sup>
24. Balachandran Manavalan<sup>1</sup> \*, Tae H. Shin<sup>1,2</sup>, Myeong O. Kim<sup>3</sup> and Gwang Lee<sup>1,2</sup> \*
25. Mst. Shamima Khatun<sup>1†</sup>, Md. Mehedi Hasan<sup>1†</sup> and Hiroyuki Kurata<sup>1,2</sup> \*
26. Fatemeh Bamdad<sup>1</sup>, Seonghee Bark<sup>1</sup> , Chul Hee Kwon<sup>1</sup> , Joo-Won Suh<sup>2,\*</sup> and Hoon Sunwoo<sup>1,\*</sup>
27. Subhadeep Chakrabarti<sup>1</sup>, †, Snigdha Guha<sup>2</sup>, † and Kaustav Majumder<sup>2</sup>, \*
28. Sudheer Gupta†, Ashok K. Sharma†, Vibhuti Shastri, Midhun K. Madhu and Vineet K. Sharma\*
29. Zekai Halici a, \*, Gunnur Ozbakis Dengiz b, Fehmi Odabasoglu c , Halis Suleyman a , Elif Cadirci d , Mesut Halici
30. Armando Ialenti<sup>1</sup>, Vincenzo Santagada<sup>2</sup>, Giuseppe Caliendo<sup>2</sup>, Beatrice Severino<sup>2</sup>, Ferdinando Fiorino<sup>2</sup>, Pasquale Maffia<sup>1</sup>, Angela Ianaro<sup>1</sup>, Francesco Morelli<sup>3</sup>, Biagio Di Micco<sup>4</sup>, Maria Cartenó<sup>5</sup>, Paola Stiuso<sup>4</sup>, Vittoria Metafora<sup>3</sup> and Salvatore Metafora<sup>3</sup>
31. Maryam Dadar<sup>1</sup>, Youcef Shahali<sup>1</sup>, Sandip Chakraborty<sup>2</sup>, Minakshi Prasad-Fatemeh Tahoori<sup>1</sup>, Ruchi Tiwari<sup>4</sup>, Kuldeep Dhama<sup>5</sup>