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ABSTRACTS

Successful Expression of Adenovirus E3 CR1 Genes from constructs carrying Adenovirus Tripartite Leader sequences: a technical breakthrough

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Over 70 human adenovirus genotypes have been described to date and classified into seven species (HAdV-A to -G). One of the few characteristics distinguishing HAdV genomes of different species is the unique repertoire of E3 open reading frames (ORFs) encoding non-structural membrane proteins of unknown function. This species-specific feature likely contributes to the distinct pathogenic traits of each of these groups but the lack of functional information remains a major gap in the field. In our laboratory the characterization of species HAdV-B- and HAdV-E-specific E3 ORFs has been hampered by the intriguing difficulty to ectopically express the encoded proteins at adequate levels using traditional mammalian expression vectors. In infected cells transcription of these particular E3 genes is driven by the major late promoter at late time points post infection. All late transcripts carry a 5' 200 nucleotide untranslated sequence called the tripartite leader (TPL). TPL has been shown to facilitate efficient translation of late transcripts. We cloned small epitope-tagged versions of our ORFs of interest into commercially available vector pCI-Neo (Promega) with no detectable protein expression by Western Blot in lysates of transfected 293T cells. Literature searches brought to our attention vector pMT2 developed by Kaufman et al. that encodes HAdV-C TPL. To our surprise, expression of all 4 tagged proteins from the counterpart pMT2 constructs was readily detectable. We subsequently inserted the HAdV-E TPL sequence upstream of the E3 genes in the original pCI-Neo constructs and rescued protein expression for all cloned ORFs. RT-PCR analysis of gene expression showed that the mRNA levels for our transcripts of interest were also higher in the presence of TPL sequences suggesting that TPL may be contributing to both mRNA stabilization and efficient protein translation. These findings merit further investigation to identify how TPL sequences enhance protein expression of these particular E3 genes.

Optogenetic based regulation of autophagy against tauopathies

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Filamentous aggregation of microtubule associated protein tau, as neurofibrillary tangles (NFTs), is a major pathological hallmark of tauopathies including Alzheimer's disease (AD). This pathological tau (p-Tau) impairs microtubule function, axonal transport and synaptic function, which in turn strongly correlate with cognitive decline. Multiple reports have suggested impaired autophagic clearance of p-Tau within neurons leads to NFT pathology and neurodegeneration. Transcription factor EB (TFEB), which is a master regulator of autophagy flux, has recently been shown to clear p-Tau, prevent synaptic and behavioral defects in a mouse model of tauopathy. Furthermore, our group has recently demonstrated that induction of autophagy either via FDA approved drugs (Bromhexine/Flubendazole) or by overexpressed TFEB can clear inflammation-induced p-Tau in neuronal cells. However, sustained activation of TFEB and autophagy may pose the risk of burdening cellular bioenergetics and be deleterious during conditions such as ischemic stroke, which is more prevalent in aged individuals. Here we have tested a light-based gene expression system with a goal to achieve precise spatio-temporal control over TFEB expression and thus regulatable autophagy flux in neuronal cells. This technology utilizes an engineered version of EL222, a bacterial transcription factor that contains a Light-Oxygen-Voltage protein, which binds DNA when illuminated with blue light (465nm). HEK293T cells transiently transfected with EL222 and TFEB-Flag plasmids displayed robust TFEB-Flag expression when exposed to 465nm light (~2W/m2) for 9 -12 hours compared to no-light condition. As a first step in testing this approach in neuronal system, we tested inducible pluripotent stem cell derived neurons (iPSNs) from Down's syndrome patient and observed significantly elevated tau oligomers, tau hyperphosphorylated at AT180 and AT8 sites. In the ongoing studies, we are engineering lenti-viral expression system that encodes EL222 and TFEB-Flag to induce autophagy in primary neurons, iPSNs and in rTg4510 mouse model of tauopathy.

Specific and Potent Inhibitors of DNA Ligases as Cancer Therapeutics

Rhys C Brooks, Yoshihiro Matsumoto, Mark B. Carter, Larry A. Sklar, and Alan E. Tomkinson

Human DNA ligases I, III, and IV have unique functions that preserve genomic integrity by joining Okazaki fragments in DNA replication, and completing DNA damage repair through sealing of single- and double-strand DNA breaks. Dysregulation of these ligases has been correlated with reduced survival in leukemia, breast cancer, and neuroblastoma providing evidence for DNA ligases as therapeutic targets in limiting cancer progression. To elucidate such inhibitors we have optimized and validated a highly sensitive fluorescent-based ligation assay which utilizes an Alexa-488 labeled nicked DNA substrate that, when ligated to an upstream quencher, reduces the fluorescence output at a predictable rate. Our group has subsequently adapted this assay to characterize the kinetic and inhibitory properties of various compounds as they affect the nick repair capacity of these ligases. Recently, the compound SCR7 has been identified by others as a ligase IV specific inhibitor proposed to reduce tumor growth. However, we demonstrate that SCR7 is neither a selective nor potent inhibitor of ligases, suggesting it of little role as an effective adjunct. These data provide insight regarding the need for a sensitive and reliable assay to identify ligase inhibitors for cancer therapies. Moreover we have modified this novel fluorescent-based assay for high-throughput use of FDA approved chemical libraries with the aim of repurposing these compounds for cancer treatment.

Quantitating dendritic cell clustering in the lymph node

Janie Rae Byrum, Matthew Fricke, Justyna Tafoya, Melanie Moses, Judy L Cannon

The efficiency of the T cell search for antigen presented by dendritic cells (DCs) in lymph nodes (LNs) is a determinant of the overall timing of the T cell immune response to infection. While there is suggestion that DCs are clustered in LNs, there has been little quantitative analysis done to precisely analyze DC positioning in LNs. We present the quantitation of murine DC motility, surface area, and volume in the lymph node. We also use computational analysis of 2 photon microscopy images of explanted murine lymph nodes from CD11c-YFP mice to determine the degree of clustered-ness of DCs. Our analysis indicates a degree of DC clustering within the lymph node and that T cells and DCs may share positional information. Previously our lab identified sites in the lymph node visited with greater frequency by T cells than would be expected by random motility. We hypothesize such sites demonstrate that DC clusters may actively attract T cells. Elucidating whether T cell motility around DC clusters is distinctive from T cell motility in areas where DCs are non-clustered will help decipher T cell search strategy and the timing of the adaptive immune response.

Precision autophagy mediated by TRIMs governs key innate immunity systems

Tomonori Kimura, Seong Won Choi, Michael Mandell, Vojo P Deretic

The present paradigms of selective autophagy in mammalian cells cannot fully explain the specificity and selectivity of autophagic degradation. In this paper, we report that a subset of tripartite motif (TRIM) proteins act as specialized receptors for highly specific autophagy (precision autophagy) of key components of the inflammasome and type I interferon response systems. TRIM20 targets the inflammasome components, including NLRP3, NLRP1, and pro–caspase 1, for autophagic degradation, whereas TRIM21 targets IRF3. TRIM20 and TRIM21 directly bind their respective cargo and recruit autophagic machinery to execute degradation. The autophagic function of TRIM20 is affected by mutations associated with familial Mediterranean fever. These findings broaden the concept of TRIMs acting as autophagic receptor regulators executing precision autophagy of specific cytoplasmic targets. In the case of TRIM20 and TRIM21, precision autophagy controls the hub signaling machineries and key factors, inflammasome and type I interferon, directing cardinal innate immunity response systems in humans.

Pathological tau induces inflammasome activation and neuroinflammation relevant to Alzheimer's disease

Shanya Jiang, Jessica Binder, Nicole Maphis, Lea Weston, Walter Duran, Crina Floruta, Stephen Jett, Eicke Latz and Kiran Bhaskar

Hyperphosphorylation and aggregation of tau protein is a pathological hallmark of Alzheimer's disease (AD) and related tauopathies. Our previous studies demonstrated that activation of microglia leads to accelerated tau pathology and cognitive impairment. However, it remains elusive how the microglial activation occurs and precede tau pathology. Here, we show that pathological Tau (p-Tau) is secreted in either exosome-dependent or –independent manner from neuroblastoma (N2a) cells expressing human p-Tau. This led to uptake of p-Tau by BV2 microglial cells, expression of various pro-inflammatory genes and activation of inflammasome. Incubation of ASC-cerulean macrophages with paired helical filaments (PHFs) purified from rTg4510 transgenic mice brains or from human AD patient brain resulted in inflammasome activation and IL-1 secretion into the media. Furthermore, rTg4510 mice showed age-dependent increase in the pro-inflammatory gene expression, which can be mitigated by the suppression of human tau via doxycycline treatment. Taken together, our results suggest that p-Tau derived from neurons can be taken up into the microglia and serve as damage-associated molecular pattern to elicit inflammation by activating inflammasome and inducing the maturation of IL-1β, which in turn can exacerbate tau pathology and lead to neurodegeneration.

IRGM Governs the Core Autophagy Machinery to Conduct Antimicrobial Defense

Suresh Kumar, Santosh Chauhan, Michael Mandell, and Vojo P Deretic

IRGM, encoded by a uniquely human gene conferring risk for inflammatory diseases, affects autophagy through an unknown mechanism. Here, we show how IRGM controls autophagy. IRGM interacts with ULK1 and Beclin 1 and promotes their co-assembly thus governing the formation of autophagy initiation complexes. We further show that IRGM interacts with pattern recognition receptors including NOD2. IRGM, NOD2, and ATG16L1, all of which are Crohn's disease risk factors, form a molecular complex to modulate autophagic responses to microbial products. NOD2 enhances K63-linked polyubiquitination of IRGM, which is required for interactions of IRGM with the core autophagy factors and for microbial clearance. Thus, IRGM plays a direct role in organizing the core autophagy machinery to endow it with antimicrobial and anti-inflammatory functions.

ANALYSIS OF DNA REPLICATION DURING THE RE-ENTRY OF QUIESCENT CELLS INTO THE CELL CYCLE

Po-Hsuen Lee and Mary Ann Osley

Cellular quiescence is a stable and non-growing state that is critically important for the survival of all organisms in the face of limiting nutrients. The defining characteristics of quiescent cells are their low level of gene transcription compared to growing cells, their resistance to cellular stresses, their long-term viability, and their ability to synchronously re-enter the cell cycle when nutrients are restored. Quiescent cells are in a G0 phase that is characterized by the absence of DNA replication. A number of studies suggest that G0 phase is not similar to G1 phase, in which DNA replication is also absent. We use budding yeast Saccharomyces cerevisiae as a model to characterize the similarities and differences between G0 and G1 phases with respect to the DNA replication program utilized as cells enter the cell cycle. To examine the program that regulates the initiation of DNA replication during the re-entry of quiescent G0 cells into the cell cycle, we first measured the cellular levels of ORC, Mcm4, and Cdc45, the markers for origin binding, pre-RC formation and origin activation, respectively, before and after release of these cells into the cell cycle. We also performed chromatin immunoprecipitation (ChIP) to examine the binding of these replication proteins to origins in G0 cells and during release into the cell cycle. Our preliminary ChIP data indicate that fewer origins are active when G0 cells enter the cell cycle compared to G1 cells. In support of this conclusion, hydroxyurea (HU) and methyl methanesulfonate (MMS) induced low levels of Rad53 phosphorylation in G0 released cells, another indication of fewer active replication forks.

Adipokine Regulation of Type 2 Immunity and Browning of Fat

Yan Luo, Xiaofeng Ding, Handong Zheng, Xin Yang, Xuexian Yang, Meilian Liu

Group 2 innate lymphoid cells (ILC2s) have been shown to orchestrate type 2 innate and adaptive immune responses and drive browning and prevent the development of obesity. However, how adipose-resident ILC2s are recruited and activated remains largely unknown. Here, we show that adiponectin deficiency greatly increases the fraction and activity of group 2 innate lymphoid cells (ILC2s). In addition, adiponectin deficiency promotes the expression of IL-4 and IL-13, activation of M2 macrophages, and production of norepinephrine in iWAT; all well characterized downstream events of ILC2s activation. Consistent with these findings, adiponectin treatment suppresses the production of IL-13 induced by IL-7 and IL-33 in primary ILC2s from iWAT, and absence of ILC2s diminishes the suppressing effect of AdipoRon, an adiponectin receptor agonist on the expression of uncoupling protein (UCP1) in presence of eosinophils and macrophages in brown adipocytes. Consistent with this, basal, acute, and chronic cold-induced energy expenditure as well as the browning effect are enhanced in adiponectin knockout (KO) mice compared to wild-type control mice. Furthermore, administration of adipoRon downregulates the expression of UCP1 in iWAT and suppressed basal and cold-induced energy expenditure in adiponectin KO mice. Taken together, our study strongly suggest that adiponectin inhibits the browning effect and thermogenesis through regulating the function of ILC2s in adipose tissue.

Response of quiescent cells to exogenous DNA damage

Lindsey J. Long, Jacqueline S. Welty, and Mary Ann Osley

Under certain conditions, such as nutrient deprivation, cells exit the cell cycle and enter G0, a state of quiescence. Quiescent cells are viable but non-growing and can re-enter the cell cycle when appropriate stimuli are provided. Quiescence is an important feature of adult stem cells, where it provides a pool of cells for self-renewal or differentiation into appropriate cell lineages. Quiescent cells must respond to exogenous stresses such as DNA damage so that deleterious mutations are not transmitted to progeny upon differentiation. Our data show that quiescent cells are more sensitive to UV irradiation when compared to growing cells. We find that the majority of UV lesions are removed from quiescent cells before these cells re-enter the cell cycle. Moreover, we observe that the frequency of UV-induced mutations is significantly higher in quiescent cells than in G1 arrested cells. We are currently using genetic, molecular, and genomic approaches to investigate the hypothesis that UV induced lesions are directly repaired in G0 cells through the gap-filling activity of mutagenic translesion DNA polymerases.

PIK3CA mutations lead to upregulation of HPV16 E6/E7 through deregulation of Hippo/Yap and activation of EGFR/MEK Signaling pathways

Adrian J. Luna, Rosa T. Sterk and Michelle A. Ozbun

Recent genomic studies reveal that activating PI3K pathway mutations are enriched in HPV16-positive (HPV+) cancers with the most commonly mutated gene being PIK3CA, encoding the catalytic subunit of the PI3K pathway. The PIK3CA gene is mutated ~33% of the time in cervical, anal, penile, and oropharyngeal cancers. The prevalence of this mutation in HPV related cancers leads us to hypothesize that PIK3CA mutations cooperate with the HPV oncogenes to transform keratinocytes. We postulate that PIK3CA mutations lead to the loss of contact inhibition through inhibition of the Hippo tumor suppressor pathway. This allows YAP, an oncogenic transcription factor negatively regulated by the Hippo pathway, to enter the nucleus and drive expression of the epidermal growth factor receptor (EGFR) and its ligands. The EGFR ligands activate the EGFR signaling and drive expression of HPV E7 and E6 oncogenes. To test our hypothesis we are using cell lines that represent the pre-neoplastic state and are able to recapitulate the entire HPV life cycle when grown as epithelial raft tissues. We find that EGFR stimulation by downstream targets of YAP upregulate E7 protein expression whereas an ERK1/2 inhibition abolishes E7 expression. Furthermore, we show that E7 expression is down regulated as the cells become confluent suggesting a contact inhibition mechanism is involved in the regulation of E7 expression. Notably, we found that the Hippo pathway is largely inactive in the SiHa HPV16+ cervical cancer cell line, which harbors PIK3CA gene amplification, even when the cells are at increased cell density when compared to our pre-malignant cells. These results suggest that the Hippo tumor suppressor pathway is abrogated by PIK3CA mutations allowing uncontrolled expression of E7. We will investigate this directly by introducing canonical PIK3CA mutant genes into the HPV16+ pre-neoplastic cell lines.

Retroviral recognition by restriction factor TRIM5α triggers autophagy

Michael A Mandell and Vojo P Deretic

The TRIM family of proteins is notable because a high proportion of its constituents act as cell-autonomous antiviral defenses. Of antiviral TRIMs, the most well-known is TRIM5α due to its potent antiretroviral activity. TRIM5α blocks retroviruses in a species-specific manner, with rhesus TRIM5α effectively inhibiting HIV infection but human TRIM5α lacking this ability. We recently found that most TRIMs, including TRIM5α, regulate autophagy, a degradative pathway with known antiviral potential. This finding led us to consider whether autophagy regulation may contribute to TRIM5α's antiviral activities. We took advantage of TRIM5α's viral species specificity to test the hypothesis that TRIM5α might induce autophagy in response to capsid engagement by its cognate virus. We find HIV infection activates autophagy in cells expressing rhesus, but not human, TRIM5α. When we assessed TRIM5α's ability to induce autophagy, we found that TRIM5α assembles and activates key autophagy regulators ULK1 and Beclin 1. Interactions between TRIM5α and autophagy factors are required for TRIM5α's ability to stimulate autophagy. In addition to activating autophagy in response to HIV infection, rhesus TRIM5α directs its own autophagic degradation along with that of HIV capsid protein p24. This activity of TRIM5α requires its interactions with autophagy effector proteins (LC3s and GABARAPs) as well as TRIM5α's enzymatic activity as an ubiquitin E3 ligase. Collectively, these data indicate that TRIM5α acts as a pattern recognition/autophagic receptor for incoming retroviral capsids transducing pro-autophagy signaling while simultaneously directing removal of incoming viral components by autophagy.

pTau-VLP vaccine reduces tau phosphorylation, aggregation, neuroinflammation, neuronal apoptosis, mitigates structural MR changes and rescues behavioral deficits

Maphis N, Crossey E, Peabody J, Ahmad FAJ, Alvarez M, Yang Y, Sillerud L, Peabody D, Chackerian B and Bhaskar K

Alzheimer's disease (AD) is characterized by progressive cognitive decline leading to dementia. One of the major pathological processes in AD is the neuronal accumulation of Microtubule Associated Protein Tau (MAPT or Tau). Tau typically provides support for neuronal cytoarchitecture; however, in AD, it undergoes a process called hyperphosphorylation, which in turn leads to the accumulation of tau as tangles within neurons, causing cell death and brain inflammation, culminating into dementia. In the current study, we conjugated a pathological form of p-Tau (MAPTpT181) to virus-like particles (VLP) to utilize the body's immune response, specifically B cells, to generate antibodies against phosphorylated tau. We used VLPs derived from a bacteriophage called 'Qb', which contain a high density of viral surface proteins to which MAPTpT181 will adhere forming p-Tau VLPs. We administered (intramuscular) pTau-VLP and VLP (control) to a humanized tau mouse model of AD (rTg4510), bi-weekly for 6-weeks. First, we observed a robust antibody response against p-Tau in the serum and brains of vaccinated mice. Next, we observed significant improvement in recognition memory and spatial memory by the Novel Object Recognition (NOR) and the Morris Water Maze (MWM) tests, respectively. The rTg4510 animals receiving the control VLP did not perform well on either task. In addition, p-Tau VLP-vaccinated rTg4510 mice had a significant reduction in phosphorylated tau, Gallyas silver-positive tau tangles (in the cortex and hippocampus), insoluble tau, CD45 (brain inflammation), and TUNEL (apoptotic neurons) immunoreactivity. Furthermore, pTau-VLP vaccination was shown to mitigate some of the white matter changes observed in the rTg4510 mice, which received the control VLP vaccine. Overall, pTau-VLP treatment in the rTg4510 animals rescued cognitive function by decreasing levels of pTau, tau tangles and neuroinflammation while simultaneously preventing white matter damage. In conclusion, a VLP-based vaccination targeting pathological tau is an effective therapy and should be investigated further.

ROCK enables interstitial movement of T cells along the vasculature of inflamed lungs

Paulus Mrass, Sreenivasa Rao Oruganti, Matthew G. Fricke, Justyna Tafoya, Janie R. Byrum, Melanie Moses, and Judy L. Cannon

Effector T cell migration through tissues enables control of infection or mediates inflammatory damage. Nevertheless, the molecular mechanisms that regulate migration of effector T cells within the interstitial space of inflamed lungs remain incompletely understood. Here, we studied T cell migration in a murine model of acute lung injury with two-photon imaging of intact lung tissue. Computational analysis revealed that T cells switched between confined and virtually straight “ballistic” migration, which was facilitated by guidance along lung-associated vasculature. Mechanistically, chemokine-dependent Gi signaling regulated speed but not straight migration of lung-infiltrating T cells. In contrast, ROCK, a regulator of the actomyosin cytoskeleton, was required for both high-speed migration and ballistic migration. These data suggest that T cells are squeezing through preformed tissue channels that enables tissue-sampling by T cells during acute lung injury.

CARMA1 is a Novel Regulator of T-ALL disease and leukemic cell migration to the CNS

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Despite significant progress in therapeutic treatment of acute lymphoblastic leukemia (ALL), ALL remains the leading cause of cancer-related death in children. 15% of ALL cases are T-lineage (T-ALL), one major therapeutic obstacle in T-ALL treatment is the involvement of the central nervous system (CNS). In this study, we identify CARMA1 (CARD11) as a novel regulator of T-ALL disease. Using multiple animal models of T-ALL, we show that CARMA1 deficiency leads to increased survival in animals with T-ALL. Interestingly, decreased CARMA1 expression does not affect in vitro T-ALL cell proliferation or survival, but instead inhibits T-ALL cell migration. While overall tumor burden is decreased in the absence of CARMA1 expression, specific organs such as the CNS show a particularly dramatic decrease in leukemic cell accumulation. In agreement with results from animal models, we show that CARMA1 is upregulated in T-ALL primary patient samples in cases where CNS disease was present at diagnosis. These results support the hypothesis that CARMA1 regulates T-ALL disease, and our findings suggest that CARMA1 may specifically affect T-ALL cell migration to the CNS, offering a mechanistic basis for future studies involving better control of T-ALL in the CNS compartment.

Inhibition of MK2 Reduces Chronic Inflammation and Regresses Tumors in a Mouse Model of Colorectal Cancer

Anita L. Ray, Eliseo F. Castillo, Robert A. Nofchissey, and Ellen J. Beswick

Chronic inflammation is a known risk factor for colorectal cancer (CRC). Cancers in patients with increased inflammatory cytokines in tumor tissue are associated with increased drug resistance, metastasis, and mortality. We have identified mitogen-activated protein kinase-activated protein kinase 2 (MK2) as a regulator of pro-inflammatory cytokines and promoter of proliferation in CRC progression. MK2 signaling induces IL-1, IL-6, and TNF-α production, which have been associated with CRC development and progression. We investigated this pathway in an inflammation-related model of CRC. This model relies on an initial dose of the carcinogen azoxymethane, followed by administration of dextran sodium sulfate to model chronic inflammation. C57BL/6 mice were found to develop colon tumors by day 54 in this model. Thus, we treated mice with MK2 inhibitors starting at this time point, 3 times a week for 3 weeks. At day 80, neoplasm number and size were measured, as well as pro-inflammatory cytokines and immune cell profiles in the colon using flow cytometry and multiplex bead-based arrays. MK2 inhibition drastically reduced colon pro-inflammatory cytokines, influx of immune cells, and tumor burden compared to vehicle control treated mice. Upon testing two separate MK2 inhibitors, 6/7 and 5/7 mice were completely free of tumors after treatment. We conclude that this pathway is an important contributor to CRC and could be a promising therapeutic target.

IL-10 deficiency enhances tau phosphorylation in a mouse model of LPS-induced systemic inflammation

Lea Weston, Shanya Jiang, Nicole Maphis, and Kiran Bhaskar

Tauopathies include a number of neurodegenerative diseases associated with accumulation of hyperphosphorylated microtubule associated protein tau (MAPT or tau) as neurofibrillary tangles (NFTs). The presence of hyperphosphorylated tau (pathological tau) has been shown to strongly correlate with cognitive decline. Furthermore, neuroinflammation is a common feature of tauopathies and studies from our lab have suggested that microglia-mediated neuroinflammation promotes tau phosphorylation in a mouse model of tauopathy. Given that anti-inflammatory cytokines are also key players in regulating immune responses in the brain, the direct effects of certain prominent anti-inflammatory cytokines in tau pathology is still unclear. One of the most established anti-inflammatory cytokines is interleukin-10 (IL-10), which plays a role in downregulating pathways involved in inflammation and activation of kinases that may be involved in tau phosphorylation. To determine if IL-10 has a role in regulating pathological tau phosphorylation, here we compared the effects of lipopolysaccharide (LPS) administration in 5-6 month old C57BL/6 (WT) and IL-10 knockout (KO) mice. First, consistent with our previously published results, LPS administration increased tau phosphorylation (on AT8, AT180 sites) within 24 h in the hippocampus of WT mice compared to vehicle injected WT mice. Second, IL-10 KO mice injected with the same dose of LPS showed significantly enhanced AT8 and AT180 site tau phosphorylation compared to LPS injected WT mice. Third, levels of total tau were significantly reduced in LPS-injected IL-10 KO mice compared to vehicle injected IL-10 KO and WT control mice (with or without LPS). Fourth, LPS injected IL-10 KO mice show significantly elevated levels of activated (pT180/pY182) p38 mitogen activated protein kinase (p38 MAPK) compared to LPS injected WT mice. Finally, basal levels of interleukin-1β (IL-1β) are elevated in IL-10 KO mice compared to WT mice. Our results suggest IL-10 plays a role to reduce inflammation-induced tau pathology relevant to tauopathy.

CIS stabilizes regulatory T cells through antagonizing TH2 program

Handong Zheng, Eliseo Castillo, Chen Dong, Xuexian Yang

Abstract: Regulatory T (Treg) cells play an essential role in immune homeostasis. Under the pro-inflammatory settings such as autoimmune diseases, the function of Treg cells is impaired, in which pro-inflammatory cytokines are involved in destabilizing Treg cells. However, the pathways that stabilize Treg cells have not been well understood. We have shown that cytokine-induced SH-2 protein (CIS) inhibits STAT protein activation; our current study indicates that CIS is required for stabilizing Treg cells in a Treg cell-intrinsic manner. We found that Cis-deficient iTreg cells had impaired suppressive activity in vitro. Both Germline and Treg-specific Cis-deficient mice developed lymphadenopathy, splenomegaly and multiple organ inflammation, which is associated with spontaneous loss of Foxp3 and gain of Th2 cytokine expression in iTreg cells. Autocrine IL-4 induced pSTAT6, which silenced Foxp3 transcription and resulted in destabilization of iTreg cells.