10 best publications (in order of importance):

1. Liu CSC, Mandal T, Biswas P, Hoque MA, Bandopadhyay P, Sinha BP, Sarif J, D'Rozario R, Sinha DK, Sinha B, **Ganguly D***. Piezo1 mechanosensing regulates integrin-dependent chemotactic migration in human T cell. **eLife, 2023**, in production, doi: https://doi.org/10.1101/2022.08.16.504114v2
   Citations: 0 (in production)
   Summary: First evidence for a crucial role of the Piezo1 mechanosensors in integrin-drive chemotactic migration of human T lymphocytes. T cells are crucial for efficient antigen-specific immune responses and thus their migration within the body, to inflamed tissues from circulating blood or to secondary lymphoid organs, play a very critical role. A migrating T cell is expected to sense diverse external and membrane-intrinsic mechano-physical cues, but molecular mechanisms of such mechanosensing in cell migration are not established. We found that deficiency of Piezo1 in human T cells interfered with integrin-dependent cellular motility on ICAM-1-coated surface. Piezo1 recruitment at the leading edge of moving T cells is dependent on and follows focal adhesion formation at the leading edge and local increase in membrane tension on chemokine receptor activation. Piezo1 recruitment and activation, followed by calcium influx and calpain activation, in turn are crucial for the integrin LFA-1 recruitment at the leading edge of the chemotactic human T cells. Thus we found that Piezo1 activation in response to local mechanical cues constitutes a membrane-intrinsic component of the 'outside-in' signaling in human T cells, migrating in response to chemokines, that mediates integrin recruitment to the leading edge.

2. Liu CSC, Raychaudhuri D, Paul B, Chakrabarty Y, Ghosh AR, Rahaman O, Talukdar A, **Ganguly D***. *Cutting Edge:* Piezo1 mechanosensors optimize human T cell activation. **Journal of Immunology, 2018** Feb 15;200(4):1255-1260.
   Citations: 104
   Summary: Discovery of a hitherto unknown regulatory mechanism for human T cell activation and provide the first evidence for the involvement of Piezo1 mechanosensors in immune regulation. TCRs recognize peptides on MHC molecules and induce downstream signaling, leading to activation and clonal expansion. In addition to the strength of the interaction of TCRs with peptides on MHC molecules, mechanical forces contribute to optimal T cell activation, as reflected by the superior efficiency of immobilized TCR-cross-linking Abs compared with soluble Abs in TCR triggering, although a dedicated mechanotransduction module is not identified. We found that the professional mechanosensor protein Piezo1 is critically involved in human T cell activation. Although a deficiency in Piezo1 attenuates downstream events on ex vivo TCR triggering, a Piezo1 agonist can obviate the need to immobilize TCR-cross-linking Abs. Piezo1-driven Ca2+ influx, leading to calpain activation and organization of cortical actin scaffold, links this mechanosensor to optimal TCR signaling.

3. Ghosh AR, Bhattacharya R, Bhattacharya S, Nargis T, Rahaman O, Duttagupta P, Raychaudhuri D, Chen Liu CS, Roy S, Ghosh P, Khanna S, Chaudhuri T, Tantia O, Haak S, Bandyopadhyay S, Mukhopadhyay S, Chakrabarti P, Ganguly D*. Adipose Recruitment and Activation of Plasmacytoid Dendritic Cells Fuel Metaflammation. **Diabetes. 2016** Aug 25. 65 (11): 3440-3452.
   Citations: 88

Summary: First evidence for involvement of plasmacytoid dendritic cells and type I interferons in obesity associated metabolic syndrome in humans. In obese individuals, visceral adipose tissue (VAT) is the seat of chronic low-grade inflammation (metaflammation), but the mechanistic link between increased adiposity and metaflammation largely remains unclear. In obese individuals, deregulation of a specific adipokine, chemerin, contributes to innate initiation of metaflammation by recruiting circulating plasmacytoid dendritic cells (pDCs) into VAT through chemokine-like receptor 1 (CMKLR1). Adipose tissue-derived high-mobility group B1 (HMGB1) protein activates Toll-like receptor 9 (TLR9) in the adipose-recruited pDCs by transporting extracellular DNA through receptor for advanced glycation end products (RAGE) and induces production of type I interferons (IFNs). Type I IFNs in turn help in proinflammatory polarization of adipose-resident macrophages. IFN signature gene expression in VAT correlates with both adipose tissue and systemic insulin resistance (IR) in obese individuals, which is represented by ADIPO-IR and HOMA2-IR, respectively, and defines two subgroups with different susceptibility to IR.

4. **Ganguly D***. Do type I interferons link systemic autoimmunities and metabolic syndrome in a pathogenetic continuum? (Review) **Trends in Immunology, 2018** Jan;39(1):28-43.
   Citations: 54
   Summary: First proposition of a pathogenic continuum encompassing autoimmune diseases and metabolic disorders. The central pathogenetic role of type I interferons (IFNs) in several systemic autoimmune diseases is well established. Recent studies have also discovered a similar crucial role of type I IFNs in different components of metabolic disorders. Self nucleic acid-driven Toll-like receptor (TLR) activation in plasmacytoid dendritic cells (pDCs) and type I IFN induction appear to be the key initiating events shared by most of these autoimmune and metabolic diseases. Further strengthening this link, many patients with systemic autoimmunities also present with metabolic disorders. This concurrence of autoimmunities and metabolic disorders may be explained by a single pathogenetic continuum, and suggests shared targets for potential new therapies.

5. Ray Y*, Paul SR, Bandopadhyay P, D'Rozario R, Sarif J, Lahiri A, Bhowmik D, Vasudevan JS, Maurya R, Kanakan A, Sharma S, Kumar M, Singh P, Roy R, Chaudhury K, Maiti R, Bagchi S, Maiti A, Perwez MM, Mondal A, Tewari A, Mandal S, Roy A, Saha M, Biswas D, Maiti C, Chakraborty S, Sharma Sarkar B, Haldar A, Saha B, Sengupta S, Pandey R, Chatterjee S, Bhattacharya P, Paul S, **Ganguly D***. A Phase 2 Single Center Open Label Randomised Control Trial for Convalescent Plasma Therapy in Patients with Severe COVID-19. **Nature Communications, 2022**, 13(1):383.
   Citations: 89
   Summary: A single center open label phase 2 randomised control trial (Clinical Trial Registry of India No. CTRI/2020/05/025209) was done to assess clinical and immunological benefits of passive immunization using convalescent plasma therapy. Primary outcomes were all-cause mortality by day 30 of enrolment and immunological correlates of response to therapy if any, for which plasma abundance of a large panel of cytokines was quantitated before and after intervention to assess the effect of CPT on the systemic hyper-inflammation encountered in these patients. The secondary outcomes were recovery from ARDS and time taken to negative viral RNA PCR as well as to report any adverse reaction to plasma therapy. Transfused convalescent plasma was characterized in terms of its neutralizing antibody content as well as

proteome. The trial was completed and it was found that primary outcome of all-cause mortality was not significantly different among severe COVID-19 patients with ARDS randomized to two treatment arms (Mantel-Haenszel Hazard Ratio 0.6731, 95% confidence interval 0.3010-1.505, with a P value of 0.3424 on Mantel-Cox Log-rank test). No adverse effect was reported with CPT. In severe COVID-19 patients with mild or moderate ARDS no significant clinical benefit was registered in this clinical trial with convalescent plasma therapy in terms of prespecified outcomes.

6. Bandopadhyay P#, Rozario R#, Lahiri A#, Sarif J#, Ray Y#, Paul SR#, Roy R, Maiti R, Chaudhuri K, Bagchi S, Maiti A, Perwez MM, Sharma Sarkar B, Roy D, Chakraborty R, Vasudevan JS, Sharma S, Biswas D, Maiti C, Saha B, Bhattacharya P, Pandey R, Chatterjee S, Paul S, **Ganguly D***. Nature and dimensions of the systemic hyper-inflammation and its attenuation by convalescent plasma in severe COVID-19. **Journal of Infectious Diseases. 2021**. Aug 16;224(4):565-574.
Citations: 60
Summary: Identification of an anti-inflammatory role of COVID-19 convalescent plasma independent of its neutralizing antibody content. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has led to significant morbidity and mortality. While most suffer from mild symptoms, some patients progress to severe disease with acute respiratory distress syndrome (ARDS) and associated systemic hyperinflammation. First, to characterize key cytokines and their dynamics in this hyperinflammatory condition, we assessed abundance and correlative expression of a panel of 48 cytokines in patients progressing to ARDS as compared to patients with mild disease. Then, in an ongoing randomized controlled trial of convalescent plasma therapy (CPT), we analyzed rapid effects of CPT on the systemic cytokine dynamics as a correlate for the level of hypoxia experienced by the patients.

7. Rahaman O, Bhattacharya R, Liu CSC, Raychaudhuri D, Ghosh AR, Bandopadhyay P, Pal S, Goswami RP, Sircar G, Ghosh P, **Ganguly D***. Cutting Edge: Dysregulated endocannabinoid-rheostat for plasmacytoid dendritic cell activation in a systemic lupus endophenotype. **Journal of Immunology, 2019** Mar 15;202(6):1674-1679.
Citations: 15
Summary: Discovery of a novel regulatory pathways in human plasmacytoid dendritic cells, driven by a lipid metabolite (2-arachidonyl glycerol). Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, characterized by loss of tolerance toward self nuclear Ags. Systemic induction of type I IFNs plays a pivotal role in SLE, a major source of type I IFNs being the plasmacytoid dendritic cells (pDCs). Several genes have been linked with susceptibility to SLE in genome-wide association studies. We aimed at exploring the role of one such gene, α/β-hydrolase domain-containing 6 (ABHD6), in regulation of IFN-α induction in SLE patients. We discovered a regulatory role of ABHD6 in human pDCs through modulating the local abundance of its substrate, the endocannabinoid 2-arachidonyl glycerol (2-AG), and elucidated a hitherto unknown cannabinoid receptor 2 (CB2)-mediated regulatory role of 2-AG on IFN-α induction by pDCs. We also identified an ABHD6High SLE endophenotype wherein reduced local abundance of 2-AG relieves the CB2-mediated steady-state resistive tuning on IFN-α induction by pDCs, thereby contributing to SLE pathogenesis.

8. Raychaudhuri D, Bhattacharya R, Sinha BP, Liu CSC, Ghosh AR, Rahaman O, Bandopadhyay P, Sarif J, D'Rozario R, Paul S, Das A, Sarkar DK, Chattopadhyay S, **Ganguly D***. Lactate Induces Pro-tumor Reprogramming in Intratumoral Plasmacytoid Dendritic Cells. **Frontiers in Immunology. 2019** Aug 7;10:1878.
Citations: 79
Summary: Discovery of a novel regulatory pathways in human plasmacytoid dendritic cells, driven by a oncometabolite (lactate). Plasmacytoid dendritic cells are the most efficient producers of type I interferons, viz. IFNα, in the body and thus have the ability to influence anti-tumor immune responses. But repression of effective intra-tumoral pDC activation is a key immuno-evasion strategy exhibited in tumors-tumor-recruited pDCs are rendered "tolerogenic," characterized by deficiency in IFNα induction and ability to expand regulatory T cells in situ. But the tumor-derived factors that drive this functional reprogramming of intra-tumoral pDCs are not established. In this study we aimed at exploring if intra-tumoral abundance of the oncometabolite lactate influences intra-tumoral pDC function. We found that lactate attenuates IFNα induction by pDCs mediated by intracellular Ca2+ mobilization triggered by cell surface GPR81 receptor as well as directly by cytosolic import of lactate in pDCs through the cell surface monocarboxylate transporters, affecting cellular metabolism needed for effective pDC activation. We also found that lactate enhances tryptophan metabolism and kynurenine production by pDCs which contribute to induction of FoxP3+ CD4+ regulatory T cells, the major immunosuppressive immune cell subset in tumor microenvironment. We validated these mechanisms of lactate-driven pDC reprogramming by looking into tumor recruited pDCs isolated from patients with breast cancers as well as in a preclinical model of breast cancer in mice. Thus, we discovered a hitherto unknown link between intra-tumoral abundance of an oncometabolite resulting from metabolic adaptation in cancer cells and the pro-tumor tolerogenic function of tumor-recruited pDCs, revealing new therapeutic targets for potentiating anti-cancer immune responses.

9. Sinha BP, Mehta P2, Hoque MA, Bandopadhyay P, Nandi A, Saha I, Nandi Mitra A, Mondal A, Bhattacharjee B, Chamilos G, Pandey R*, Basu K*, **Ganguly D***. Deficient phagocytosis in circulating monocytes from patients with COVID-19-associated mucormycosis. **mBio, 2023** Jun 27;14(3):e0059023.
Citations: 1
Summary: First evidence for monocyte dysfunctions contributing to susceptibility to mucormycosis in severe COVID-19 patients. A number of cases of mucormycosis, often fatal, were reported among severe COVID-19 patients from India as well as from some other parts of the world. However, specific immunocellular mechanisms that underlie susceptibility to this fungal infection in COVID-19 remain largely unexplored. Our study reports a deficiency in phagocytosis by monocytes in COVID-19 patients who are concomitantly afflicted with mucormycosis, with this deficiency being linked to a characteristic monocyte transcriptome as well as a circulating cytokine signature. The functional phenotype and cytokine signature of the monocytes may provide useful biomarkers for detecting potential susceptibility to mucormycosis in COVID-19 as well as in other viral infections.

10. Mukherjee A#, Raychaudhuri D#, Sinha BP#, Kundu B, Mitra M, Paul B, Bandopadhyay P, **Ganguly D***, Talukdar A*. A chemical switch for transforming a purine agonist for toll-like receptor 7 to a clinically relevant antagonist. **Journal of Medicinal Chemistry. 2020** May 14;63(9):4776-4789.

Citations: 18

Summary: First purine antagonist for toll-like receptor 7, validated in a preclinical model in vivo. Toll-like receptor 7 (TLR7) is an established therapeutic target in myriad autoimmune disorders, but no TLR7 antagonist is available for clinical use to date. Herein, we report a purine scaffold TLR7 antagonist, first-of-its-kind to our knowledge, which was developed by rationally dissecting the structural requirements for TLR7-targeted activity for a purine scaffold. Specifically, we identified a singular chemical switch at C-2 that could make a potent purine scaffold TLR7 agonist to lose agonism and acquire antagonist activity, which could further be potentiated by the introduction of an additional basic center at C-6. We ended up developing a clinically relevant TLR7 antagonist with favorable pharmacokinetics and 70.8% oral bioavailability in mice. Moreover, the TLR7 antagonists depicted excellent selectivity against TLR8. To further validate the in vivo applicability of this novel TLR7 antagonist, we demonstrated its excellent efficacy in preventing TLR7-induced pathology in a preclinical murine model of psoriasis.