Final Report

Inflammation is a fundamental biological program, which responds to tissue injury and infection. The program involves migration of neutrophils and macrophages to the injured or infected tissue site, phagocytosis of dead cells (efferocytosis) and pathogens, apoptosis of neutrophils, clearance of apoptotic neutrophils by macrophages and reprogramming of inflammatory macrophages to alternatively activated macrophages that guide the healing process. Every day millions of cells also die by apoptosis as part of the normal cell turnover. While phagocytosis of a variety of targets normally triggers a battery of pro-inflammatory responses in macrophages, ingestion of apoptotic cells by macrophages induces an anti-inflammatory phenotype. As a result the everyday removal of apoptotic cells is silent, in addition, clearance of apoptotic neutrophils plays a key role also in the initiation of the resolution phase of inflammation. In our studies we used the thymic apopto-phagocytosis program as a model to describe the interactions between apoptotic cells and macrophages and to identify molecules that regulate phagocytosis of apoptotic cells and the response of macrophages to apoptotic cells involving enhanced phagocytosis, inhibition of inflammation and regulation of apoptosis.

Results we have published during 2012-2016 with the support of the OTKA fund:

Transglutaminase 2 and apoptosis of T cells

Role of transglutaminase 2 in T cell apoptosis

Previous studies from our laboratory have indicated that transglutaminase 2 (TG2) is associated with the in vivo apoptosis program of T cells. Previous studies have shown that TG2 can contribute to the apoptosis program as a BH3 only protein, as a protein kinase that phosphorylate p53 or a cross-linking protein that prevents the leakage of the apoptotic cell content before phagocytosis. However, the role of the protein was not investigated so far in the T cell apoptosis. Now we have shown that timed overexpression of both the wild type (wt) and the cross-linking mutant of TG2 induced apoptosis in Jurkat T cells, the wt being more effective. Part of TG2 colocalised with mitochondria. WtTG2-induced apoptosis was characterized by enhanced mitochondrial Ca(2+) uptake. Ca(2+)-activated wtTG2 cross-linked RAP1, GTP-GDP dissociation stimulator 1, an unusual guanine exchange factor acting on various small GTPases, to induce a yet uncharacterized signaling pathway that was able to promote the Ca(2+) release from the endoplasmic reticulum via both Ins3P and ryanodine sensitive receptors leading to a consequently enhanced mitochondrial Ca(2+)uptake. Our data indicate that TG2 might act as a Ca(2+) sensor to amplify endoplasmic reticulum-derived Ca(2+) signals to enhance mitochondria Ca(2+) uptake. Since enhanced mitochondrial Ca(2+) levels were previously shown to sensitize mitochondria for various apoptotic signals, our data demonstrate a novel mechanism through which TG2 can contribute to the induction of apoptosis in T cells (**Hsieh et al. 2013**) and possibly also in other cell types.

Signals produced by macrophages engulfing macrophages drive the expression of transglutaminase 2

Previous studies from our laboratory have shown that though TG2 is upregulated in dying thymocytes, the apoptosis signal alone cannot induce the expression of the protein indicating that factors present in the tissue environment also participate. The first indication that these signals arrive from the engulfing macrophages came from studies on TG2 null mice which identified macrophage-derived TGF-β as a contributor to the induction of TG2 expression (Szondy et al. PNAS 2003). Now we found that macrophages engulfing apoptotic cells produce retinoids in a lipid sensing nuclear receptor-dependent manner (**Garabuczi et al. 2013**) and adenosine (**Sándor et al. 2017**). Adenosine is derived from ATP released by apoptotic cells via the 5'nucleotidase expressed by engulfing macrophages. Both retinoids and adenosine contribute to the upregulation of TG2 in dying thymocytes, the later by activating the adenylate cyclase pathway (**Garabuczi et al. 2013; Sándor et al. 2017**).

Transcriptional regulation of transglutaminase 2 expression in dying thymocytes

Though some data were published about the promoter of Tgm2, no information was available about the enhancers of the mouse Tgm2 gene. To identify its enhancers we used publicly available results from DNase I hypersensitivity analysis followed by deep sequencing and chromatin immunoprecipitation followed by deep sequencing against CCCTC-binding factor (CTCF), H3K4me3, H3K4me1 and H3K27ac to map a putative regulatory element set for Tgm2 in thymocytes. By measuring eRNA expressions of these putative enhancers in retinoid, rTGF-β or dibutiryl cAMP-exposed thymocytes we determined which of them are functional. By applying ChIP-qPCR against SMAD4, retinoic acid receptor, retinoid X receptor, cAMP response element binding protein, P300 and H3K27ac under the same conditions, we identified two enhancers of Tgm2, which seem to act as integrators of the TGF-β, retinoid and adenylate cyclase signaling pathways in dying thymocytes. Our study also described a novel strategy to identify and characterize the signal-specific functional enhancer set of a gene by integrating genome-wide datasets and measuring the production of enhancer specific RNA molecules (**Sándor et al. 2016**).

Retinoids and thymocytes

Retinoids induce apoptosis in immature thymocytes

Retinoids not only induce the expression of TG2 in dying thymocytes, but also activate their apoptosis program via ligating the retinoic acid receptor (RAR) gamma. Now we have shown that retinoic acids induce the expression of Nur77. Nur77 is a known transcription factor, which plays a determinant role in mediating T cell receptor-induced cell death of thymocytes. In addition to regulation of transcription, Nur77 is known to contribute to apoptosis induction also by targeting mitochondria, where it can convert Bcl-2, an anti-apoptotic protein into a proapoptotic molecule. We found that retinoid-induced apoptosis is completely dependent on Nur77, as retinoids were unable to induce apoptosis in Nur77 null thymocytes. In wild-type thymocytes retinoids induced enhanced expression of the apoptosis-

related genes FasL, TRAIL, NDG-1, Gpr65 and Bid, all of them in a Nur77-dependent manner. The combined action of these proteins led to Caspase 8-dependent Bid cleavage in the mitochondria. In addition, we could demonstrate the Nur77-dependent induction of STAT1 leading to enhanced Bim expression, and the mitochondrial translocation of Nur77 leading to the exposure of the Bcl-2/BH3 domain. The retinoid-induced apoptosis was dependent on both Caspase 8 and STAT1. Our data together indicate that retinoids induce a Nur77-dependent cell death program in thymocytes activating the mitochondrial pathway of apoptosis (**Kiss et al. 2015**).

Macrophage-derived retinoids affect thymic homeostasis

Based on our present and past data related to the involvement of retinoids of the proliferation, selection and death of immature thymocytes, we wrote a review paper in which we described the complex crosstalk between developing thymocytes and engulfing macrophages mediated by retinoids produced by engulfing macrophages. The interaction results in the harmonization of the rate of cell death of dying double positive cells with their clearance and replacement, and in promotion of the differentiation of the selected cells in the thymus (**Sarang et al 2013**). We also suggested that engulfing macrophage-derived retinoids might play other biological roles depending on the tissue or the biology context in which apopto-phagocytosis takes place. Thus retinoids can contribute to Treg formation during inflammation to prevent autoimmunity, or might be needed for proper regeneration following tissue injury.

Retinoids and clearance of apoptotic cells

Retinoids are produced in an LXR-dependent manner by engulfing macrophages to promote phagocytosis of apoptotic cells

Previous work in our laboratory has shown that TG2 acting as a coreceptor for integrin β3 is required for proper phagocytosis of apoptotic cells. In the absence of TG2, systemic lupus erythematosus-like autoimmunity develops in mice, similarly to other mice characterized by a deficiency in the clearance of apoptotic cells. Now we demonstrated that increasing TG2 expression alone in wild-type macrophages is not sufficient to enhance engulfment. However, during engulfment, the lipid content of the apoptotic cells triggers the lipid-sensing receptor liver X receptor (LXR), which in response upregulates the expression of the phagocytic receptor Mer tyrosine kinase and the phagocytosis-related ABCA1, and that of retinaldehyde dehydrogenases leading to the synthesis of a nonclassical retinoid. Based on our retinoid analysis, this compound might be a dihydro-retinoic acid derivative. The novel retinoid then contributes to the upregulation of further phagocytic receptors including TG2 by ligating retinoic acid receptors. Inhibition of retinoid synthesis prevents the enhanced phagocytic uptake induced by LXR ligation. Our data indicate that stimulation of LXR enhances the engulfment of apoptotic cells via regulating directly and indirectly the expression of a range of phagocytosis-related molecules, and its signaling pathway involves the synthesis of a nonclassical retinoid (**Sarang et al. 2014**).

Loss of retinol saturase does not affect the phagocytic capacity of macrophages, but leads to impaired in vivo clearance

Since the data above indicated that the retinol saturase pathway might be involved in the regulation of the apoptotic cell uptake, we decided to investigate the phenotype of retinol saturase mice. Though these mice, similar to other clearance deficient mice, develop autoimmunity at old age with splenomegaly and glomerular nephritis and accumulation of apoptotic cells in the spleen, no deficiency in the apoptotic cell uptake or upregulation of retinoid-dependent phagocytic receptors were found by macrophages from these mice. However, the in vivo clearance of injected apoptotic cells was delayed by the peritoneal macrophages indicating the derivatives of retinol saturase pathway might be involved in the migration of macrophages. Chemotactic migration of retinol saturase null macrophages is now under investigation in our laboratory.

Retinoids might promote the anti-inflammatory response of apoptotic cells in engulfing macrophages

Apoptotic cells are known to inhibit the pro-inflammatory cytokine formation in engulfing macrophages. Our preliminary data indicate that macrophages exposed to retinaldehyde dehydrogenase inhibitors produce more pro-inflammatory cytokines than wild type macrophages, when engulf apoptotic cells. The phenotype is related partly to the fact that retinoids upregulate Nur77 in macrophages as well, and Nur77 interferes with the NFκB pathway (experiments are still in progress).

Adenosine and clearance of apoptotic cells

Adenosine produced on the surface of engulfing macrophages regulates the pro-inflammatory cytokine formation

Previous studies from our laboratory have demonstrated that macrophages upregulate their adenosine A_{2A} (A2AR), while downregulate their adenosine A_3 receptors (A3R) during apoptotic cell engulfment. While A2AR mediated inhibition of neutrophil chemoattractant formation during engulfment via activating of the adenylate cyclase pathway, we now demonstrated that A3Rs act in an opposite way by inhibiting the adenylate cyclase pathway (**Duró et al. 2014**). We have also identified the signaling pathway through which adenosine can interfere with the pro-inflammatory cytokine formation by finding DUSP1 expression as a target of the adenylate cyclase pathway (**Köröskényi et al. 2016**).

Adenosine A3 receptors are required for the chemotactic migration of macrophages toward apoptotic cells

The first step in the clearance of apoptotic cells is chemotactic migration of macrophages toward the apoptotic cells guided by find-me signals provided by the dying cells. Upon sensing the chemotactic signals, macrophages release ATP. ATP is then degraded to ADP, AMP and adenosine to trigger purinergic receptors concentrated at the leading edge of the cell. Previous studies have shown that in addition to the chemotactic signals, this purinergic autocrine signaling is required to amplify and translate chemotactic signals into

directional motility. Now we investigated the involvement of adenosine A_3 receptors (A3R) in the chemotactic migration of macrophages directed by apoptotic thymocyte-derived find-me signals. We developed a new experimental system to study migration in vitro. By taking video images in vitro, we demonstrated 1, by administering apyrase, which degrades ATP and ADP, that the purinergic autocrine signaling is required for maintaining both the velocity and the directionality of macrophage migration toward the apoptotic thymocytes; 2, by readding 5'-N-ethylcarboxamidoadenosine, an adenosine analogue, to apyrase treated cells that the adenosine receptor signaling alone is sufficient to act so; and 3, by studying migration of various adenosine receptor null or adenosine receptor antagonist-treated macrophages, that the individual loss of the A3R signaling leads to the loss of chemotactic navigation. Though loss of A3Rs does not affect the phagocytotic capacity of macrophages, intaperitoneally-injected apoptotic thymocytes were cleared with a delayed kinetics by A3R null macrophages in vivo due to the impaired chemotactic navigation. These data demonstrate the involvement of macrophage A3Rs in the proper chemotactic navigation and consequent in vivo clearance of apoptotic cells (**Joós et al. revised version submitted**). Altogether our data indicate that first A3Rs navigate macrophages toward the apoptotic cells, but when they find their pray these receptors are downregulated, while A2ARs come up to mediate the anti-inflammatory effect of apoptotic cells by adenosine.

mTNF-α signaling in macrophages

mTNF-α activates the MKK4 signaling pathway leading to TGF-β production to inhibit lipopolysaccharide-induced pro-inflammatory cytokine production in macrophages, but is not triggered by apoptotic cells

TNF-α, a potent proinflammatory cytokine, is generated in a precursor form called transmembrane (m)TNF-α that is expressed as a type II polypeptide on the surface of certain cells. mTNF-α was shown to act both as a ligand by binding to TNF-α receptors, as well as a receptor that transmits outside-to-inside (reverse) signals back into the mTNF-α-bearing cells. Previous studies have shown that triggering mTNF-α interferes with the LPS-induced pro-inflammatory cytokine formation. However, neither the mechanism of inhibition, nor whether this signaling pathway is used by apoptotic cells for immune silencing were known. Now we showed that nonactivated macrophages express basal levels of mTNF-α and respond to anti-TNF-α Abs by triggering the MAPK kinase 4 signaling pathway. The pathway induces TGF-β. Based on inhibitory experiments, the production of TGF-β1 is regulated via Jun kinases, whereas that of other TGF-βs is regulated via p38 MAPKs. Exposure to LPS further induced the expression of mTNF-α, and triggering of mTNF-α strongly suppressed the LPS-induced proinflammatory response. Neutralizing TGF-β by Abs prevented the mTNF-α-mediated suppression of LPS-induced proinflammatory cytokine formation, indicating that the immune-suppressive effect of mTNF-α is mediated via TGF-β. Although apoptotic cells are also known to suppress LPS-induced proinflammatory cytokine formation in macrophages by upregulating TGF-β, we show that they do not use the mTNF-α signaling pathway, because

they downregulate or shed their TNF receptors, which are the ligands for mTNF-α (**Pallai et al. 2016**).

mTNF-α signaling is selectively triggered by TNF targeting molecules

Since the discovery that TNF-α plays a determining role in the pathogenesis of several chronic inflammatory diseases, anti-TNF agents are increasingly being used in the treatment of a rapidly expanding number of rheumatic and systemic autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, psoriasis, psoriatic arthritis, ankyloting spondylitis, Wegener granulomatosis and sarcoidosis. There are 5 TNF antagonists currently available: etanercept, a soluble TNF receptor construct; infliximab, a chimeric monoclonal antibody; adalimumab and golimumab, fully human antibodies; and certolizumab pegol, an Fab' fragment of a humanized anti-TNF-α antibody. Though each compound can efficiently neutralize TNF-α, increasing evidence suggests that they show different efficacy in the treatment of these diseases. These observations indicate that in addition to neutralizing TNF-α, other biological effects induced by TNF-α targeting molecules dictate the success of the therapy. Since we found that mTNF-α reverse signaling leads to transforming growth factor (TGF)-β production in macrophages, we investigated and found that anti-TNF agents selectively trigger this pathway. In this review we focused on the potential contribution of the activation of the mTNF-α signaling pathway to the success of the anti-TNF therapy (**Szondy and Pallai**, 2016).

Loss of transglutaminase 2 sensitizes for various inflammatory diseases

Uric acid-induced acute inflammation

Previous studies have shown that loss of TG2 sensitizes mice for chronic inflammation. In this study we demonstrated that loss of TG2 also sensitizes for uric acid induced acute inflammation. We found that TG2 expression was up-regulated in the synovium tissue and SFMCs from patients with gouty arthritis. The levels of MTA1, TG2, TGF-β1, IL-1β and TNF-α mRNAs were consistently increased in MSU crystal-stimulated RAW264.7 cells. si-MTA1 impaired the basal, as well as the MSU crystal-induced expression of TG2 and TGF-β1, but increased that of IL-1β and TNF-α. TG2 overexpression dramatically suppressed MSU crystal-induced IL-1β and TNF-α, but significantly enhanced the TGF-β1 production. Neutralizing TGF-β antibodies or inhibition of the crosslinking activity of TG2 attenuated these effects. On the contrary, loss of TG2 resulted in a reduced TGF-β, but in an increased IL-1β and TNF-α production in MSU crystal-stimulated RAW264.7 cells and mouse embryonic fibroblasts (MEFs). MSU crystal-stimulated IL-1β production was Janus kinase 2 (JAK2)-signaling dependent and TG2-induced TGF-β suppressed the activity of it. Finally, TG2-deficient mice exhibited hyper inflammatory responses after being challenged with MSU crystals in an in vivo peritonitis model. These findings reveal an inherent regulatory role of the MTA1-TG2 pathway in the self-limitation of MSU crystal-induced inflammation via

positively regulating the levels of active TGF-β1 in macrophages that opposes the MSU crystal-induced JAK2-dependent pro-inflammatory cytokine formation (**Yen et al. 2015**).

Chronic inflammation in obesity

Increasing amount of evidence indicate that defective clearance of dying cells leads to the development of chronic systemic inflammatory diseases. Obesity is characterized by chronic low-grade inflammation. It is recognized that this chronic inflammatory state is involved in the pathogenesis of obesity-related insulin resistance, metabolic syndrome and type 2 diabetes. At present we are investigating the effects of the loss of TG2 on the development of obesity, insulin resistance and obesity related inflammation. We performed a 17-week long feeding experiment in which TG2 KO mice and their wild type counterparts were fed with either low or high fat diet. Our preliminary results indicate that TG2 deficient mice - kept on low or on high fat diet - are characterized by enhanced insulin, adipokine and macrophage derived inflammatory cytokine production as well as prediabetic insulin resistance as compared to their wild type counterparts. Our data describe a new phenotype of transglutaminase 2 null mice.

Enhancing clearance of apoptotic cells

Since more and more chronic inflammatory diseases are found to be associated with impaired clearance of apoptotic cells there is an intensive search to find compounds which enhance phagocytosis of apoptotic cells. In addition to retinoids, we investigated the effect of glucocorticoids and daidzein

Glucocorticoids

Glucocorticoids are widely used in the therapy of chronic inflammatory diseases, and increasing evidence suggests that they act partly via enhancing efferocytosis by macrophages. Glucocorticoids were previously shown to promote both protein S- and MFG-E8-dependent efferocytosis. Since previous studies in our laboratory have demonstrated that glucocorticoids induce the expression of retinaldehyde dehydrogenases in macrophages, we decided to further investigate the possible involvement of retinoids in the glucocorticoid-induced efferocytosis in mouse bone marrow derived macrophages. We have shown that glucocorticoids promote not only short-term, but also long-term clearance of apoptotic cells. Glucocorticoids seem to directly induce the expression of the phagocytosis-related genes MERTK, C1q, UCP2, and the transcription factor C/EBPβ. C/EBPβ contributes to the further induction of the phagocytosis-related genes, and is required for the induction of lipid sensing receptors LXRs, PPARδ, RARα, RXRα and RALDH1, the latter one in an LXR- and RARα-dependent manner. Glucocorticoid-induced enhancement in long-term efferocytosis was dependent on the induction of lipid sensing receptors known to be triggered by the lipid content of the engulfed cells to enhance phagocytic capacity. Retinoids did not affect the glucocorticoid-induced short term phagocytosis of apoptotic cells, but were required for the glucocorticoid-induced enhancement of efferocytosis during prolonged clearance of apoptotic cells by promoting efficient LXR and PPARδ upregulation. Our data indicate that retinoids could be considered as potential promoters of the efficacy of glucocorticoid treatment in inflammatory diseases (**Garabuczi et al. 2015**).

Daidzein

Our previous finding showed that ethanolic extract from Glycine tomentella Hayata (GTH) can enhance mouse macrophage RAW264.7 clearance of apoptotic cells. We have demonstrated that the major components of GTH are daidzein, catechin, epicatechin and naringin. Now we explored the potential of each of its components in modulating efferocytic capability. We found that daidzein is the main component of GTH, and it can enhance RAW264.7 efferocytosis dose-dependently. Moreover, the enhancive effect of daidzein on macrophage efferocytic capability is accompanied by increased TG2 expression at both mRNA and protein levels. TG2 knockdown attenuated daidzein increased macrophage efferocytic capability. After treatment with daidzein, increased phosphorylation was observed in Erk, but not in p38 and JNK. Finally, we found that after daidzein treatment, Rac1 activity was markedly increased and the mitochondrial membrane potential was decreased, which may contribute to efferocytosis. Taken together, these data suggest that enhancement of macrophage efferocytic capability by daidzein treatment was mainly through up-regulation of TG2 expression and Rac1 activity. Daidzein may have the therapeutical potential in the treatment of inflammatory diseases (**Yen at al. 2014**).

Potential possibilities in influencing clearance of apoptotic cells

Based on our and other results we reviewed how we can influence clearance of apoptotic cells in various chronic inflammatory diseases (**Szondy et al. 2014)**.

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