EBioMedicine 36 (2018) 12–13

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

# mTOR-dependent autophagy contributes to end-organ resistance and serves as target for treatment in autoimmune disease

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Activation of the mechanistic target of rapamycin (mTOR) has emerged as a key checkpoint and biomarker of pro-inflammatory lineage development in the immune system that underlies the pathogenesis of autoimmune disorders, cancer, obesity and aging [1]. mTOR plays a central role in sensing metabolic stress and promoting growth and proliferation by inhibiting autophagy in most types of mammalian cells [2]. In *EBioMedicine*, Zhou et al. recently unveiled an mTOR-dependent impairment of autophagy in patients with ulcerative colitis (UC), which is a form of autoimmune inflammatory bowel disease (IBD) and in mice with experimental colitis [3]. Using human intestinal epithelial cells as models, mTOR was found to modulate TLR4-MyD88-MAPK signaling and the activation of the NF-κB pathway. Silencing mTOR remarkably attenuated, while genetically inactivating autophagy-controller ATG5 aggravated, inflammation and oxidative injury induced by lipopolysaccharide (LPS) [3]. Importantly, pharmacological blockade of mTOR with rapamycin mitigated the LPS-induced intestinal inflammation as measured by weight loss, colon length shortening, and inflammatory cell infiltration of the bowel wall epithelium. In addition, rapamycin reduced LPS-induced splenomegaly and oxidative stress, suggesting that its anti-inflammatory effects were likely mediated through redox-dependent modulation of the immune system. By contrast, inhibition of autophagy with 3-methyladenine (3-MA) remarkably aggravated oxidative injury and colonic inflammation in LPS-treated mice [3]. These findings are consistent with earlier observations that mTOR activation causes oxidative stress in the immune system as well as hepatocytes of mice genetically predisposed to autoimmune disease, systemic lupus erythematosus (SLE) [4]. In particular, mTOR activation is required for incorporation of subunit NDUFS3 into complex I of the electron transport chain (ETC) which is responsible for production of reactive oxygen intermediates (ROI) in mitochondria [5]. Obviously, it would be of interest to determine whether expression of NDUFS3 is also increased within intestinal epithelial cells of LPS-treated mice. mTOR-dependent oxidative stress also involves the accumulation of mitochondria, as recently unveiled by ancillary biomarker studies that were conducted within the context of a clinical trial. Accordingly, treatment with rapamycin, which has been designated as sirolimus in human pharmacology, reduced mitochondrial mass in $CD3^+CD4^-CD8^-$ double-negative (DN) T cells of patients with SLE [6]. Such DN T cells are considered a source of oxidative stress and pro-inflammatory necrotic debris and cytokines in SLE patients [7].

The role of oxidative stress and mTOR activation have been demonstrated earlier in LPS-treated piglets [8]. In this preceding study, LPS was also found to reduce intracellular glutathione within intestinal epithelial cells of piglets, which was accompanied by the activation of the PI3K/Akt/mTOR axis, the TLR4/NF-κB pathway and enhanced production of type I interferon. Importantly, the TLR4 and interferon pathways are also activated in SLE and other autoimmune diseases [9]. Similar to patients with lupus [10], treatment with *N*-acetylcysteine (NAC), which is an amino acid precursor of glutathione, blocked oxidative stress, mTOR activation and intestinal inflammation of LPS-treated piglets [8].

Of note, mitochondrial ROI production is major source of oxidative stress in patients with SLE which is not confined to the immune system. Consequently, oxidative stress, mTOR activation, and impairment of autophagy may contribute to disease pathogenesis by compromising end-organ resistance in patients with a wide spectrum of autoimmune diseases. As a critical example, through end-organ resistance, genetic factors have profound influence on the development of nephritis that represents a potentially fatal outcome in SLE [11]. Therefore, one could readily assume that pharmacological interventions with NAC or rapamycin may also afford therapeutic benefit by limiting end-organ damage in patients with UC and other forms of IBD.

## Acknowledgement

This work was supported in part by grants AI 048079, AI 072648, AI 122176, and DK 078922 from the National Institutes of Health, the Central New York Community Foundation, and an Investigator-Initiated Research Grant P0468X1-4470/WS1234172 from Pfizer.

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DOI of original article: https://doi.org/10.1016/j.ebiom.2018.08.035.
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https://doi.org/10.1016/j.ebiom.2018.09.033

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