RESEARCH HIGHLIGHT

An anti-inflammatory autophagic target in chronic diseases

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An optimal duration of inflammation protects against pathogens while a drawn-out inflammatory response is associated with chronic disease. Wang and colleagues propose the WSTF protein, whose autophagic degradation during prolonged inflammation results in a pro-inflammatory environment, as a target for therapeutic augmentation to devise new treatments for chronic inflammatory diseases.

The key premise of the study recently published in *Nature*[1] is that the causes of chronic inflammation including the type of inflammation in ageing-associated pathologies, arthritis, pre-cancerous states, autoimmunity and liver diseases such as metabolic dysfunction-associated steatohepatitis (MASH) are not easily separable from responses during infection-associated acute inflammation. This is usually ascribed to the fact that pathogen-associated molecular patterns (PAMPs) released by microbes and danger-associated molecular patterns (DAMPs) elaborated by our own cells or entering our bodies from inanimate environmental sources often target similar innate immunity pattern recognition receptors (PRRs) stimulating similar signaling pathways, leading to production of a multitude of inflammatory mediators.[2] A plethora of prior studies have implicated canonical autophagy, a homeostatic intracellular degradative pathway, as a process that removes PRRs, PAMPs and DAMPs thus suppressing inflammation.[3,4] Furthermore, nondegradative noncanonical membrane atg8ylation pathways, employing mammalian ATG8 proteins (a family of seven members including LC3B and GABARAP) along with ubiquitylation-like atg8ylation conjugation systems,[5] have begun to emerge as factors in intracellular homeostasis with potential to modulate inflammation.[6,7]

In the study by Wang et al.,[1] the authors now report that inflammation is more centrally regulated at the chromatin level and that this occurs by canonical autophagic degradation of Willams syndrome transcription factor (WSTF), a subunit of a chromatin-remodeling complex known as ISWI (Fig. 1).[8] Chromatin components are commonly found in proteomic studies, as can be gleaned by inspecting many deposited mass spectrometry data associated with proteomic analyses, and are often ignored as possible contaminants or in other instances chromatin pellets are a priori discarded. However, Wang et al. found this potential noise to be a treasure trove. They found that WSTF binds mammalian ATG8 proteins and undergoes selective autophagic degradation during chronic, but importantly not acute, inflammation. The downstream effect of this autophagy-dependent degradation of WSTF is a pro-inflammatory phenotype. The authors showed that blocking the degradation of WSTF by specially designed 'stabilizing peptides' prevents this pro-inflammatory phenotype under chronic inflammatory conditions while preserving the pathways to combat pathogens during acute inflammation. They went on to demonstrate the effects of modulating WSTF in various contexts such as cell senescence, cancer, and chronic inflammatory diseases.

Cell senescence was a useful model for the authors to make initial progress. Senescent cells can occur as part of normal ageing or after DNA damage, oncogene activation, inflammation, etc. A characteristic feature in senescence is the senescence-associated secretory phenotype (SASP) where secretory products of senescent cells induce senescence in the surrounding cells and recruit inflammatory cells to their surroundings. Senescent cells have also been reported to undergo nuclear autophagy.[9] The chromatin-remodeling complex, which WSTF is a part of, changes chromatin from an open to a closed state repressing a host of downstream genes, potentially linking the autophagic degradation of WSTF to a pro-inflammatory SASP phenotype. The authors also cast a broader net and delved into an oncogenic NRAS (G12V) mouse model and investigated the role of WSTF. In this model, expression of oncogenic Ras in mouse hepatocytes induces senescence, the SASP and immunosurveillance of pre-malignant hepatocytes. In a subset of these mice, the authors co-expressed WSTF. Compared to livers with NRAS expression, the livers that co-expressed NRAS and WSTF showed impaired pro-inflammatory response, reduced immune cell infiltration, and by month 6, severe formation of intrahepatic tumors in 10 out of 10 mice in this cohort. In essence, transgenic expression of WSTF in these oncogenic mice reduced the immune cell surveillance, which may have allowed the precancerous cells to develop into overt liver tumors.

Returning to the theme that suppression of inflammation may be beneficial rather than harmful to survival, the authors next studied the effects of stabilization of WSTF on immunophenotype in diseases characterized by chronic inflammation such as MASH[10] and osteoarthritis (OA). In human liver samples, the authors noted a substantial reduction in nuclear WSTF in patients with MASH, compared to control individuals without MASH. In a diet-induced (MCDE) mouse model of MASH with reduced levels of WSTF in the liver, stabilization of WSTF (by introducing peptides that inhibit WSTF–ATG8 binding and subsequent degradation via autophagy), resulted in impaired expression of inflammatory cytokines, reduced accumulation of macrophages, and attenuated liver fibrosis. In a different disease context, introduction of WSTF-stabilizing peptides into ex-vivo cultured articular cartilages from OA patients resulted in decreased production of inflammatory cytokines (IL-6, IL-8) and a collagenase (MMP-13) that degrades cartilage matrix. The authors then replicated these findings in a mouse model where transection of medial meniscus and anterior cruciate ligaments induces OA. In these arthritic mice, the WSTF translocated from nucleus to cytosol, co-localizing with LAMP1, suggesting a potential autophagic degradation of WSTF with an associated increase in IL-8 and MMP13. Introduction

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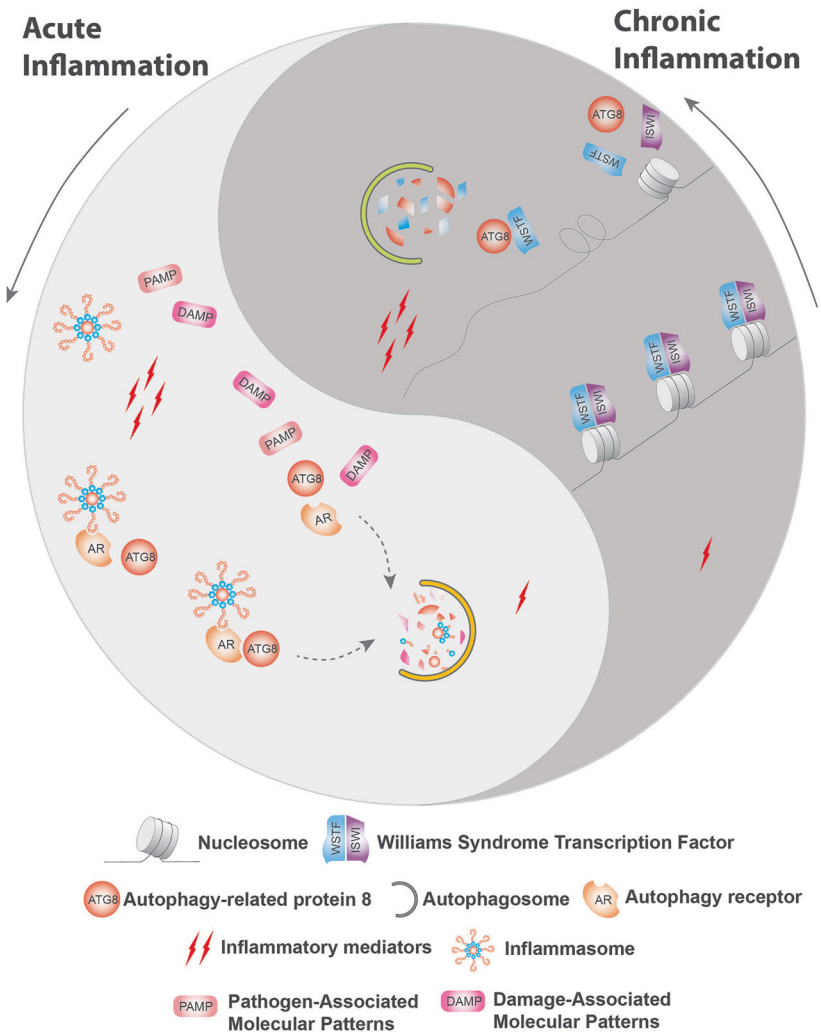

Fig. 1 The Yin and Yang of autophagy in inflammation. Autophagy was long thought of being anti-inflammatory by removing PAMPs, DAMPs and PRRs, the ligands and molecular machineries that stimulate inflammation. A recent study by Wang et al. found the Yin to this Yang, implicating autophagy as a contributor to chronic inflammation. Autophagy degrades WSTF of the ISWI chromatin-remodeling complex thus increasing expression of inflammatory mediators associated with senescence, cancer, steatohepatitis, and OA.

of WSTF-stabilizing peptides reduced these inflammatory cytokines and attenuated cartilage damage. These results provide insights into how therapeutic augmentation of WSTF could be an effective strategy to combat chronic inflammation that otherwise drives the pathogenesis of many human diseases.

As multicellular organisms, we owe our survival to inflammation which fights invading pathogens and cancer cells and lays foundation for regenerative changes after local tissue injury. These desirable characteristics are generally attributed to the short-lived 'acute inflammation', whereas a prolonged 'chronic inflammation' may result in the development of chronic, often incurable diseases such as inflammatory bowel disease, MASH, some forms of arthritis and cancer. The traditional approach to treating such chronic inflammatory diseases involves suppressing inflammation. Because inflammation is closely tied to normal immunity, this approach often has undesirable effects in diseases such as infections and cancers. The simple take-home message of this study is a call for redirecting efforts to combat the ill effects of chronic inflammation in these diseases without suppressing beneficial acute inflammation from continuing to protect the patient (Fig. 1). Perhaps some of the answers are already available in the study by Wang et al.[1] However, they also beckon to approach this therapeutic concept more broadly, as autophagy may or may not be the central driver of this dichotomy. Autophagy also controls many acute immune responses that protect us from infections.[2–4]

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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