Sensing of RNA stress by mTORC1 drives autoinflammation

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RNA metabolism and RNA sensing

The human genome is transcribed to generate an extraordinary diversity of RNA, which is subject to complex regulation to maintain cellular homeostasis. The turnover and quality control of ribosome-associated mRNA are controlled by the cytoplasmic RNA exosome, an RNA degradation machinery acting in concert with the super-killer (SKI) complex (1). The SKI complex consists of the SKIV2 helicase, two subunits of the WD-repeat protein WDR61, and the tetratricopeptide repeat motif containing protein TTC37 (2). It associates with the 80S ribosome and extracts mRNA that is no longer needed or recognized as being faulty to initiate ribonucleolytic degradation from the 3’ end by the RNA exosome (Figure 1) (3, 4).

RNA metabolism is also critical for immune homeostasis, as self-RNA occurring in the wrong place at the wrong time can turn into a danger signal that triggers immune responses leading to autoimmunity (5). Sensing of viral RNA by receptors of the innate immune system is an essential strategy in antiviral immunity (6). A central challenge for the host cell is to discriminate between harmful foreign RNA and self-RNA. Ligand specificity of RNA sensors, such as the cytosolic RNA helicases RIG-I and MDA5, relies largely on unique structural properties of viral RNA (5, 6). Thus, while RIG-I senses 5’-triphosphate-RNA or 5’-diphosphate-RNA, MDA5 recognizes long, double-stranded RNA (7–9). Engagement of these RNA sensors triggers type I interferon (IFN) signaling, resulting in the activation of numerous antiviral transcriptional programs (5, 6). The processes of RNA metabolism and RNA sensing must be tightly regulated to avoid accumulation of potentially immunostimulatory self-RNA and to prevent inappropriate innate immune activation. The SKIV2L RNA exosome has been shown to degrade immunostimulatory self-RNA arising as a cleavage product of the endonuclease IRE-1 during endoplasmic reticulum stress (10), thereby limiting type I IFN–dependent immune activation. However, the role of the SKIV2L RNA exosome for immune homeostasis in the absence of ER stress remains poorly understood.

RNA stress due to SKIV2L deficiency activates mTORC1 signaling

Loss-of-function mutations in SKIV2L cause trichohepatoenteric syndrome (THES2), a rare inborn error of immunity characterized by intrauterine growth retardation, early-onset chronic diarrhea, brittle hair with trichorrhexis nodosa, skin lesions, and immunodeficiency (11, 12). In this issue of the JCI, Yang et al. (13) set out to dissect the functional consequences of SKIV2L deficiency in mice. To bypass embryonic lethality of mice with complete Skiv2l knockout, they turned to mice with tamoxifen-inducible whole-body deletion of Skiv2l. These mice developed inflammatory skin lesions due to impaired epidermal stratification with loss of epidermal barrier integrity. Skin-specific deletion of Skiv2l also led to epidermal hyperplasia with defective hair morphogenesis, recapitulating the human disease phenotype. Interestingly, these phenotypic changes were not accompanied by activation of the type I IFN axis, as shown by a lack of expression of IFN-stimulated genes in Skiv2l-deficient epidermis or primary keratinocytes. Moreover, mice with myeloid-specific Skiv2l knockout did not show any skin pathology or signs of inflammation, suggesting that skin pathology in Skiv2l deficiency occurs independent of the hematopoietic system. Together, these findings indicate a cell-intrinsic mechanism by which the SKI-associated RNA exosome regulates keratinocyte function and which is required for skin barrier integrity independent of type I IFN signaling.

Transcriptional profiling of epidermal tissue of mice with keratinocyte-specific Skiv2l deletion revealed enrich-

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with THES2 develop reactive hemophagocytic syndrome, a hyperinflammatory state caused by hyperactivation of T cells and macrophages (12, 15). Moreover, the findings by Yang et al. indicate that a lack of cytoplasmic RNA quality control due to dysfunction of the SKI-associated RNA exosome is sensed by mTORC1, although the exact nature of the metabolites that are actually sensed by mTORC1 under these circumstances is still unknown.

Cell growth and proliferation requires increased DNA replication, which depends on a sufficient supply of nucleotides (deoxyribonucleotides), the building blocks of DNA synthesis (14). An increased demand for nucleotides is also controlled downstream of mTORC1 through stimulation of de novo nucleotide biosynthesis (16–19). However, the major pathway for biosynthesis of DNA precursors is mediated by ribonucleotide reductase, which generates deoxyribonucleotides from ribonucleotides (20), the end product of the RNA exosome. Thus, while RNA degradation is an inherent step in RNA quality control mechanisms, it also contributes to uncontrolled proliferation and immune activation.

Conclusions and implications
The mTORC1 pathway promotes cell growth through activation of anabolic processes, including the biosynthesis of proteins, lipids, and nucleotides, as well as through cell-cycle acceleration (14). Thus, enhanced mTORC1 signaling observed in keratinocytes and T cells of Skiv2l-deficient mice provides a mechanistic explanation for uncontrolled hyperproliferation, which is initiated cell-autonomously, resulting in the loss of skin barrier integrity and T cell homeostasis (Figure 1). The T cell phenotype described in Skiv2l-deficient mice is intriguing, because some patients with THES2 develop reactive hemophagocytic syndrome, a hyperinflammatory state caused by hyperactivation of T cells and macrophages (12, 15). Moreover, the findings by Yang et al. indicate that a lack of cytoplasmic RNA quality control due to dysfunction of the SKI-associated RNA exosome is sensed by mTORC1, although the exact nature of the metabolites that are actually sensed by mTORC1 under these circumstances is still unknown.

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the recycling of the nucleotide pool in the cell (Figure 1). However, whether changes in cellular nucleotide concentrations underlie mTORC1 signaling in SKIV2L deficiency remains to be investigated.

Interestingly, the authors describe a lack of type I IFN activation in skin and blood of Skiv2l-deficient mice, arguing against a pathogenetic role of RIG-I-dependent innate immune activation by unprocessed self-RNA in SKIV2L deficiency. This result contrasts with work by Eckard et al., which demonstrates an IFN signature in the blood of two patients with THES2, but not in three patients with THES1 who carried mutations in the SKI complex component TTC37 (10, 21), despite having indistinguishable clinical features. The findings by Yang et al. (13) are also in line with a clinical report, demonstrating absence of an IFN signature in a patient with THES2 (15). Nonetheless, a moderately increased expression of MX1, an IFN-regulated gene, was found in skin lesions of the patient studied by Yang et al. (13). The type I IFN activation observed in patients with THES2 might act as a permissive factor rather than as the primary cause of inflammation. This notion is also supported by the therapeutic efficacy of rapamycin in Skiv2l-deficient mice. Patients with THES develop intractable diarrhea commonly leading to failure to thrive (11, 12). Although mice with Skiv2l deficiency do not exhibit intestinal symptoms, it is possible that a loss of intestinal barrier integrity due to aberrant mTORC1 signaling may account for intestinal dysfunction in patients with THES2. As such, rapamycin may provide a promising and potentially curative therapy for these patients.

Perturbations of the mTORC1 pathway have been implicated in a variety of human diseases, including common autoimmune diseases such as systemic lupus erythematosus (22). Given the genetic and phenotypic heterogeneity of these complex diseases, mTORC1 hyperactivation may represent a useful endotype, enabling further stratification of patients based on mechanistic insight.

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