Global Center of Excellence at Kobe University presents a Special Seminar-series 74

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15:00～
***Shinryoku* Hall**

a seminar by:

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"Endoplasmic reticulum stress, inflammation, and tumorigenesis in the intestine"

Unresolved endoplasmic reticulum (ER) stress in the epithelium can provoke intestinal inflammation. Polymorphisms in genes involved in the ER stress response, such as X-box binding protein 1 (XBP1), anterior gradient 2 homologue (AGR2), and ORM1-like 3 (ORMDL3) confer genetic risk for inflammatory bowel disease. Intestinal epithelial hypomorphic function of Xbp1, a critical transcription factor of the unfolded protein response (UPR), causes ER stress in the intestinal epithelium and consequent development of spontaneous intestinal inflammation that resembles human inflammatory bowel disease (IBD). Similarly, Agr2–/– mice spontaneously develop granulomatous ileocolitis. Moreover, ER stress appears to be a more general characteristic of the intestinal epithelium in IBD, irrespective of whether patients are carriers of ER stress-related genetic risk variants or not.

We now find that hypomorphic Xbp1 function also instructs a multilayered regenerative response in the intestinal epithelium. This is characterized by intestinal stem-cell activation as shown by an inositol requiring enzyme 1α (Ire1α)-mediated expansion of Lgr5+ and Olfm4+ intestinal stem cells and a Stat3-dependent increase in the proliferative output of the transit amplifying compartment. These consequences of hypomorphic Xbp1 function are associated with an increased propensity to develop colitis-associated and spontaneous, APC-related tumors of the intestinal epithelium which in the latter case is shown to be dependent upon Ire1α. These studies reveal an unexpected role for Xbp1 in suppressing tumor formation through restraint of a pathway that involves an Ire1α- and Stat3-mediated regenerative response of the epithelium as a consequence of ER stress. As such, Xbp1 in the intestinal epithelium not only regulates local inflammation but at the same time also determines the propensity of the epithelium to develop tumors.

For more information
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