

To Eat or Not to Eat: Targeting autophagy to enhance memory immune responses

Keywords: RUBCN, autophagy, memory B cell

Memory B cells depend on autophagy for their survival, but the protein Rubicon is thought to hinder this process. Dr. Chao-Yuan Tsai and the researchers of Osaka University have discovered a shorter isoform of Rubicon called RUBCN¹⁰⁰, which enhances autophagy in B cells. Mice that lacked the longer isoform, RUBCN¹³⁰, produced more memory B cells in a way that relied on autophagy. These findings provide further insight into the role of Rubicon in autophagy.

Autophagy is a mechanism that degrades and recycles damaged components or organelles in cells, which plays an important role in various systems. In the immune system, autophagy is involved in B cell self-renewal and the survival of memory and plasma B cells. However, the effects of enhancing autophagy in B cells are not well understood.

The protein Rubicon (RUBCN) inhibits autophagy and impacts various conditions like fatty liver, kidney fibrosis, brain α -synuclein accumulation, systemic fat atrophy, osteoporosis, and myocardial ischemia/reperfusion injury. However, RUBCN deficiency can also lead to metabolic syndrome and decreased Sertoli cell function in mice. RUBCN also regulates noncanonical autophagic processes like LC-3-associated phagocytosis (LAP), LC-3-associated endocytosis (LANDO), or micropinocytosis (LAM). Loss of RUBCN impairs LAP/LANDO and enhances fungal infection and neurodegeneration, but enhances antitumor "T cell" responses and germinal center (GC) B (B_{GC})-cell differentiation in mouse models. However, the exact mechanisms of RUBCN's control over autophagy and other functions are still not fully understood.

Here, the research group has identified and characterized a RUBCN isoform called RUBCN¹⁰⁰. RUBCN¹⁰⁰ is translated from alternative start codons of the same messenger RNA that encodes RUBCN¹³⁰. Autophagy is enhanced in B cells deficient in RUBCN¹³⁰ (Figure 1) or expressing RUBCN¹⁰⁰.

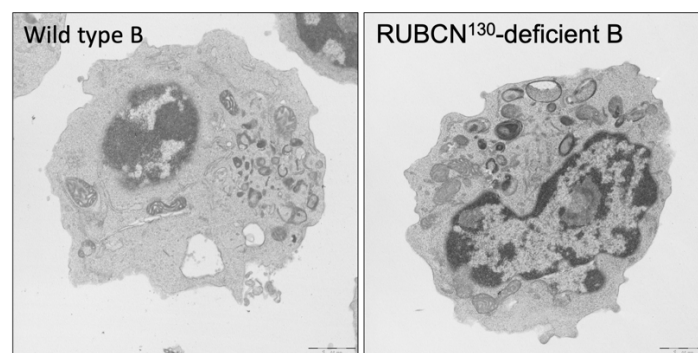


Figure 1. Autophagy is enhanced in the RUBCN¹³⁰-deficient B cells. License: CC BY-NC 4.0

In mice, selective deficiency of RUBCN¹³⁰ in B cells enhances the generation of memory B cells in an autophagy-dependent manner (Figure 2). The increase in B cell memory is further increased by enhanced recall responses in B cell-specific RUBCN¹³⁰ knockout (RUBCN B-KO) mice. Importantly, elevated canonical autophagy alters the fate of B_{GC} cell differentiation without affecting GC formation or cell survival in RUBCN B-KO mice.

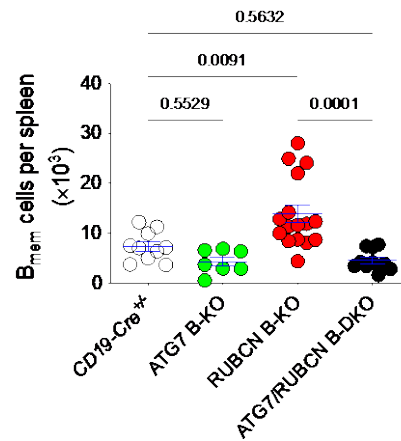


Figure 2. Mice lacking RUBCN¹³⁰ specifically in B cells produce a greater number of memory B cells in an autophagy-dependent manner. *CD19-Cre^{+/+}*: wild-type; ATG7 B-KO: B cell-specific ATG7 KO (autophagy-deficient); ATG7/RUBCN B-DKO; double KO (autophagy-deficient). License: CC BY-NC 4.0

The presence or absence of the RUN domain in RUBCN isoforms may explain their distinct functions in regulating autophagy (Figure 3). RUBCN¹⁰⁰-VPS34 complexes enhance VPS34 activity, promoting autophagosome formation. On the other hand, RUBCN¹³⁰-VPS34 complexes suppress autophagy by inhibiting VPS34 activity and autophagosome-lysosome fusion. Additionally, RUBCN¹⁰⁰ restrains mTORC1 in early endosomes, delaying its activation. Put simply, RUBCN¹⁰⁰ promotes autophagy, while RUBCN¹³⁰ has a suppressive role.

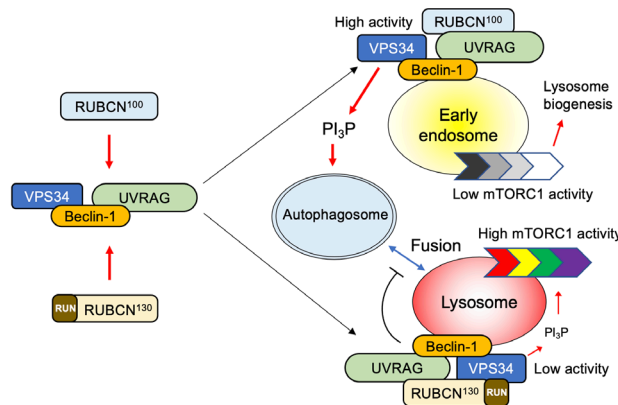


Figure 3. A model for the functional interaction between RUBCN¹⁰⁰ and RUBCN¹³⁰ in regulating autophagy. License: CC BY-NC 4.0

In summary, the group found a RUBCN isoform called RUBCN¹⁰⁰ and showed that the interaction between the two RUBCN isoforms is important for regulating autophagy. The balance of these isoforms is crucial for maintaining cellular balance and controlling autophagy and mTORC1 activity. A deficiency in RUBCN¹³⁰ and enhancing autophagy with drugs can increase memory B cell generation. The discovery of RUBCN¹⁰⁰ not only resolves conflicting findings about RUBCN's functions but also sheds light on manipulating B cell memory.



Conceptual Figure: A RUBCN¹⁰⁰ stick cues the "Autophagy" ball to pocket the "B" ball into the "Mem" pocket.

(GC: germinal center; B: B cells; PB: plasma cells; Mem: memory B cells)

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