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「BRISC-SHMT2 複合体による代謝制御は免疫系シグナル伝達を制御する」

核酸やアミノ酸代謝に関わるセリンヒドロキシメチル基転移酵素(SHMT, serinehydroxymethyl transferase2) は 1 炭素の転移反応を触媒する酵素であり、ピリドキサール 5'リン酸 (PLP, pyridoxal-5'-phosphate) を補因子とする。また、SHMT は代謝酵素として機能するのみならず、特定のアイソザイムが脱ユビキチン化 BBRC36 イソペプチダーゼ (BRISC) との分子間相互作用によって、炎症性サイトカインシグナル伝達を促進する役割を担う。しかしながら、この分子間相互作用が具体的に代謝とどのように関わるのかについては未解明であった。筆者らは、クライオ電子顕微鏡解析によってヒト由来 SHMT2-BRISC 複合体の構造解析により、PLP の細胞内濃度と炎症性のサイトカイン応答、及び BRISC-SHMT2 分子間相互作用の関係を解明した。このことから筆者らは、代謝産物が脱ユビキチン化酵素活性を介し、炎症性シグナル伝達を調節するメカニズムを明らかにした。

紹介論文

Metabolic control of BRISC–SHMT2 assembly regulates immune signalling.

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要旨

Serine hydroxymethyltransferase 2 (SHMT2) regulates one-carbon transfer reactions that are essential for amino acid and nucleotide metabolism, and uses pyridoxal-5′-phosphate (PLP) as a cofactor. Apo SHMT2 exists as a dimer with unknown functions, whereas PLP binding stabilizes the active tetrameric state. SHMT2 also promotes inflammatory cytokine signalling by interacting with the deubiquitylating BRCC36 isopeptidase complex (BRISC), although it is unclear whether this function relates to metabolism. Here we present the cryo-electron microscopy structure of the human BRISC–SHMT2 complex at a resolution of 3.8 Å. BRISC is a U-shaped dimer of four subunits, and SHMT2 sterically blocks the BRCC36 active site and inhibits deubiquitylase activity. Only the inactive SHMT2 dimer—and not the active PLP-bound tetramer—binds and inhibits BRISC. Mutations in BRISC that disrupt SHMT2 binding impair type I interferon signalling in response to inflammatory stimuli. Intracellular levels of PLP regulate the interaction between BRISC and SHMT2, as well as inflammatory cytokine responses. These data reveal a mechanism in which metabolites regulate deubiquitylase activity and inflammatory signalling.