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How Metabolic Pathway get Involved in the Pathogenesis of SLE

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a highly variable and unpredictable disease course as well as prognosis. It affects predominantly women of childbirth age, impacts their quality of life and brings huge economic burdens [1]. Due to earlier diagnosis and improved management of the disease, survival has greatly improved in the past decade [2]. Despite the significant improvement in mortality, the underlying pathogenic mechanisms remains to be elucidated. With the advent of new technologies, metabolomics studies have attribute to understanding the pathogenic mechanisms in SLE [3]. Although these studies mainly focused on exploring the metabolites profiling in SLE patients [4–7], the discoveries might link metabolic pathway to pathogenic mechanism and expand our knowledge in the pathogenesis of SLE. In other words, the disturbed metabolites profiling might yield clues to the underlying pathogenic mechanisms of SLE. Recently, Simanta and colleagues' work have given a good illustration on how a key player in a metabolic pathway contributes to the development of SLE. In Simanta and colleagues' study, they have revealed fatty acid amide hydrolase (FAAH), a primary hydrolytic enzyme for endogenous lipids, as a novel player in the pathogenesis of SLE [8].

FAAH is a membrane bound serine hydrolase which is the principal catabolic enzyme for endogenous bioactive fatty acids [9]. The primary substrates of FAAH include anandamide (AEA), oleoyl ethanolamide and palmitoyl ethanolamide and their effects are mediated by cannabinoid receptors (CB_1 and CB_2) and peroxisome proliferator-activated receptors (PPARs) [9,10]. Both genetic deletion and pharmacological inhibition of FAAH displayed analgesia, anxiolysis and anti-depression effects in mice [10-13]. While most studies focused on the therapeutic target of FAAH in central nervous system, other studies also demonstrate the anti-inflammation effects of FAAH inhibition, indicating the role of FAAH in autoimmune diseases. In experimental autoimmune encephalitis (EAE), blockade of FAAH in mice resulted in a less severe disease and improved long term outcome which might be mediated by its anti-inflammation and neuroprotective effects [14,15]. In inflammatory bowel disease (IBD) animal model, FAAH-deficient mice showed significant protection against drug induced colon inflammation [16]. Similarly, FAAH inhibitor reduced carrageenan-induced hind paw inflammation in mice [17]. More interestingly, plasmacytoid dendritic cells in multiple sclerosis patients expressed higher levels of FAAH [18] and FAAH expression was increased in patients' astrocytes [19].However, the pathogenesis role of FAAH in SLE has not been revealed. The work by Simanta and colleagues for the first

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time demonstrated how FAAH got involved in the pathogenesis of SLE by using a transgenic mouse model [8].

Congenic dissection studies have revealed *Sle1*, *Sle2*, and *Sle3* as three major lupus susceptibility loci in the lupus murine model NZM2410 [20]. *Sle2*locus on chromosome 4 breaches B cell tolerance, promotes B cell hyperactivity and B1 cell expansion [21, 22]. While *Sle2* locus was proved to contain several subintervals [21], the exact gene within this locus that impacts B cell tolerance remains unknown. Peripherally, B cell receptor (BCR) revision acts as an important mechanism for regulating self-reactive B cells during an ongoing immune response [23]. Simanta and colleagues used subcongenic recombinant mice to progressively narrow*Sle2* interval and found *FAAH*, a gene within *Sle2*locus, contributes to autoimmunity through heightened BCR revision in B cells [8]. By breedingB6.Sle2 mice onto hen egg lysozyme (HEL) BCR transgenic mice, they first proved that *Sle2*was responsible for enhanced BCR revision, leading to the emergence of serum auto antibodies. Next, they identified a telomeric subinterval (D4MIT331-D4MIT12) of the *Sle2* interval responsible for enhanced BCR revision and recognized *FAAH* as the candidate responsible gene within the subinterval. Finally, in order to justify the hypothesis that *FAAH* was the responsible gene, FAAH gene expression and FAAH enzyme activity were measured and FAAH inhibitor was used. Strikingly, they found inhibition of FAAH reversed enhanced BCR revision by regulation of RAG expression, resulting in a significant decrease in serum autoantibody levels. Their findings indicate that FAAH might be a promising therapeutic target in the treatment of lupus.

FAAH inhibitorswere first developed to increase the concentration of endocannabinoids. In the past few years, it has become an attractive therapeutic approach inconditions which could benefit from elevated levels of endocannabinoid. These conditions include neuropathic pain, depression, anxiety disorders, Parkinson disease, multiple sclerosis, colitis, and cancer [24-26]. The benefit of FAAH inhibitor in the above conditions exclusively depends on the endocannabinoid system. In the lupus model studied by Simanta and colleagues, this benefit seems to be independent of the endocannabinoid system. Instead, it was related to the ability of FAAH inhibitor to reverse the enhanced BCR revision and polyreactivity in mature B cells. The findings in this study have revealed a novel mechanism involved in FAAH inhibitory therapy. Further preclinical and clinical studies are warranted to evaluate the efficacy of FAAH inhibitor in reduce autoimmunity.

On the other hand, the endocannabinoid system has not been widely studied in SLE. CB2 receptors and ligands are found primarily in immune cells, with B cells have the most abundant receptors [27]. A Polymorphism study suggest CB2 gene variation was related to reduced endocannabinoids' immunomodulatory response and may be a risk factor for autoimmunity [28]. Endocannabinoids have been shown to suppress immune functions through modulation of The cell development, inhibition of cytotoxic NK cells, and regulation chemotaxis and cytokine secretion [27]. These evidences lead to an important question: whether FAAH inhibitor treatment functioned through the endocannabinoid system in the *Sle2* congenic mice? It is rational to believe that FAAH inhibitor increased endocannabinoid level and in turn activate the CB2 receptor. Activation of CB2 further regulates the immune system through various mechanism. However, this was not further explored in Simanta and colleagues' work, which warrants further study.

In summary, the recent study by Simanta et al. provide several novel perspectives on the role of FAAH in the pathogenesis of SLE. For the first time, FAAH was revealed to regulate receptor revision in mature B cell. Being a key enzyme in the metabolic pathway of endocannabinoids, the story of FAAH offers a good example on

how metabolic pathway get involved in the pathogenesis of diseases. Furthermore, FAAH inhibitor might be a novel therapeutic target in SLE.

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