It is notable that there is a bidirectional regulatory relationship between microglia and astrocytes. The mutual activation of the two forms a continuous inflammatory cycle, which is an important driver of chronic hypothalamic inflammation and also provides a potential target for MetS intervention (Lawrence et al., 2023).

5 Key pathways and targets of central inflammatory cytokines

5.1 Up-regulating SOCS3 and PTP1B triggers leptin resistance

Leptin is a key hormone secreted by fat cells, which regulates appetite and energy expenditure through the hypothalamus to maintain energy balance. The leptin levels in the blood of obese and MetS patients are always high, but the hypothalamus is not sensitive to leptin, resulting in leptin resistance. This is directly related to the increase of SOCS3 (cytokine signal suppressor 3) and PTP1B (protein tyrosine phosphatase 1B)-SOCS3 weakens leptin signaling by inhibiting the JAK2/STAT3 pathway PTP1B further blocks the signal by dephosphorylating JAK2 (Mezzasoma et al., 2023).

An increase in SOCS3 and PTP1B in the afferent neurons of the hypothalamus and vagus nerve will reduce leptin sensitivity, resulting in increased appetite and weight gain (Zieba et al., 2020). Endoplasmic reticulum stress can exacerbate this condition. For instance, a high-fat diet can induce endoplasmic reticulum stress in the hypothalamus, leading to an upregulation of PTP1B expression.Animal studies have shown that inhibition or knockdown of SOCS3/PTP1B can restore leptin sensitivity and reduce obesity, indicating that these molecules are important targets for intervention of central leptin resistance (Roy et al., 2025).

5.2 The NF-κB/JNK pathway mediates central insulin resistance

Central insulin signaling is crucial for regulating blood sugar, appetite and energy expenditure. Under inflammatory conditions, pro-inflammatory factors activate stress pathways such as NF-κB (nuclear factor κB) and JNK (c-Jun N-terminal kinase), interfering with insulin signaling (Park et al., 2022). These kinases promote serine phosphorylation of insulin receptor substrates (IRS), inhibit downstream signals, and lead to central insulin resistance.

The continuous activation of the NF-κB/JNK pathway is driven by pro-inflammatory factors such as TNF-α and IL-1β, forming a vicious cycle of inflammation and insulin resistance (Khalid et al., 2021; Garg et al., 2023; Mobeen et al., 2025). Central insulin resistance can aggravate blood sugar disorders and increase appetite. Preclinical studies have shown that interventions targeting this pathway (such as antioxidants and kinase inhibitors) can improve insulin sensitivity (Park et al., 2022; Mobeen et al., 2025).

5.3 TLR4/NLRP3 activation promotes the maturation and release of IL-1β

The continuous amplification of central inflammatory responses is closely related to the activation of innate immune receptors TLR4 and NLRP3 inflammasomes. TLR4 can be activated by danger signals such as saturated fatty acids, initiating the NF-κB/ JNK-mediated inflammatory cascade, promoting the transcription of pro-inflammatory factors and inducing the assembly of NLRP3 inflammasome (Khalid et al., 2021). After NLRP3 activation, caspase-1 mediates the cleavage of the precursor IL-1β into active IL-1β.

The release of IL-1β is the key to the spread of central inflammation, which further weakens insulin and leptin signaling, aggravates neuronal dysfunction, and maintains the inflammatory environment (Xu and Nunez, 2022). The activation of NLRP3 is regulated by metabolic status, post-translational modifications and molecular chaperone proteins (such as p58IPK), among which p58IPK can inhibit inflammasome activity and limit the production of IL-1β. TLR4 and NLRP3 play a core role in inflammatory amplification and are potential therapeutic targets for intervening in neuroinflammation and metabolic disorders related to metabolic syndrome (Figure 2) (Mezzasoma et al., 2023; Unterberger et al., 2023).

6 The Development Process of Metabolic Syndrome

6.1 Increased food intake, reduced heat production and energy imbalance

The development of metabolic syndrome is often characterized by long-term energy excess, that is, energy intake consistently exceeds expenditure. Inflammatory factors in the brain can interfere with the hypothalamus'