

methionine supplementation also suppressed tumor growth, while mice with T cell-specific deletion of DOT1L exhibited aggressive cancer progression.

The afore-summarized findings demonstrate that the methionine-induced, SAM-mediated H3K79 dimethylation is a limiting factor for CD8⁺ T cell cancer immunosurveillance. To explore how T cells were outcompeted by cancer cells in methionine acquisition, Bian et al. examined the expression of methionine transporters, including the system L transporters SLC7A5 and SLC43A2 (Alexander et al., 2019). Of note, while T cells expressed high levels of SLC7A5, which accounted for most of their methionine transport activities (Sinclair et al., 2019), cancer cells additionally expressed SLC43A2. Intriguingly, shRNA knockdown of SLC43A2 resulted in diminished tumor growth in association with enhanced expression of effector molecules in CD8⁺ T cells. In addition, a system L transporter inhibitor, BCH, synergized with the immune checkpoint inhibitor anti-PD-L1 to suppress tumor growth, presumably through its blockade of methionine uptake in cancer cells. As BCH blocks SLC43A2 and SLC7A5, it is unclear how SLC7A5-mediated methionine uptake in T cells was spared. Future develop-

ment of SLC43A2-specific inhibitors will likely provide a more effective approach in restoring T cell immunity to cancer.

The study by Bian et al. established a crucial role for the tug-of-war between cancer cells and T cells over methionine in cancer immunity control, supporting the notion that nutrient competition can be an important tumor immune evasion mechanism (Sugiura and Rathmell, 2018). Unraveling the H3K79me2-mediated gene expression program and the functions of other SAM-dependent pathways in T cells may pave the way for additional therapeutic interventions beyond methionine uptake (Figure 1).

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Hypothalamic Regulation of Glucose Homeostasis: Is the Answer in the Matrix?

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Neurons within the arcuate nucleus control energy balance and represent the functional substrates through which FGF1 deploys its anti-diabetic action. Alonge et al. (2020) now report that the integrity of arcuate perineuronal nets, an extracellular matrix component that enmeshes GABAergic neurons, is reversibly altered in diabetic rats and a key component for FGF1-mediated diabetic remission. These novel insights unravel how perineuronal nets dynamically contribute to the central control of glycemia.

The brain has emerged as a prominent player in the control of feeding behavior, energy expenditure, and glucose homeostasis. The arcuate nucleus (ARC) of the

hypothalamus contains highly specialized neuronal populations, including AgRP- and POMC-producing neurons, which represent the two main opposite

branches of the melanocortin system (Morton et al., 2014). Several studies have consolidated the role of ARC neurons in the regulation of feeding



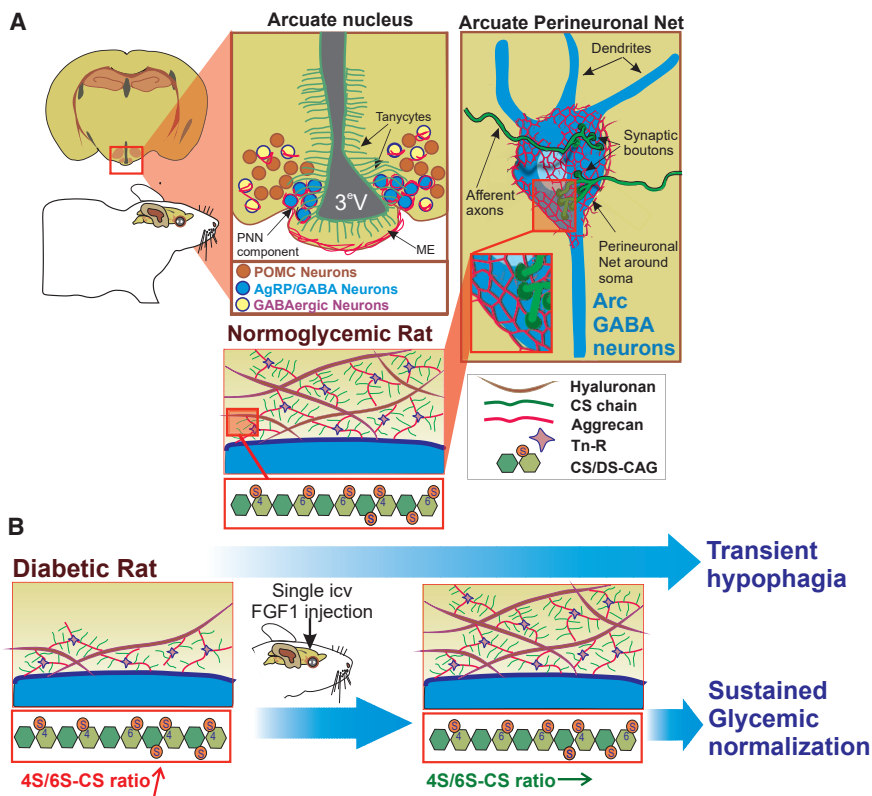


Figure 1. The Integrity of Arcuate Perineuronal Nets Is Essential for the Control of Glucose Homeostasis

(A) Arcuate perineuronal nets (PNNs) enmesh GABAergic neurons, among which include AgRP-expressing neurons, and form a functional continuum with the median eminence (ME). Core components of PNNs are hyaluronan, chondroitin sulfate (CS) and dermatan sulfate (DS) glycosaminoglycan isomers (CS/DS-GAGs), and proteins interacting with proteoglycans or GAGs, such as aggrecan and tenascin (Tn-R). (B) In diabetic-hyperglycemic ZDF rats, the abundance of ARC PNNs is decreased and the proportion of disaccharides bearing sulfation in position 4 increases over that bearing sulfation in position 6 (4S/6S-CS ratio). A single i.c.v. injection of FGF1 results in normalization of both abundance of PNNs and corrected "sulfation code." The proper integrity of ARC PNNs is required for FGF1-mediated diabetic remission but is dispensable for the acute hypophagic response.

behavior, metabolism, and nutrient partitioning. Among these, recent reports have shown that a single intracerebroventricular (i.c.v.) injection of the fibroblast growth factor 1 (FGF1), a peptide produced in the brain by neurons, astrocytes, and ependymal cells, leads to strikingly long-lasting normalization of blood glucose in a diabetic rodent model (Scarlett et al., 2016). The ARC and the median eminence (ME) were subsequently identified as primary targets for the anti-diabetic action of FGF1 (Brown et al., 2019). Taking advantage of various histological and molecular techniques in combination with *in vivo* metabolic analysis, Alonge et al. (2020) have now explored the role of perineuronal nets (PNNs) in FGF1-induced diabetic remission.

First described by Camillo Golgi more than a century ago, PNNs are specialized components of the condensed extracellular matrix that form honeycomb-like structures enmeshing the cell bodies of fast-spiking neurons, thereby controlling their activity and synaptic plasticity (Celio et al., 1998; Testa et al., 2019). The building blocks for PNN assembly, consisting of proteoglycans (PGs), chondroitin sulfate glycosaminoglycans (CS-GAGs), and PG-interacting proteins, are provided by neurons, glial cells, and cerebrospinal fluids to form a condensed mesh around neurons, leaving space for the synaptic buttons of afferent synapses and offering physical protection while structuring neuron plasticity and activity. PNN-constituting GAG polysaccharides are composed of variable sequences of

disaccharide units, and the tightness of the scaffolding structure surrounding neurons depends on both protein interactions and polysaccharide modifications. The appearance of PNNs coincides with the closure of the critical period during brain development, and the integrity of PNNs has been involved in various brain functions and dysfunctions including memory storage and neurodegenerative and psychiatric disorders (Testa et al., 2019).

The study of Alonge et al. (2020) represents a converging point of several observations, mostly made by the same group. Indeed, the founding observation was that a single i.c.v. injection of FGF1 produced transient hypophagia and long-lasting (>3 weeks and up to 17 weeks) reduction in blood glucose levels in rodent models of type 2 diabetes (T2D) (Scarlett et al., 2016). Subsequent work reported that the postnatal formation of PNNs around ARC GABAergic neurons (mostly AgRP neurons) and in the ME parallels the maturation of energy-sensing ARC neurocircuits in a leptin-dependent manner (Mirzadeh et al., 2019). In adults, the hypothalamic ARC/ME was therefore identified as a primary target for the anti-diabetic action of FGF1 (Brown et al., 2019).

Now, Alonge et al. (2020) report a sharp decrease in the abundance of ARC PNNs in a hyperglycemic T2D rat model. Using a mass spectrometry technique, they highlight an imbalance in the sulfation patterns of CS disaccharide isomers toward an increased 4S/6S CS ratio that was associated with hyperglycemia in Zucker diabetic fatty (ZDF) rats compared to normoglycemic animals (Figures 1A and 1B), while central delivery of FGF1 resulted in a rapid (24 h) restoration of ARC PNN abundance and sulfation patterns (Figure 1B). To gain insight into the function of ARC PNNs, the authors locally microinjected chondroitinase ABC (ChABC), an enzyme that dissolves GAG into its disaccharide core units, in combination with i.c.v. FGF1 delivery in diabetic ZDF rats. While the targeted disruption of the components of ARC PNNs did not affect the anorectic responses associated with the central action of FGF1, it selectively surfeits diabetic remission. Indeed, unlike vehicle-treated diabetic rats, animals treated with ChABC

experienced a transient decrease in blood glucose, which rapidly returned to diabetic hyperglycemia levels. Thus, these results reveal that the integrity of ARC PNNs is necessary for the central action of FGF1 in eliciting a sustained, feeding-independent diabetes remission (Figure 1B).

Overall, these results introduce the structure of PNNs as a new cytological architecture critically involved in the central control of energy balance and offer a yet unappreciated target for anti-diabetic strategies. However, some questions remain. For instance, local ChABC application would disrupt the whole ARC PNN cyto-structure, thereby limiting the identification of precise neural substrates. Similarly, while the PNN/AgRP-neuron assembly seems a reasonable target for mediating the action of FGF1, it is likely that other ARC GABAergic neurons may participate in the long-lasting regulation of blood glucose, and so far, no clear molecular mechanisms connecting PNNs and ARC neurons have been identified. By the same token, ME tanycytes are gatekeepers for the entry of metabolic signals and their action on ARC neurons (Prevot et al., 2018), and they strongly respond to FGF1 (Brown et al., 2019). Hence, it is tempting to speculate that the integrity of PNNs is required for tanycyte-neuron communication within the ARC/ME microenvironment, allowing for an optimized regulation of hypothalamic circuits by circulating hunger and satiety signals.

Given the role of PNNs in the maturation of hypothalamic networks (Mirzadeh et al., 2019), one would expect that any genetic or pathophysiological alteration of PNNs during development will increase the susceptibility for metabolic

disorders in adulthood. Interestingly, genetic variants in the semaphorin 3A signaling pathway have recently been associated with an impaired development of hypothalamic melanocortin circuits and obesity in humans (van der Klaauw et al., 2019). As member of the chemorepulsive molecules family, semaphorin 3A is a well-known regulator of the function of PNNs (de Winter et al., 2016; Testa et al., 2019) and, as such, could represent an interesting molecular link between ARC PNN formation and the central control of energy homeostasis.

In conclusion, Alonge et al. (2020) unveil a role for PNNs in the central regulation of glucose homeostasis. Further studies are warranted to precisely ascertain the role of PNNs in the development and functions of hypothalamic metabolic circuits together with the physiological mechanisms by which ARC PNNs/neurons regulate peripheral organ activity in promoting sustained diabetic remission. Unraveling how individual components of PNNs participate in energy homeostasis may ultimately lead to novel and effective strategies against metabolic disorders.

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