mokine receptors, such as CXCR3 for Th1 and CCR6 for Th17 cells, are similarly present on some Tregs. As a result, Tregs home to the same regions in inflamed organs as their proinflammatory targets to control exuberant immune responses. This notion is suggested by several studies in the recent years\(^1\)\(^,\)\(^2\)\(^,\)\(^3\); however, Eller et al.\(^1\) did not find Tregs in inflamed kidneys of wild-type animals. This observation is surprising because it contradicts previous studies in other organs as well as our own unpublished data, which show regular presence of Tregs in kidneys of mice with NTS, and in various human renal pathologies.

A possible explanation for this discrepancy is that numbers of infiltrating Tregs depend on the severity of disease, which was mild in the study by Eller et al.,\(^1\) a common issue with NTS in mice on the BALB/c background. Furthermore, modulation of an immune response by Tregs might follow a certain time course in which Tregs are first found in secondary lymphoid tissues and only then infiltrate inflamed target organs at later stages. The current study supports this latter hypothesis.

Eller et al.\(^1\) show that Tregs have the potential to downregulate the immune response directly at the systemic site of antigen-specific T cell priming, namely the lymph node. Tregs are guided to this location, in analogy to activated dendritic or naive T helper cells, by the chemokine receptor CCR7. Thus, there are not only Tregs matching committed T cell lineages of the effector arm but also a population designed to monitor the activation of naive T cells. As a result, it is guaranteed that every step of a potentially hazardous T cell response, from priming within secondary lymphoid organs to damaging the parenchyma of target organs, is under the control of Tregs. The most common form of obsessive-compulsive disorder in humans, compulsive checking, therefore seems to be an issue for Tregs as well.

**DISCLOSURES**

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**Sorting out Lysosomal Trafficking of the Thiazide-Sensitive Na-Cl Co-transporter**

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The aldosterone-sensitive distal nephron is a key site for regulated renal sodium reabsorption and, hence, plays a critical role in the long-term control of arterial BP and extracellular fluid volume. Coupled Na+ and Cl− transport across the luminal surface of the most proximal portion of the aldosterone-sensitive distal

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nephron, the distal convoluted tubule, occurs through the thiazide-sensitive Na-Cl co-transporter (NCC). NCC bears a similar structure to other members of the SLC12 family of electroneutral cation chloride co-transporters, containing 12 transmembrane domains flanked by large cytoplasmic amino and carboxyl termini and two sites for N-linked glycosylation. It exists functionally as a homodimer at the apical surface of the distal convoluted tubule, where it reabsorbs 5 to 10% of the filtered sodium chloride load. NCC is the molecular target of thiazides and thiazide-like diuretics, which, because of their cardiovascular benefits, are recommended first-line agents for patients with newly diagnosed essential hypertension.

Given the relevance of NCC function in human hypertension, it is not surprising that the co-transporter has become the subject of intense investigation in recent years. The greatest impetus that stimulated the recent explosion of NCC research is the seminal discovery in 2001 that familial hyperkalemic hypertension (FHHt; also known as PHA-2, or Gordon syndrome), a Mendelian disorder of NCC overactivity, is caused by mutations in the with-no-lysine (WNK) kinases WNK1 and WNK4. These serine threonine kinases, so named for the atypical placement of a key catalytic lysine, are central regulators of an intricate signaling network that affects NCC activity through changes in co-transporter phosphorylation and trafficking.

Although the details of these two processes are still being unraveled, several important insights have been gleaned. WNK1 and WNK4 activate the Ste20-type kinase SPAK (STK39), which binds to the NCC amino terminus and phosphorylates residues near its docking site, stimulating NCC activity. In addition to its effects on NCC phosphorylation, WNK4 can affect NCC surface abundance. WNK4, whether expressed endogenously or overexpressed, suppresses NCC expression at the plasma membrane. FHHt-causing mutations of WNK4 seem to activate NCC both by locking the co-transporter in a phosphorylated state and by switching the inhibitory effect to a stimulatory one; this results in constitutively active distal NaCl reabsorption and hypertension. Thus, in FHHt, WNK4 mutations cause hypertension by “turning on” individual co-transporters and by increasing the total number of co-transporters expressed at the apical surface of the distal convoluted tubule, through effects on both phosphorylation and trafficking.

Recent work has elucidated the mechanism by which WNK4 downregulates NCC surface expression. WNK4 selectively suppresses the rate of NCC plasma membrane delivery, without affecting the net rate of internalization of the co-transporter. During this process, WNK4 alters the course of post-Golgi NCC traffic, diverting the co-transporter to the lysosome, where it ultimately is degraded. Consistent with this finding, WNK4 stimulates a physical interaction between NCC and the AP-3 complex, a cytosolic adaptor that marks cargo for transport from endosomes to lysosomes. Interestingly, WNK4 globally stimulates lysosomal activity, because the kinase increases total cellular lysosomal content. Thus, WNK4 might promote the lysosomal sorting and degradation of cargo other than NCC, resulting in generalized changes in distal convoluted tubule viability and function. Indeed, transgenic mice overexpressing WNK4 exhibit a salt-wasting hypertensive phenotype similar to Gitelman syndrome, owing to reduced NCC abundance and marked hypoplasia of the distal convoluted tubule. In light of the observation that WNK4 induces such potent effects on cellular proteostasis, it would be reasonable to speculate that the kinase takes advantage of multiple pathways to divert cargo to the lysosome as it carries out its inhibitory effects on distal convoluted tubule mass and NCC surface expression.

In this issue of JASN, Zhou et al. present thought-provoking evidence that lends support to this possibility. Their data suggest that WNK4 modulates physical interactions between the N-terminus of NCC and sortilin, a distal convoluted tubule–expressed mammalian homologue of the yeast Vps10p sorting receptor. Similar to Vps10p in yeast and the mannose-6-phosphate receptor in mammals, sortilin is a single-pass transmembrane protein that ferries newly synthesized soluble hydrolases from the Golgi to the lysosome. The cytoplasmic tail of sortilin is essential for this function, because it contains signals that mediate binding to the GGAs [golgi-localized, gamma-ear containing, ARF (ADP ribosylation factor)-binding proteins] and AP-1–clathrin adaptors, which, in addition to AP-3, facilitate cargo delivery to the endolysosomal pathway. Sortilin is distributed in multiple compartments, including the trans-Golgi network and the plasma membrane and in biosynthetic and postendocytic vesicles. Consistent with this heterogeneous subcellular distribution, sortilin participates in a variety of trafficking operations separate from its effects on lysosomogenesis. Nevertheless, overexpression of a sortilin construct that lacks its cytoplasmic tail may have specific effects on NCC degradation, because it diminishes the WNK4-mediated downregulation of NCC abundance in mammalian cells. These findings suggest that the truncated sortilin construct somehow prevents WNK4 from diverting the co-transporter to lysosomes. The authors speculate such an effect occurs through the dominant negative regulation of endogenous sortilin, which may lead to NCC retention in the trans-Golgi network.

A limitation of this study is that the data are largely derived from transient overexpression experiments and indirect protein–protein interaction studies; consequently, this novel finding will benefit from verification through other, more physiologically relevant experimental approaches. Even so, the study by Zhou et al. points toward a new role for sortilin in the WNK4-mediated lysosomal routing of NCC. Coupled with the observation that itinerant co-transporters are also governed by a sortilin-independent AP-3 trafficking program, these data provide evidence that multiple separate processes could regulate the lysosomal routing of NCC. This is particularly intriguing when one considers recent observations that NCC degradation or endolysosomal routing is stimulated by various physiologic maneuvers that modulate the renin-angiotensin-aldosterone system, ranging from treatment with angiotensin-converting enzyme inhibitors to the generation of acute hypertension or hyperkalemia. Further efforts to elucidate the mechanisms by which NCC is conveyed to and degraded by
lyosomes under such physiologically relevant conditions will undoubtedly provide insights into how the spatial distribution of NCC is coordinated in health and misregulated in disease.

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DISCLOSURES

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Management of Symptomatic Carotid Stenosis in Individuals with CKD

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Despite recent interest in carotid stenting for treatment of carotid stenosis, carotid endarterectomy remains the standard of care, particularly for individuals with symptoms referable to that carotid and with moderate to severe stenosis. Interest in stenting has increased in individuals with more medical comorbidities, including renal disease, despite lack of clear data contraindicating endarterectomy in these patients.

The article by Mathew et al. in this issue of JASN analyzes existing data from the North American Symptomatic Carotid Endarterectomy trial (NASCET),2 the only large randomized carotid endarterectomy trial in which creatinine levels were routinely measured. The authors show that carotid endarterectomy not only may benefit individuals with symptomatic carotid stenosis and chronic kidney disease (CKD) but also is safe and without major operative complications. In their anal-

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