"Inactivation of phosphorylated endothelial nitric oxide synthase (Ser-1177) by O-GlcNAc in diabetes-associated erectile dysfunction"

by Biljana Musicki, Melissa F. Kramer, Robyn E. Becker, and Arthur L. Burnett

[Biljana Musicki et al. demonstrate that the glycosylation of endothelial nitric oxide synthase (eNOS) by the monosaccharide O-GlcNAc inhibits proper erectile function in rats with type 1 diabetes. The phosphorylation of eNOS at Ser-1177 is an important step in the promotion of tumescence. The enzyme's activity is regulated by extracellular stimuli including electrical stimulation, shear stress, and VEGF signaling. Previous research has shown that hyperglycemia-induced O-GlcNAc modification inhibits eNOS activity in blood vessels, but the physiologic relevance of this modification in diabetic vascular tissues is unclear. Musicki et al. induced diabetes in rats and examined the penile tissues of the animals. Increased levels of eNOS-linked O-GlcNAc were detected, and significant decreases in the levels of both Ser-1177-phosphorylated eNOS and phosphorylated Akt, the upstream mediator of eNOS phosphorylation, were observed. Although electrical stimulation increased blood flow in penile tissue of control and diabetic rats, an increase in activated eNOS in diabetic rats was not seen. VEGF administration and shear stress were similarly ineffective in the diabetic animals, with rates of full erectile status decreased by 40%, magnitude of erectile response decreased by 30%, and tumescence rise time decreased by 70%. — F.A.

Medical Sciences

Deep-organ malaria parasite not associated with cerebral complications

Blandine Franke-Fayard et al. demonstrate that cerebral malaria pathology can occur in the absence of parasite sequestration. The sequestration of the malaria parasite Plasmodium falciparum in the microvasculature of deep organs (e.g., brain, liver, and lung) has been thought to underlie the severe complications of infection, such as cerebral malaria. Although parasite-encoded proteins on the surface of infected red blood cells are thought to act as anchors to endothelial cells within the brain, the relationship of sequestration with cerebral complications has never been firmly established. Franke-Fayard et al. visualized the interactions between infected red blood cells and the putative host receptor, CD36. By tagging rodent Plasmodium berghei parasites with luciferase, sequestration in expected organs, such as lung and spleen, was observed, but adipose tissue was also a major sequestration site. CD36 was shown to be the major receptor for P. berghei sequestration. Mice lacking CD36, the presumed
host receptor for infected red blood cells, showed no parasite sequestration, but still developed cerebral malaria. With an eye on the development of novel antimalarial therapies, these results help pinpoint relevant interactions between parasite-infected cells and host cells. — M.M.

**Distribution of malaria parasites in live rodents.**

"Murine malaria parasite sequestration: CD36 is the major receptor, but cerebral pathology is unlinked to sequestration" by Blandine Franke-Fayard, Chris J. Janse, Margarida Cunha-Rodrigues, Jai Ramesar, Philippe Büscher, Ivo Que, Clemens Löwik, Peter J. Voshol, Marion den Boer, Sjoerd G. van Duinen, Maria Febbraio, Maria M. Mota, and Andrew P. Waters [Full Text]

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**Neuroscience**

**TRPM7 allele may increase risk of Guamanian ALS and parkinsonism dementia**

Meredith Hermosura et al. report that a mutation in the transient receptor potential melastatin 7 (TRPM7) ion channel may contribute to Guamanian amyotrophic lateral sclerosis (ALS-G) and parkinsonism dementia (PD-G). These conditions are related neurodegenerative disorders found in high incidence on Guam and other western Pacific islands. TRPM7 is involved in homeostatic regulation of intracellular calcium (Ca^{2+}) and magnesium (Mg^{2+}), elements whose deficiency has been epidemiologically linked to ALS-G and PD-G. Hermosura et al. show that the missense mutation T1482I (affecting threonine 1482, or Thr-1482) results in a functional TRPM7 channel that displays similar kinase activity to wild type but has increased sensitivity to inhibition by intracellular Mg^{2+}. Mg^{2+} inhibition correlates with phosphorylation of Thr-1482, though the exact mechanism is not known. The authors propose that cells expressing the TRPM7 variant will have a higher likelihood of becoming deficient in Ca^{2+} and Mg^{2+}, and, therefore, the T1482I genotype may confer susceptibility to ALS-G and PD-G in regions that have low concentrations of these ions, such as some environments in the western Pacific. — N.Z.