Amy Banes-Berceli

Assistant Professor
Department of Biological Sciences

The causes of high blood pressure

In Amy Banes-Berceli's laboratory, researchers study the molecular mechanisms that contribute to the development of diseases of the vascular system, such as hypertension (high blood pressure) and diabetes. One intracellular pathway that they focus on is the JAK/STAT pathway, a series of reactions that allows the presence of a specific extracellular molecule to influence gene expression in the cell nucleus. The protein JAK2 is a key molecule in this pathway. Angiotensin II (ANG II), a protein that constricts blood vessels, utilizes both JAK2 dependent and independent mechanisms to raise blood pressure. In an ANG II/high salt rat model of hypertension, treatment with AG490 – a molecule that inhibits JAK2 – significantly lowered mean arterial pressure.

Researchers have also found that AG490 treatment prevented decreases in the Glomerular Filtration Rate and sodium excretion in the kidney that occurred in animals treated with ANG II alone, suggesting that there is a vasoconstriction of the afferent arteriole and this involves the activation of the JAK2/STAT pathway. Furthermore, ANG II utilizes JAK2 to cause vascular smooth muscle contraction in the aorta and superior mesenteric arteries via an interaction with p24/44 MAPK (another signaling pathway). Banes-Berceli's team is currently investigating the mechanisms by which JAK2 participates in vascular contraction and how its contribution varies among the vascular beds.

Norepinephrine is another molecule that can constrict blood vessels. In a model of norepinephrine-induced hypertension, researchers also have observed an increase in the levels of JAK2 activation, suggesting that activation of JAK2 is a factor in a second mechanism of hypertension. However, norepinephrine may not directly activate JAK2, as it is not observable in vascular smooth muscle cells or in myograph studies. Banes-Berceli's team is currently investigating this mechanism of activation of JAK2 in this model of hypertension.

Additionally, in collaboration with Dr. Michael Brands at the Medical College of Georgia, Banes-Berceli and her coworkers used a high dose ANG II model with normal salt intake to demonstrate that AG490 prevents the chronic increase of MAP (a molecule in the p24/44 MAPK pathway) as well as JAK2 activation by ANG II. These data also suggest that ANG II utilizes both JAK2 dependent and independent mechanisms to control blood pressure.

A final project currently underway in Banes-Berceli's lab looks at the mechanisms in which the molecule serotonin activates ANG II and the protein endothelin-1 (ET-1). This study focuses on the effects in the kidney under the conditions of diabetes. In a patient with diabetes, the levels of all three of these vasoactive agents (ANG II, ET-1, and the serotonin receptor 5-HT) are elevated and inhibition of them in animal models provides renal protection. However, the molecular mechanisms are as yet unclear. Banes-Bercelli proposes that 5-HT potentiates the actions of ANG II and ET-1 to exacerbate the development of diabetic nephropathy and that this involves the actions of the 5-HT2B receptor and the JAK/STAT and p42/44 MAPK pathways.

Representative Recent Publications

1. Banes-Berceli AK, Ketsawatsomkron P, Ogbi S, Patel B, Pollock DM, Marrero MB. 2007. Angiotensin II and Endothelin-1 augment the vascular complications of diabetes via JAK2 activation. *Am J Physiol* 293:1291-1299.

2. Banes-Berceli AK, Shaw S, Ma G, Brands M, Eaton DC, Stern DM, Fulton D, Caldwell RW, Marrero MB. 2006. Effect of simvastatin on high glucose-and angiotensin II-induced activation of the JAK/STAT pathway in mesangial cells. *Am J Physiol* 291:F116-F121.

3. Marrero MB, Banes-Berceli AK, Stern DM, Eaton DC. 2006. Role of the JAK/STAT signaling pathway in diabetic nephropathy. *Am J Physiol* 290: F762- F768.

4. Banes-Berceli AK, Ogbi S, Tawfik A, Patel B, Shirley A, Pollock DM, Fulton D, Marrero MB. 2005. Endotlin-1 activation of JAK2 in vascular smooth muscle cells involves NAD(P)H oxidase-derived reactive oxygen species. *Vasc Pharmacol* 43:310-319.

5. Banes AK, Shaw S, Tawfik A, Patel B, Ogbi S, Fulton D, Marrero MB. 2005. Activation of the JAK/STAT pathway in vascular smooth muscle by serotonin. *Am J Physiol* 288:805-812.

6. Banes AK, Shaw S, Jenkins JA, Redd H, Amiri F, Pollock DM, Marrero MB. 2004. Angiotensin II blockade prevents hyperglycemia-induced activation of JAK and STAT proteins in diabetic rat kidney glomeruli. *Am J Physiol* 286:F653-F659.

7. Banes AK, Watts SW. 2003. Arterial expression of 5-HT2B and 5-HT1B receptors during development of DOCA-salt hypertension. *BMC Pharmacol* 3:12.