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Angiotensin II and JAK2 put on the pressure

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Researchers have long known that the peptide angiotensin II is central to blood pressure control—but there is yet more to learn. A new study shows how angiotensin II cooperates with the JAK2 kinase, better known for its role in cytokine signaling, to regulate blood vessel contraction and influence blood pressure.

High blood pressure is a major contributor to heart disease and stroke, the leading killers of people in the US and Europe. There are three major contributors to blood pressure control: the contraction of small arteries, the control of blood volume and the regulation of the amount of blood pumped by the heart. Although many factors influence one or another of these parameters, the eight–amino acid peptide angiotensin II influences all three.

Angiotensin II is a powerful vasoconstrictor of the smooth muscle in blood vessels. It also acts to increase the vascular volume and the amount of blood pumped by the heart, coordinately raising blood pressure. Not surprisingly, blocking the formation of angiotensin II or blocking its actions are key therapies to treat hypertension and heart disease.

Despite its central role in regulating blood pressure, not everything is known about how angiotensin II works at a molecular level. In this issue of *Nature Medicine*, Guilluy *et al.*[1] examine this question, uncovering a crucial role for the intracellular tyrosine kinase JAK2 in angiotensin II–induced smooth muscle contraction. Normally, JAK2 is associated with the signaling pathways for cytokines, such as erythropoietin. The discovery that this kinase phosphorylates a single biochemical intermediate, Arhgef1, and that this is essential for angiotensin II–mediated high blood pressure, resets our thinking about the biochemistry of angiotensin II. In short, an unexpected outsider, JAK2, is key in the process by which angiotensin II induces smooth muscle contraction.

Angiotensin II exerts its major effects by binding to a seven-transmembrane cell surface receptor called AT_1 (ref. 2). Initial conceptualizations of how this receptor signals focused on heterotrimeric G proteins, because, as for many similar receptors, ligand binding induces G protein activation by GDP-GTP exchange. In vascular smooth muscle, this signaling leads to an increase in intracellular Ca^{2+}, which, in turn, activates myosin light chain kinase, phosphorylating myosin light chain and inducing vascular smooth muscle contraction (Fig. 1).

Guilluy *et al.*[1] show that JAK2 kinase–mediated tyrosine phosphorylation of the GEF Arhgef1 is a central event in angiotensin II–induced contraction of blood vessel smooth muscle. Angiotensin II stimulates blood vessel smooth muscle by binding to the seven-transmembrane, G protein–coupled AT_1 receptor (AT_1R). This binding then stimulates phospholipase C (PLC)-mediated release of intracellular Ca^{2+}, which, through calmodulin (CAM), activates myosin light chain kinase (MLCK). The result is phosphorylation of myosin light chain (MLC), blood vessel smooth muscle contraction and elevation of blood pressure. Through mechanisms that are not yet fully understood but probably involve Ca^{2+} and possibly PYK2 kinase or SRC kinase, angiotensin II also activates intracellular JAK2. JAK2 then phosphorylates and activates Arhgef1, which stimulates the RhoA-Rho kinase–

myosin phosphatase target subunit (MYPT) cascade, inhibiting myosin light chain phosphatase (MLCP), which has the effect of promoting phosphorylation of MLC and ultimately increases blood pressure. Guilluy *et al.*[1] show that, in the absence of functional JAK2 within smooth muscle cells, angiotensin II will not induce hypertension. IP_3, 1,4,5-triphosphate.

This simple pathway became more complex in the 1990s with the discovery of a second pathway promoting the phosphorylation of myosin light chain. Angiotensin II activates the monomeric (small) GTPase Rho, which, together with its target Rho kinase, regulates the activity of myosin light chain phosphatase [3, 4].

Rho activation inhibits myosin light chain phosphatase, promoting phosphorylation of myosin light chain and smooth muscle contraction. Rho proteins are often described as molecular switches, as they cycle between an inactive and an active form by exchanging bound GTP for GDP, a process markedly accelerated by guanine nucleotide exchange factors (GEFs). GEFs are themselves regulated by upstream signals, such as receptors, resulting in a biochemical dance of GDP, GTP and GDP binding and phosphorylation and dephosphorylation that generates a signal of limited duration to contract a smooth muscle cell.

Although it was known that angiotensin II activates RhoA (one of three Rho isoforms)[5], the details of this process were not well understood.

Guilluy *et al.*[1] present a series of biochemical studies that identify the GEF Arhgef1 as crucial for RhoA activation by angiotensin II and then show that, for this to happen, Arhgef1 must be phosphorylated on tyrosine. Experiments blocking JAK2 with either a relatively specific inhibitor or with siRNA implicated it as the responsible kinase. Blocking JAK2 activity blocked angiotensin II activation of Arhgef1 or RhoA.

To investigate the physiologic consequences, Guilluy *et al.*[1] then created a mouse model in which Arhgef1 was eliminated from vascular smooth muscle cells. Such mice were resistant to blood pressure elevation by angiotensin II but still sensitive to several other blood pressure drugs that operate through other pathways. Finally, Guilluy *et al.*[1] showed that the inhibitor of JAK2 prevented angiotensin II–mediated hypertension in a control mouse. Although it was previously known that angiotensin II stimulated JAK2 activation[6], it was not known that this kinase was so important in facilitating angiotensin II–induced smooth muscle contraction and ultimately in blood pressure control.

The study of Guilluy *et al.*[1] does contain a conundrum, namely the exact relationship between JAK2 kinase and intracellular Ca^{2+}. Blocking JAK2 activation with an inhibitor blunts, but does not prevent, angiotensin II–mediated intracellular Ca^{2+} elevation[7]. Given the importance of Ca^{2+} in stimulating the smooth muscle of blood vessels, one may ask why angiotensin II does not raise blood pressure even in the presence of a JAK2 inhibitor. Guilluy *et al.*[1] respond with evidence linking Ca^{2+} release and JAK2 activation, essentially outlining a regulatory network in which Ca^{2+} release is a sensitizer for Arhgef1-RhoA signaling, but in which JAK2 has an obligate role in angiotensin II–mediated elevation of blood pressure. Whether the network they outline is precisely correct, and its finer details, are topics for future investigation.

Other highlights of this paper include the identification of Arhgef1 as a key player in blood pressure regulation and, potentially, a target for pharmaceutical intervention. Many drugs are now available to treat high blood pressure, and only time will tell whether there is a unique advantage in developing an Arhgef1 inhibitor. Ultimately, what may be more important is the identification of JAK2 as having a central role in angiotensin II actions.

This finding, and future details on how JAK2 and intracellular Ca^{2+} interact, will inevitably redraw the model of how we envision angiotensin II signaling and will certainly lead to further basic and applied advances in hypertension research.

Although the area of angiotensin II and blood pressure regulation has been intensively studied for over 30 years, the new findings show that we cannot yet set the textbooks in stone. Ultimately, the findings in Guilluy *et al.*[1] reiterate the absolute ease with which cells deal with biochemical complexity—in this case with the waves of guanidine nucleotide exchange and the balance of kinases and phosphatases that regulate vascular smooth muscle tone and ultimately human blood pressure. Perhaps this ease with which cells integrate and balance so many biochemical signals is not surprising, as for a cell the control of actin and myosin filaments is one of the basic processes of life[8].

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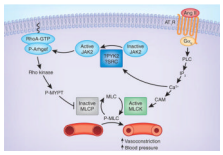

Figure 1.
The contraction of blood vessel smooth muscle by angiotensin II.