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Vascular autoregulation:

A century ago, Dr. Bayliss and colleagues originally described vascular autoregulation as a mechanism of blood flow maintenance in response to changing perfusion pressure (Bayliss, 1902). It is an essential mechanism that ensures adequate supply of blood and oxygen delivery to critical organs (Bayliss, 1902). One of the mechanisms by which autoregulation is achieved is through myogenic control, where the diameter of blood vessels decreases or increases after an increase or decrease in transmural pressure, respectively. From a mechanistic standpoint, intraluminal pressure acts on smooth muscle, causing downstream calcium signaling and influencing contractility (Bayliss, 1902). Understanding the biochemical underpinnings of vascular autoregulation could thus allow for better understanding of the molecular drivers of this mechanism and appreciation for its role in health and disease.

TRPV1:

TRPV1 is an ion channel reported to be found in sensory ganglia, important for sensations and response to temperature, pain, and itch. TRPV1 is thus well-characterized in regulating sensory mechanisms, as its activation can occur through high temperature and acidosis, among others. TRPV1 is made of multiple interacting subunits, which underscore the kinetics of its interactions (Bevan *et al.*, 2014). Such interactions have been proposed to occur through voltage, ligand-binding, and temperature, but all largely without reference to vascular autoregulation (Bevan *et al.*, 2014). Nonetheless, the importance of TRPV1 in modulating the response to changing temperatures is reflected by it being the subject of the 2021 Nobel Prize in Physiology and Medicine. Now, less than a year later our understanding of TRPV1 in physiology continues to be developed. The emerging role of TRPV1 in vascular autoregulation points to yet another

regulatory mechanism that this channel protein drives, supporting the need for further exploration and clinical translation (Phan *et al.*, 2022).

In 2020, Phan and colleagues performed functional mapping of TRPV1 throughout the mouse circulation, showing extensive expression of TRPV1 in arterioles suplying the skeletal muscle, heart, and adipose tissue (Phan *et al.*, 2020). Recently, they showed that those TRPV1 channels control most of the myogenic response (Phan *et al.*, 2022). This was proved through administration of TRPV1 antagonists, such as BCTC, both ex- and in-vivo (Phan *et al.*, 2022). The ex-vivo experiments revealed dilation of the pressurized arterioles. In-fact, dilation caused by BCTC exhibited a concentration-dependent relationship. Similarly, such dilation was observed in-vivo upon local perfusion of BCTC. Further, the addition of BCTC significantly increased coronary flow, and decreased the systemic blood pressure (Phan *et al.*, 2022). In contrast, the dilation of arterioles was not observed upon administartion of pharmacologic inhibitors to TRPV1-null mice, further proving the specificity of the TRPV1 inhibitors (Phan *et al.*, 2022).

Not only was TRPV1 found to be important in myogenic response, but also important for its regulation. This was demonstrated by pressurizing the arterioles in a stepwise manner and recorded the corresponding reflexive constrictions. Notably, the higher the pressure level the faster the myogenic response (Phan *et al.*, 2022). Upon inhibition of TRPV1, using BCTC, such rapid myogenic response was significantly reduced, impairing the rate of development of the myogenic tone (Phan *et al.*, 2022).

Dr. Philip S. Clifford previously reported that skeletal muscle is shown to dilate at the onset of physical activity (Clifford, 2007). Building upon this work, Phan and colleagues examined whether such dilation is mediated by TRPV1. To investigate this, they applied vasoconstricive stimuli, such as the administration of KCl or blue light (40s), to examine the consequential vascular effects on the corresponding arterioles. Notably, a rebound vasodilation was observed following a rapid deactivation of TRPV1. Importantly, such dilation was significantly reduced in TRPV1-null mice which demonstrates the critical role of TRPV1 in enabling rapid reactive vasodilation.

Signaling pathway:

Since TRPV1 channels expressed elsewhere are activated by PLC-dependent pathway, they investigated whether a similar signaling pathway is observed in TRPV1-mediated myogenic response (Phan *et al.*, 2022). Indeed, a decrease in the arterial tone was observed upon inhibition of PLC and PKC, indicating their involvement in the signaling pathway (Phan *et al.*, 2022).

Non-TRPV1 mediated myogenic response:

To investigate the myogenic response by other TRP channels, they screened mRNA expression levels of certain TRP channels in both wild-type and TRPV1-null mice (Phan *et al.*, 2022). Their results indicated an increase in levels of TRPM4 and TRPP1 (Phan *et al.*, 2022). TRPM4's contribution to myogenic response was later confirmed through inhibition experiments. Interestingly, despite the significant increase in expression levels of TRPM4, the kinetic properties of myogenic tone were still not restored and therefore cannot fully replace TRPV1. Such result emphasizes the irreplaceable importance of TRPV1 in the vasculature (Phan *et al.*, 2022).

Conclusion:

Elaborating the role of TRPV1 as a biochemical driver of myogenic tone and blood flow allows for an increasingly precise understanding of this essential physiological process. By showing that TRPV1 plays a functional role in triggering physiological responses to arteriolar myocyte stretching and elevated intraluminal pressure, the researchers underscored a modulatory role for the protein. Such dynamic regulation of blood flow demonstrates TRPV1's importance to ensure adequate supply of oxygen and nutrients to the heart and skeletal muscles, complicating its already well characterized role in physiology. These findings could potentially support a mechanism of myogenic response adaptability in high-intensity cardiac and exercise performance. Thus, the finding of Phan and colleagues support the need for further study and exploration of the protein in subsquent clinical contexts.

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