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Editorial

The sodium-hydrogen antiporter: a new target to boost post-ischemic angiogenesis in diabetes?☆

Gaia Spinetti [1]

Laboratory of Cardiovascular Research, IRCCS MultiMedica, Via Fantoli 16/15, 20138 Milan, Italy

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We as researchers in the biomedical field all have our favorite molecule, pathway, cell type to study, but the complexity of pathophysiological processes make us face a reality: we are only looking at the tip of an iceberg. This is the case also in the study of post-ischemic angiogenesis, a topic that is the object of intense research [1]. The understanding of the cellular and molecular mechanisms underlying the neoformation of capillaries in tissues where the oxygen concentration has decreased may lead to new solutions for a huge sanitary problem of our time. In the last decades, in fact, the sedentary habits in conjunction to unhealthy food intake has led the world population of increasingly old people to deal with an epidemic number of subjects with type 2 diabetes, a complex metabolic syndrome associated with micro- e macro-vascular disease. Data from the World Health Organization indicate that 1/11 person suffers from diabetes. Of the 422 million diabetic patients, about 60 million are in Europe, of which around 10.3% are men and 9.6% women aged 25 years and over. It is now well established that the high circulating glucose concentrations consequent to the lack or malfunction of the cellular buffering systems typical of diabetes damage the endothelium, the inner layer of the vessels. Endothelial cells (ECs) are not able anymore to efficiently reorganize themselves to give rise to new capillaries to irrigate the ischemic tissue. This particular aspect has been investigated also in the study from Zhang and colleagues where they show that high glucose conditions in vitro trigger ECs dysfunction, i.e. impairment in the ability to form networks on an extracellular matrix mimicking substrate [2]. The authors newly point at the concomitant alteration of the intracellular pH balance. This is intriguing, but what happens to the other cells that cooperate in the neovessel formation?

Following ischemia, resident ECs proliferate, migrate, and secrete pro-angiogenic cytokines and chemokines (VEGF-A, SDF-1a, IL-8 among others) in addition to other molecules including new classes of non-coding RNAs that help them to grow new vessels. However, to accomplish this goal ECs need the support of circulating progenitor cells of bone marrow origin and of other tissue resident cells, i.e. skeletal muscle pericytes (MPs) a class of stromal cells residing adjacent to capillaries and embedded within the same basement membrane [1,3]. The interaction between these cells is complex and regulated by factors affecting the cell of origin and the nearby surrounding and distant cells [4].

This articulated and complex process is less efficient in diabetes. First of all classical resident and circulating reparative cells are dramatically decreased in number and functionally impaired thus decreasing the chances of tissue recovery as has been shown studying animal models of diabetes and subject with both type 1 and type 2 diabetes [5–7]. In addition, recent meta-analyses demonstrate that lowering glycemia in diabetic patients do not effectively prevent from ischemic vascular complications calling out for new strategies of vascular protection [8].

Having said that, although cell complexity exists, there are some molecules that control vital cell processes and that are ubiquitously expressed. For this reason, one can envision to target such central mechanisms to amend the whole vasculature. On the other side, their ubiquitous nature makes this kind of molecules risky targets due to unexpected side effects in other districts. One of such factors is the sodium-hydrogen antiporter 1 (NHE-1). NHE-1 also known as sodium/hydrogen exchanger 1 or SLC9A1 (SoLute Carrier family 9A1) in humans is encoded by the SLC9A1 gene. Of the 9 existing isoforms of NHE, NHE-1 is the ubiquitously expressed one, a membrane protein deputized to the control of cell volume trough maintaining pH and intracellular $Na+/Ca++$ concentration. NHE-1 expellees $H+$ and transport $Na+$ in the cell in response to changes in cellular metabolism typical of ischemia. Several kinases can regulate its action by phosphorylation including MAPK family members and Protein kinase C-β [9]. The control of intracellular pH influences angiogenesis and NHE-1 finely tunes it in both negative and positive manners depending on the cellular microenvironment [10]. Since NHE-1 has been associated with the hypertrophic and ischemia/reperfusion injury damage of the myocardium it has been studied as a target for developing cardioprotective

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E-mail address: gaia.spinetti@multimedica.it.
[1] IRCCS MultiMedica, Milan, Italy. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

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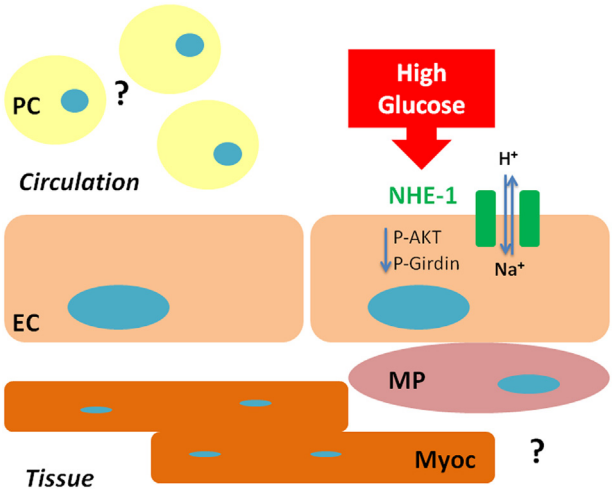

Fig. 1. Schematic view of the cells contributing to neoangiogenesis. In the event of ischemia in the limb, the tissue responds by activating endothelial cells (ECs), but also muscle cells including myocytes (Myoc) and pericytes (MPs). In aid of the process progenitor cells (PCs) are mobilized from the bone marrow and reach the tissue traveling in the peripheral circulation. Whether the NHE-1 antiporter is altered by high glucose in these other cells similar to what Zhang and colleagues showed for ECs, via AKT and Girdin phosphorylation (P-AKT, P-Girdin) impairment, deserve to be investigated further.

drugs. Cariporide is an example of a selective NHE-1 inhibitor with cardioprotective and antitumor activity. In the study of Zhang and others, the EC loss of function was associated with a change in intracellular pH via the NHE-1 activation. This effect was dependent on the AKT-Gridin pathway via regulation of phosphorylation and was reversible by treatment with amiloride another NHE-1 inhibitor less selective than cariporide. Whether this is the case also in cells isolated from diabetic patients is still an open question. Of note in the current article [2] amiloride was effective also in vivo on the restoration of blood perfusion in a mouse model of limb ischemia. The author point to the potential use of amiloride for improving tissue oxygenation in patients. Nowadays, treatment strategies to restore blood flow for diabetic limb ischemia are based on angioplastic or surgical intervention. Gene and cell therapies are promising but still not made it to the normal clinical practice [1]. Amiloride is an anti-hypertensive drug of the diuretic class altering the Na/K balance in the market for several years. Although the new evidence presented by Zhang shade new light on the possibility of exploiting an old drug for a new purpose, the translation of experimental results to the patient bed may give disappointing results. Subjects with diabetes have a high risk of kidney problems and associated hyperkalemia (increased circulating potassium). As the developer of amiloride state in their recommendations, the use of a drug that alter potassium balance and therefore kidney function in diabetic people may be well pondered before prescription and monitored to prevent toxicity. In conclusion, the manuscript from Zhang and colleagues add on the knowledge of ion homeostasis in the control of pathophysiological processes, providing new hope to find new valuable targets for improving post-ischemic angiogenesis, but remind us of the complexity of the body response to ischemia leaving a lot still to be discovered before reaching bedside (Fig. 1).

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Conflict of interest

No conflict of interest to be declared.

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