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REVIEW

Regulation of Vascular Smooth Muscle Cell Contraction during Early Postnatal Ontogenesis

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Abstract—Growth of the body in early postnatal ontogenesis is associated with changes in the functioning of many systems, including the cardiovascular system. The circulatory system of newborns is characterized by numerous structural and functional features, which are manifested at the systemic level in significantly lower arterial pressure. This review considers the differences in the mechanisms regulating vascular smooth muscle cell contraction in early postnatal ontogenesis and in adulthood, including age-related changes in the functioning of ion channels, the activity of which affects the level of membrane potential and intracellular concentration of calcium ions as well as changes in the calcium sensitivity of the contractile apparatus. The final section of the review discusses the relationship between the mechanisms regulating contraction and differentiation of vascular smooth muscle cells during their maturation.

Keywords: vascular tone, ion channels, calcium sensitivity of the contractile apparatus, reactive oxygen species, differentiation

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1. FEATURES OF SYSTEMIC HEMODYNAMICS IN EARLY POSTNATAL ONTOGENESIS

Intensive growth of the body in early postnatal ontogenesis is associated with changes in the functioning of many body systems, including the cardiovascular system. Thus, the level of arterial pressure in the systemic circulation of a newborn child (50 mm Hg) is approximately half that of an adult (100 mm Hg) [1], and this is favorable for the functioning of not yet completely formed arterial vessels and heart, which contain less muscle and connective tissue in the neonatal period; therefore, high pressure can damage them. At the same time, the cardiac output of children born at term is ten times less than that of adults (500 mL/min compared with 5000 mL/min) [2], but the cardiac output is twice as high in children in relation to a body weight (3.5 and 70 kg, respectively). Thus, the total peripheral vascular resistance in a newborn child is only a quarter of the value of this indicator in adulthood, which is associated with both structural features and differences in the vascular tone regulation. Similar features of systemic hemodynamics in early postnatal ontogenesis were shown in studies of laboratory animals [3, 4].

Low vascular resistance in early postnatal ontogenesis is associated with the immaturity of the sympathetic innervation [5], as well as with the influence of nitric oxide, which is tonically produced by the vascular endothelium of many organs [6–8]. The mechanisms regulating contraction of vascular smooth muscle cells (SMCs) also differ in newborn and adult bodies. During the period of early postnatal ontogenesis, the process of vascular SMCs differentiation, the transition from the proliferative phenotype to the contractile one, has not yet been completed.

The interaction of myosin with actin during contraction of vascular SMCs is regulated by two mechanisms. The rapid contractile response is caused by an increase in the intracellular concentration of Ca^{2+} [9, 10], mainly due to its entry from the extracellular environment and, as a rule, is associated with a shift in the membrane potential (MP) towards depolarization as a result of changes in the activity of various ion channels [11]. At the same time, the maintenance of tonic contraction of SMCs often occurs due to an increase in the contractile apparatus sensitivity to Ca^{2+}, a phenomenon called Ca^{2+} sensitization [9, 10]. Due to Ca^{2+} sensitization, a sufficiently strong contraction of arterial smooth muscle can be maintained under conditions when the intracellular Ca^{2+} concentration does not increase significantly [9, 10]. The contribution of Ca^{2+} sensitization to the contraction magnitude

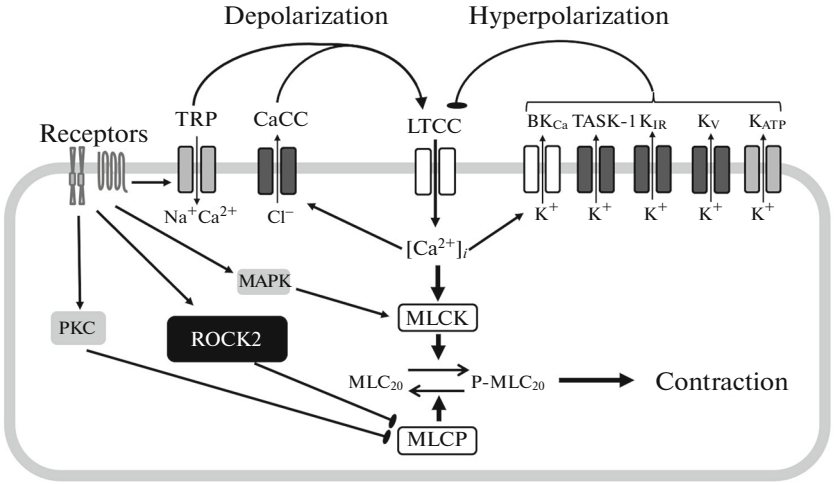

Fig. 1. Main mechanisms regulating contraction of vascular SMCs and features of their functioning in early postnatal ontogenesis. Changes in the content/activity of channels/enzymes in SMCs of a newborn body compared with an adult are coded by the fill color: dark fill is increase, white fill is decrease, and gray is no pronounced change (or there is insufficient literature data on this issue). Arrows with sharp ends indicate stimulation of activity, arrows with blunt ends indicate activity. (MLC) Myosin light chains; (MLCK) myosin light chain kinase; (MLCP) myosin light chain phosphatase; (PKC) protein kinase C; (MAPK) mitogen-activated protein kinase; (ROCK2) Rho-kinase II; (TRP) transient receptor potential, nonselective cation channels; (CaCC) Ca^{2+}-activated Cl^- channels; (LTCC) L-type Ca^{2+}-channel, voltage-gated Ca^{2+} channels of the L type; (BK_{Ca}) large conductance Ca^{2+}-activated K^+ channels; (TASK-1) weak inward-rectifying K^+ (TWIK)-related acid-sensitive K^+-channel; (K_{IR}) inward-rectifier K^+-channels; (K_V) voltage-gated K^+-channels; (K_{ATP}) ATP-sensitive K^+-channels.

depends on the caliber of the artery and/or the vascular region to which this artery belongs [12].

As will be discussed below, in early postnatal ontogenesis, not completely differentiated SMCs differ from SMCs of adult vessels in their mechanisms of MP regulation and, consequently, the intracellular Ca^{2+} concentration (Fig. 1). In addition, SMCs of developing vessels are characterized by high sensitivity of the contractile apparatus to Ca^{2+}, which affects their ability to maintain tonic contraction (Fig. 1).

2. FEATURES OF ION CHANNEL FUNCTIONING OF ARTERIAL SMCs IN EARLY POSTNATAL ONTOGENESIS

2.1. Channels Providing Ca^{2+} Entry into SMCs

The entry of Ca^{2+} through voltage-gated calcium channels is a key mechanism for increasing the Ca^{2+} concentration in the cytoplasm of SMCs under the action of various vasoconstrictor substances and the development of myogenic vascular tone [11]. In the smooth muscle of arteries, L-, T-, and P/Q-type channels have been found, while the most functionally important is the L-type (L-type calcium channel, LTCC) [11, 13], and it is this type of channels that has been best studied in the ontogenetic aspect (Fig. 1).

In general, high levels of LTCC abundance and activity are typical for differentiated SMCs [14]. In isolated aortic SMCs of newborn rats, in contrast to adults, neither depolarization nor the LTCC channel activator BayK 8644 caused the appearance of Ca^{2+} entry [15]. Accordingly, the amount of LTCC in the aorta of newborn rats was only 5% of that in adult rats [15]. In newborn rabbits, relaxation reactions of mesenteric arteries to the LTCC blocker were several times lower than in adults [16]. In rats, the LTCC content in SMCs of small mesenteric arteries gradually increases during the postnatal development: the current density through these channels increases between 6 and 12 weeks of life and does not change further by 20-week age [17]. However, in sheep that are born more mature, no differences were found when comparing the amount of LTCC in the aorta of full-term fetuses, newborns, and adult animals [18].

Interestingly, cerebral arteries demonstrate opposite changes in the functional role of LTCC during the development. Thus, the myogenic tone of cerebral arteries in newborn piglets is mainly due to the influx of Ca^{2+} into SMCs through LTCC [19]. The effects of LTCC activators and blockers on intracellular Ca^{2+} levels and norepinephrine-induced contraction of the middle cerebral artery were also more pronounced in full-term fetuses than in adult sheep [18, 20], which is consistent with the data on a higher LTCC content in cerebral arterial tissue in the antenatal period [18]. Similar results were obtained in a study of age-related changes in the vasomotor role of LTCC in pulmonary arteries of pigs and sheep: a decrease in contractile responses under the action of blockers of these channels was more pronounced in the perinatal period of

the development [21, 22]. When studying LTCC in SMCs of the pulmonary artery of rats at later stages of ontogenesis (at the age of 5–7, 10–12, and 19–23 weeks), no differences in the density of these channels were found [23]. The increase in the content and functional role of LTCC in the arteries of the brain and lungs, in contrast to other systemic arteries, may reflect the peculiarities of the mechanisms regulating vascular tone in these organs or the uneven maturation of regulatory mechanisms in different vascular beds.

In contrast to LTCC, voltage-gated T-type calcium channels are more typical for proliferating SMCs [24], but the role of these channels in postnatal changes in vascular contractility has not yet been studied.

Receptor-gated channels include the TRP (Transient Receptor Potential) family due to the ability of some representatives of this family to be activated by diacylglycerol [24]. The activation of TRP channels can directly provide the entry of Ca^{2+} into arterial SMCs, as well as promote the activation of LTCC, by creating membrane depolarization. As a rule, a decrease in the degree of SMC differentiation in the cell culture or in some vascular pathologies is accompanied by a multiple increase in the content of TRP channels [24]. At the same time, in afferent arterioles of the pig kidney from the first to the 20th day of life, an increase in expression of TRPC3 channels was observed, which correlated with an increase in contractile responses of these arterioles [25]. In general, the role of receptor-gated Ca^{2+} channels in arterial SMCs in early postnatal ontogenesis has been little studied.

2.2. Chloride Channels

Since the intracellular Cl^- concentration in vascular SMCs is relatively high (30–50 mM on average), the equilibrium potential for Cl^- is more positive compared with the resting potential [26, 27]. Thus, the Cl^- influx to SMCs is depolarizing and promotes contraction [28–32]. The most important "pathway" for the Cl^- release from arterial SMCs is Ca^{2+}-activated Cl^- channels (CaCC), which are formed by the proteins TMEM16A and bestrophin-3 [33–35].

The CaCC role in the vascular tone regulation is also changed during postnatal ontogenesis (Fig. 1). Incubation in a chloride-free solution (to reduce the Cl^- concentration in SMCs), as well as the blockade of CaCC with MONNA, resulted in weakening of contractile responses of the saphenous artery to the α_1-adrenoceptor agonist methoxamine, and these effects were more pronounced in the arteries of 1–2-week-old rats than in the arteries of adult rats [32, 36]. In the arteries of rat pups, SMC depolarization under the action of methoxamine was completely dependent on the influence of the Cl^- flux, and the expression levels of bestrophin-3 and TMEM16A, responsible for Ca^{2+}-activated conductance of the SMC membrane for Cl^-, were higher than in adulthood [32]. Thus, both depolarization and contraction upon activation of α_1-adrenergic receptors are more dependent on CaCC in SMCs of arteries in 1–2-week-old rat pups compared with adult rats.

2.3. Potassium Channels

The effect of the potassium efflux in arterial SMCs counteracts contraction (anticontractile effect) [11]. Five functional types of K^+ channels have been found in arterial SMCs: (1) voltage-gated channels (K_v, activated by membrane depolarization), (2) inward rectifier channels (K_{ir}, allow K^+ into the cell if MP is more negative than E_K), (3) ATP-dependent channels (K_{ATP}, activated by an increase in the ADP/ATP ratio in the cell), (4) two-pore-domain channels (K_{2P}, leak channels), and (5) large conductance Ca^{2+}-activated K^+ channels (BK_{Ca}, activated by depolarization and an increase in intracellular Ca^{2+}) [11].

SMCs of different arteries of the systemic circulation (aorta, saphenous artery, middle cerebral artery) in rats and sheep during early postnatal ontogenesis demonstrate more pronounced depolarization and/or contraction responses upon blockade of K_v1, K_v7, $K_{ir}2$, and TASK-1 (a member of the K_{2P} channel family) channels compared with arteries of adult animals [37–41]. First of all, this is due to increased expression of these channels: the content of pore-forming ($K_v1.2$, $K_v7.4$, $K_{ir}2.1$, $K_{ir}2.4$, TASK-1) and regulatory (KCNE4) subunits of these K^+ channels in SMCs of arteries at early age is higher than in adult age [37, 38, 40]. It should be noted that the anticonstrictor effect of TASK-1 channels in 1–2-week-old animals is also manifested at the systemic level in a more pronounced effect of the blocker of these channels on the level of blood pressure [40]. Thus, the anticonstrictor effect of K_v1, K_v7, $K_{ir}2$, and TASK-1 channels in systemic arteries during the period of early postnatal ontogenesis is higher than in adulthood (Fig. 1).

BK_{Ca} channels exhibit opposite age-related changes in the activity in SMCs of systemic arteries. Blockade of these channels did not reduce the amplitude of the potassium efflux in the aortic SMCs of 20-week-old human fetuses, in contrast to the aortic SMCs of adult humans [42]. Similarly, various BK_{Ca} channel blockers had less pronounced effects on the basal tone and on agonist-induced contraction of cerebral arteries, saphenous artery, carotid artery, and aorta in neonatal rats and/or sheep [38, 41, 43–46]. The content of pore-forming α1- and regulatory β1-subunits, which have a positive effect on the channel activity [47], was lower in the tissue of neonatal animals than in adults [38, 41, 44]. Thus, the vasomotor role of BK_{Ca} channels in systemic arteries during early postnatal ontogenesis is significantly lower than at later stages of the development (Fig. 1).

Summarizing the above data, in the systemic arteries of newborn and adult animals, the anticonstrictor effect can be mediated by different types of K^+ channels [48]: the functional role of K_v1, K_v7, $K_{ir}2$, and TASK-1 channels is more significant during early postnatal ontogenesis, while BK_{Ca} channels are more active in adulthood (Fig. 1). Interestingly, the picture is different in SMCs of the pulmonary arteries: an increase in the intracellular Ca^{2+} concentration under the blockade of K_v channels is more pronounced in adult sheep and that under the blockade of BK_{Ca} channels in fetuses, while the amount of $K_v2.1$ channel protein and mRNA in the pulmonary arteries of sheep increases with maturation and BK_{Ca} channels, on the contrary, decreases [49–51]. Such features of the K^+ channel functioning may be associated with age-related features of the response of the pulmonary arteries to changes in the O_2 content: in fetuses, the pulmonary arteries contract with an increase in p_{O2} and with a decrease in p_{O2} in adult animals [49–51].

Not all types of K^+ channels participate in the vascular tone regulation under normal physiological conditions. Brain arteries of adult sheep have a higher sensitivity to activators of K_{ATP} channels compared with arteries of full-term fetuses [39, 52]. However, the K_{ATP} blockade does not change contractile responses of these arteries in either fetuses or adult animals [38, 39] or contractile responses of the saphenous artery of 1–2-week-old rats and adult rats [38, 39]. This may be associated with a low K_{ATP} activity upon sufficient supply of SMCs with oxygen and metabolic substrates. Similarly, a K_v2 channel blocker did not change contractile responses of the saphenous artery preparations from rat pups and adult rats [38]. Thus, no anticonstrictor effect of K_{ATP} and K_v2 channels in the vessels of the systemic circulation was revealed during the perinatal period of ontogenesis.

3. FEATURES OF Ca^{2+} SENSITIVITY OF THE CONTRACTILE APPARATUS REGULATION IN ARTERIAL SMCs OF A NEWBORN BODY

The contribution of the Ca^{2+} sensitization mechanism to the development of the contractile response in SMCs also changes with age: it can be significantly higher during early postnatal ontogenesis than in an adult body. Thus, contraction of the saphenous artery in 1-week-old rats is realized with only a slight increase in the intracellular concentration of Ca^{2+}; that is, the degree of the Ca^{2+} sensitization involvement in the implementation of contractile responses at this age is extremely high [5]. With increasing age, the role of Ca^{2+} sensitization decreases simultaneously with an increase in the role of Ca^{2+}-dependent contraction regulation mechanisms [5]. Similar data on the high Ca^{2+} sensitivity of the contractile apparatus of SMCs were obtained for the femoral, common carotid, and basilar arteries of rabbits during early postnatal ontogenesis [53] as well as for the arteries of the brain of full-term sheep fetuses [54, 55].

Sensitization of the contractile apparatus of SMCs to Ca^{2+} is ensured by the functioning of a number of kinases, among which the most studied are Rho-kinase and protein kinase C (PKC) [9, 56]. The main target of these kinases is the regulatory subunit of myosin light chain phosphatase (MYPT1); activation of both Rho-kinase and PKC results in inhibition of the phosphatase activity and, as a consequence, blockade of myosin regulatory light chains (MLC_{20}) dephosphorylation, which helps maintain smooth muscle contraction.

Another group of kinases that can regulate the sensitivity of the contractile apparatus of SMCs to Ca^{2+} are mitogen-activated protein (MAP) kinases [56]. It was shown that both the protein content and the functional contribution of p42/44 MAP kinases to the regulation of contractile responses to serotonin in the carotid artery of full-term sheep fetuses are higher than in adult individuals [57]. However, in the rat saphenous artery, p42/44 and p38 MAP kinases do not participate in the regulation of contractile responses to the α_1-adrenoceptor agonist methoxamine during early postnatal ontogenesis, despite the manifold increased content of these proteins in the arteries of 1–2-week-old rats compared with adult rats [5, 58]. Differences in the results of the studies described above may be associated with species-specific characteristics of the animals (sheep or rats), differences in the vascular regions studied, and also with the activation of different types of receptors during stimulation of SMC contraction.

A study of the functional role of PKC in the regulation of SMC tone did not reveal its significant contribution in the cerebral arteries of full-term sheep fetuses [59] or in the saphenous artery of rats during early postnatal ontogenesis [4]. However, the contribution of Rho-kinase to the regulation of SMC contraction during early ontogenesis was significantly higher than in adulthood (Fig. 1). Thus, in 1–2-week-old rats, Rho-kinase inhibitors significantly reduce contractile responses of systemic arteries (using the saphenous artery as an example) [4, 60]. Similar data were obtained for the cerebral arteries of full-term sheep fetuses [59]. The more significant functional contribution of Rho-kinase to the regulation of arterial tone during early postnatal ontogenesis compared with adulthood correlates with a higher content of the Rho-kinase protein [5] and the Rho-kinase-activating RhoA protein [4] as well as with a more significant increase in the phosphorylation levels of MYPT1 (at the inhibitory site Thr855) and MLC_{20} (at the activation site Ser19) [4].

4. FEATURES OF VASOMOTOR EFFECTS OF REACTIVE OXYGEN SPECIES IN PERINATAL AND EARLY POSTNATAL PERIODS

Today, there is no doubt that reactive oxygen species (ROS) participate in the regulation of vascular tone [61]. ROS are capable of causing both relaxation and contraction of SMCs, which depends on the diameter of the vessel, its belonging to the pulmonary or systemic circulation, the concentration of ROS and the site of their production in the cell, and the developmental stage of the body [62].

Interestingly, in the perinatal period, the systemic vessels of birds and mammals contract rather than relax in response to hypoxia, as it occurs at later stages of the development. At the same time, the mesenteric arteries of bird embryos have a unique endothelium-independent mechanism of contraction under hypoxic conditions, which is associated with an increase in the ROS production by mitochondria and NADPH oxidases and subsequent activation of LTCC and Rho kinase [63]. In mammalian fetuses, ROS also play an important role in the constriction of peripheral vessels during hypoxia, which ensures priority blood supply to the brain (brain-sparing effect); however, in this case, the constrictor effect of ROS is associated primarily with a decrease in the bioavailability of endothelial NO due to an increase in the ROS production in SMCs [64, 65].

A striking example of the important vasomotor role of ROS in the first days of postnatal ontogenesis is their participation in the ductus arteriosus (DA) contraction. In studies on DA of humans and rabbits, as well as on the pulmonary part of DA in chicken embryos, which has an embryonic origin similar to that of mammals, normoxia (21% O_2) led to an increase in the ROS production (mainly H_2O_2) by mitochondria. The mechanism of the constrictor effect of H_2O_2 in DA is associated with suppression of the activity of K_v channels and stimulation of LTCC, with the activation of Rho kinase and an increase in the sensitivity of the contractile apparatus of SMCs to Ca^{2+}, as well as with an increase in the synthesis of ceramide, which is capable of activating NADPH oxidase, thereby further increasing ROS production [66–69].

Finally, ROS have a pronounced vasomotor effect at a later but still early stage of development. The production of superoxide anion radical $O_2^{\bullet-}$ by NADPH oxidases in the saphenous artery of 10–15-day-old rats is tens of times higher than in the arteries of adult rats, which correlates with a manyfold increase in the content of NOX2 and NOX4 proteins in the arterial tissue of rat pups [70]. It is important that such differences in the $O_2^{\bullet-}$ production and the content of NOX proteins were also manifested at the functional level: inhibition of NADPH oxidases (primarily NOX2) in an endothelium-independent manner weakened contractile responses of the saphenous artery of rat pups but not of adult rats [70]. The mechanisms of the constrictor effect of ROS in the arteries of a developing body are still unclear; they may be associated with an increase in the activity of both LTCC [71] and TRP channels [72] as well as Rho-kinase [73, 74].

5. RELATIONSHIP BETWEEN MECHANISMS REGULATING DIFFERENTIATION AND CONTRACTION OF SMCs IN DEVELOPING VASCULAR BED

As can be seen from the data considered above, in early postnatal ontogenesis, arterial SMCs are characterized by numerous features of regulatory mechanisms that can lead to both weakening and strengthening of contractile responses. A decrease in Ca^{2+} entry into SMCs through LTCC and an increase in the hyperpolarizing effect of K^+ channels (K_v1, K_v7, $K_{ir}2$, and TASK-1), along with the anticonstrictor effect of NO and a low level of neurogenic vascular tone, should contribute to the dilation of systemic arteries and a decrease in arterial pressure. However, such changes as an increase in the depolarizing effect of CaCC, high activity of Rho-kinase, and the constrictor effect of ROS are aimed at increasing vascular tone. It should be noted that vasoconstriction is necessary for the redistribution of cardiac output between organs depending on their needs for blood supply, and this is no less important in the early period of postnatal development than in adulthood [75, 76]. Under conditions of incompletely developed sympathetic innervation of vessels, the interaction of the above-described constrictor and anticonstrictor mechanisms ensures a regulation balance of the vascular tone that is optimal for the immature cardiovascular system.

It is important that during development of the vascular system, many vasomotor mechanisms are involved in the regulation of SMC differentiation and maturation. In 1–2-week-old rats, arterial SMCs are not yet completely differentiated into the contractile phenotype; they have significantly reduced levels of α-actin and smooth muscle myosin heavy chain [77, 78], as well as myosin light chain kinase and phosphatase, which are involved in Ca^{2+}-dependent regulation of contraction [5, 78]. The specific force of contraction of the smooth muscle layer of the arterial wall (media stress) in 1–2-week-old rats is almost half that of adults [5].

The impact on the development of the vascular system has been best studied for the signaling pathways of Rho kinase and ROS. Interestingly, at the stage of vascular system formation, these signaling pathways enhance proliferation of SMCs, which is associated with the activation of the cascade of mitogen-activated protein kinases (MAP kinases) p42/44, but they switch to regulating differentiation of SMCs into the

contractile phenotype at later stages, with their main target becoming the myocardin transcription factor [79–81]. The content of α-actin and smooth muscle myosin in SMCs directly correlates with the RhoA protein content and Rho kinase activity [81–83]. ROS at relatively low physiological concentrations also stimulate the synthesis of smooth muscle proteins [84, 85].

Vascular SMC differentiation is also regulated by trophic influences from the endothelium and maturing sympathetic nerves, and the action of these mechanisms may relate to different stages of ontogenesis. The effect of NO is manifested earlier: even in prenatal ontogenesis in rats. Thus, a decrease in the NO production in the body of females in the second half of pregnancy is accompanied by a slowdown in SMC differentiation in the aorta of newborn rats [86]. The effect of NO on SMC differentiation may be associated with an increase in the activity of the Rho-kinase signaling pathway [87, 88]. The trophic influence of sympathetic nerves is realized later, in early postnatal ontogenesis [5, 78]. On the contrary, it is associated with a decrease in the activity of Rho-kinase and the mechanism of Ca^{2+} sensitization and an increase in the contribution of Ca^{2+}-dependent mechanisms to the regulation of SMC contraction [4, 5]. Overall, further studies are needed to answer the important question about the interaction of various mechanisms regulating SMC differentiation, especially in vivo.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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