

## REVIEW ARTICLE

# Platelets in In-stent Restenosis: From Fundamental Role to Possible Prognostic Application

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**Abstract: Background:** Introduction of new generations of stents has decreased the percentage of patients experiencing in-stent restenosis (ISR) following the implantation of stent. However, a large number of patients are still afflicted with this phenomenon, which necessitates further study of ISR pathophysiology.

**Methods:** Relevant English literature was searched up to 2018 and retrieved from the PubMed database and Google Scholar search engine. The following keywords were used: "In-stent restenosis", "Platelet", "Chemokine", "Inflammation", "Vascular smooth muscle cell" and "Neointima".

**Results:** Previous studies have shown that ISR is a pathophysiologic response to damage of the artery wall after its elongation and separation of the atherosclerotic plaque. Development of neointimal hyperplasia (NIH) following this pathophysiologic response is a function of inflammation caused by platelets, monocytes, macrophages, and lymphocytes, as well as rapid migration and proliferation of generally quiescent cells in the median layer of the artery wall.

**Conclusion:** After damage to the artery wall, platelets play an essential role in the incidence of NIH by contributing to inflammation and migration of vascular smooth muscle cells and extracellular matrix remodeling, especially *via* secretion of different chemokines; therefore, developing therapeutic strategies for platelet inhibition in a controlled manner could be the basis of preventive treatments in the near future. In this study, for the first time, we hypothesize that evaluation of platelet activity profile in patients before and after stent implantation may determine the prognosis and likelihood of ISR.

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## 1. INTRODUCTION

In the last four decades, percutaneous coronary intervention (PCI) procedures, including balloon angioplasty followed by stent implantation have led to dramatic changes in the treatment of cardiac patients; nevertheless, the use of stents is still subject to limitations despite the advancement of PCI techniques. Apart from the incidence of stent thrombosis in a small group of patients, perhaps a major limitation of the stent is the likelihood of in-stent restenosis (ISR), which leads to ineffectiveness of the stent [1]. Restenosis is a pathophysiologic response to tissue damage in the site of stent, which presents a major challenge for interventional therapy [2]. In spite of these limitations, the introduction of new drug-eluting stents (DES) initially appeared to decrease

ISR [3]. However, the growing use of DES has increased ISR rates in patients, so that 3-36% of patients show recurrent stenosis, which poses a serious challenge to the healthcare system [4, 5]. In this study, we will review the pathophysiological phenomenon of ISR and consider the prominent role of platelets in its incidence as well as the potential of platelets as a major inflammatory mediator in the formulation of preventive, therapeutic, and prognostic strategies for patients at risk of ISR.

## 2. IN-STENT STENOSIS: HOW DOES IT HAPPEN?

In-stent restenosis (ISR) may be associated with cardiac symptoms such as recurrent angina and MI that facilitate its clinical diagnosis [6]. The diagnosis of ISR is confirmed by angiography showing over 50% diameter stenosis in the site of stent implantation [7]. Based on the time of incidence, ISR is divided into early (6-12 months after stent implantation) and late (one year after stent implantation) types [8]. Although neointimal hyperplasia (NIH) is deemed as the

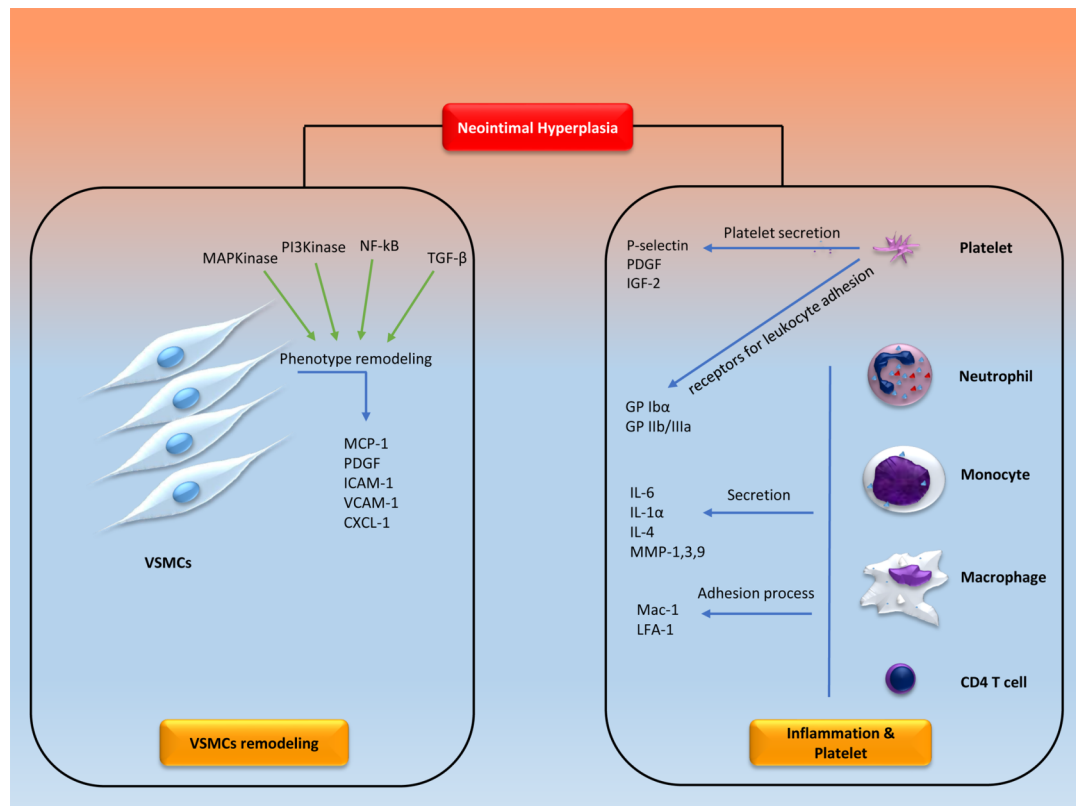
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main cause of restenosis, there are differences between early and late ISR, and integrated backscatter intravascular ultrasound shows that neointima in late ISR has a lower integrated backscatter than early ISR. Compared with bare metal stents (BMS) that show early restenosis in over 80% of cases, patients using DES have late ISR in 60% of cases, and late ISR develops earlier in DES use than BMS [8]. Tissue damage occurs at the site of the stent during its implantation, after which the recruitment, accumulation, and activity of immune agents causes inflammation and leads to NIH along with migration and proliferation of vascular smooth muscle cells (VSMCs), which is a basis for ISR [9] (Fig. 1). The arterial wall is composed of three layers: intima, media, and adventitia. Adventitia is the outermost layer of the arterial wall and contains fibroblasts, fibrocytes, and mostly type I collagen, which has the potential to repair the arterial wall [10, 11]. Media or the middle layer is isolated from adventitia by the external elastic lamina and is composed of VSMCs, elastin, and collagen (mainly type I and III). Finally, the innermost layer (intima) is separated from media by internal elastic lamina, and is made of a layer of endothelial cells whose interaction with platelets *via* secretion of pro-inflammatory factors as well as their role in leukocyte trafficking is the main reason for platelets involvement in cardiovascular diseases [10, 12]. NIH is a natural event in the aorta of aging people as well as during the involution of the uterus [13]; nonetheless, this regenerative phenomenon takes on a pathophysiological turn during atherosclerosis, balloon angioplasty, or stent implantation [14]. VSMCs are almost quiescent in normal conditions, have a low reproduction rate, and undergo phenotypic modulation in a complex

process (if necessary) in response to various chemoattractants during matrix remodeling and cytoskeletal reorganization affected by MAP kinase signaling [15].

### 3. PLATELET AGGREGATION: THE UNDERESTIMATED CORNERSTONE OF INFLAMMATION IN ISR

Previous studies highlight the mobilization and accumulation of immune cells at the site of stent tissue damage and the significant effect of such accumulation in pathophysiology of ISR, so that the role of platelets as a major contributor to this inflammatory aggregation at times appears to be less prominent than that of immunologic mediators involved in ISR, especially monocytes, neutrophils, and macrophages. Platelets are the smallest blood cells which play a major role in thrombosis and hemostasis *via* the release of dozens of active agents from their intracellular granules, especially the chemokines stored in their alpha granules (Table 1) [16, 17]. Giulio Bizzozero (1846-1901) for the first time referred to the ability of these cells in binding damaged vessel walls and forming the platelet aggregates [18]. The elongation of arteries caused by PCI procedure damages the internal and external elastic lumen [19]. After elongation and endothelial denudation, which in the first place destroys the atherosclerotic plaque, aggregation of platelet and fibrin occurs at the site of injury [9, 15]. Following aggregation, the activated platelets express P-selectin and enable the binding of leukocytes and their rolling throughout the platelet plaque [20]. Leukocytes, especially monocytes and neutrophils, firmly bind endothelial cells, extracellular matrix (ECM) proteins, and respective



**Fig. (1).** Neointimal hyperplasia is the key reason for in-stent restenosis. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

**Table 1. Chemokines released by platelets and involved in ISR pathophysiology.**

| Chemokine              | Chro.    | Role in ISR  | Receptor                  | Granule            | Refs.        |
|------------------------|----------|--|---------------------------|--------------------|--------------|
| CCL2                   | 17q11.2  | -Contributes to NIH by monocyte adhesion<br>-Promotes tissue remodeling<br>-Infiltration & production of interleukin-4 by T-cells  | CCR2                      | $\alpha$ -granules | [17, 29-31]  |
| CCL3 (MIP-1 $\alpha$ ) | 17q12    | -Chemotaxis & activation induction of immune cells (monocyte, NK cell, T-cell, B-cell)   | CCR1<br>CCR4<br>CCR5      | $\alpha$ -granules | [29, 30]     |
| CCL5 (RANTES)          | 17q12    | -Has a role in platelet rolling and monocyte & T-cell arrest in inflammation site  | CCR1<br>CCR3<br>CCR5      | $\alpha$ -granules | [29, 32]     |
| CXCL1                  | 4q21.1   | -Induction of monocyte chemotaxis & neutrophil adhesion  | CXCR2                     | $\alpha$ -granules | [29, 30]     |
| CXCL4 (PF4)            | 4q21.1   | -Probably facilitates CCL5 effect on monocytes<br>-Alongside other cytokines has a role in attracting & adhesion of neutrophils and monocytes<br>-Also has a role in monocyte differentiation                    | CXCR3                     | $\alpha$ -granules | [16, 17, 29] |
| CXCL5                  | 4q21.1   | -Chemoattractant for neutrophils   | CXCR2                     | $\alpha$ -granules | [17, 29]     |
| CXCL7                  | 4q21.1   | -By increasing neutrophil trans-endothelial immigration & adhesion of monocyte and neutrophils creates inflammation<br>-Has a role in vascular regeneration by inducing adhesion of endothelial progenitor cells | CXCR2                     | $\alpha$ -granules | [17, 29, 30] |
| CXCL8                  | 4q21.1   | -Induction of chemotaxis and activation of neutrophils   | CXCR1<br>CXCR2            | $\alpha$ -granules | [17, 29, 30] |
| CXCL12 (SDF-1)         | 10q11.21 | -Induction of P-selectin expression on platelets<br>-Attracts bone marrow derived smooth muscle progenitors  | CXCR4<br>CXCR7<br>(ACKR3) | $\alpha$ -granules | [16, 17, 33] |

**Abbreviations.** CCL2: Chemokine (C-C motif) ligand 2; NIH: Neointimal hyperplasia; CCR2: C-C chemokine receptor type 2; CCL3: Chemokine (C-C motif) ligand 3; MIP-1 $\alpha$ : Macrophage inflammatory protein 1-alpha; NK cell: Natural killer cell; CCR1: C-C chemokine receptor type 1; CCR4: C-C chemokine receptor type 4; CCR5: C-C chemokine receptor type 5; CCL5: Chemokine (C-C motif) ligand 5; RANTES: Regulated on activation, normal T cell expressed and secreted; CCR3: C-C chemokine receptor type 3; CXCL1: chemokine (C-X-C motif) ligand 1; CXCR2: C-X-C Motif Chemokine Receptor 2; CXCL4: chemokine (C-X-C motif) ligand 4; PF4: Platelet factor 4; CXCR3: C-X-C Motif Chemokine Receptor 3; CXCL5: chemokine (C-X-C motif) ligand 5; CXCL7: chemokine (C-X-C motif) ligand; CXCL8: chemokine (C-X-C motif) ligand; CXCR1: C-X-C Motif Chemokine Receptor 1; CXCL12: chemokine (C-X-C motif) ligand 12; SDF-1: Stromal derived factor -1; CXCR4: C-X-C Motif Chemokine Receptor 4; CXCR7: C-X-C Motif Chemokine Receptor 7; ACKR3: Atypical chemokine receptor 3.

platelet receptors (including GPIIb $\alpha$  glycoproteins and GPIIb/IIIa) through their adhesion molecules, especially lymphocyte function-related antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1) (CD11b/CD18) [21]. In particular, the release of Monocyte Chemoattractant Protein-1 (MCP-1) by VSMCs and endothelial cells leads to recruitment of monocytes (especially *via* CCR2 on monocyte surface) and other immune cells such as basophils and active T-cells, and the secretion of Interleukin (IL)-18 mobilizes neutrophils [22-24]. However, the role of platelets is not limited to the recruitment of immune cells and expression upregulation of adhesion molecules. Platelet binding to neutrophils also induces neutrophil activity, which in turn enhances inflammatory responses [21]. Concomitant with the exacerbation of inflammatory process by platelets, these non-nucleated cells together with VSMCs release chemoattractants such as platelet-derived growth factor (PDGF), basic fibroblast growth (FGF-2), and other growth factors like insulin-like growth factor 2 (IGF-2), thrombin, endothelin I, and angiotensin II that

result in the incidence and spread of NIH [15]. The cells involved in inflammation also contribute to NIH through ECM remodeling, degrading ECM following TLR4 activation, and secreting IL-6, IL-1 $\alpha$ , MCP-1, and matrix metalloproteinases (MMP) [25]. The essential role of platelets in NIH makes them a prime target for ISR prevention strategies. The risk of ISR is likely to be reduced by targeted and controlled inhibition of platelets using antiplatelet agents such as aspirin, dipyridamole, P1Y12 receptor antagonists such as clopidogrel, or platelet glycoprotein inhibitors including abciximab within a few days before the procedure as well as 6-12 months after it by regular follow-up of platelet counts along with cardiologic evaluation of patients implanted with stent. On the other hand, it is possible to monitor patients by checking CD 147, CD 62, CD 63, P-selectin and the like, which are highly expressed on the surface of active platelets [26-28]. Given the effective role of platelets in inflammation, higher platelet activity can be considered as an unfavorable prognostic factor in patients at risk of ISR.

#### 4. VSMCs: SLOW MEN HAPPEN TO BE PROFESSIONAL RUNNERS

Along with the inflammatory function of platelets, migration and proliferation of VSMCs also play a role in NIH development. VSMCs are generally quiescent and in G0 phase of cell cycle within media layer of adult arteries, exiting G0 phase and proliferating once stimulated by strong stimuli such as damage to the wall of arteries after stent implantation [34]. The important point is that unlike cardiomyocytes, VSMCs do not undergo final differentiation, have high plasticity, and can change phenotype, which distinguishes them in the repair of vascular tissue damage [25]. After the damage caused by stent implantation, VSMCs may be subject to apoptosis, but in case of surviving apoptosis, they migrate, proliferate, and participate in NIH following phenotype modulation [7]. MAPK signaling seems to play a crucial role in apoptosis [35-37]. Thus, changing the apoptotic process by inhibiting MAPK signaling may limit secondary cell migration and present a hypothetical strategy to prevent NIH. Migration of VSMCs is a long-term process occurring concomitant with ECM remodeling within several weeks that is affected by growth factors released from platelets, VSMCs, and leukocytes, leading to the development of restenotic plaque [20]. One of the factors preventing the proliferation of VSMCs is the interaction of base membrane proteoglycans such as heparan sulfate with cell surface integrins, prostaglandins, and nitric oxide (increasing cAMP and cGMP levels), which inhibits MAP kinase, decreases cyclin D1 expression, and changes transforming growth factor beta (TGF- $\beta$ ); however, if a potent stimulation occurs, signaling of MAP kinase and PI3 kinase pathways along with NF- $\kappa$ B transcription factor provides for proliferation of VSMC [15, 38-40]. Consequently, the effector proteins of the above-mentioned pathways and TGF- $\beta$  can be potential targets that may be theoretically affected to suppress VSMCs proliferation at the site of the stent. A crucial factor in ECM degradation is the presence of Matrix metalloproteinase (MMPs), especially MMP-9, MMP-3 and MMP-1, which are abundantly released by macrophages, monocytes, and CD4 T-cells present in the stent site [15]. NIH might be prevented by targeting and inhibiting these metalloproteases or through limiting their secretion as well as ECM remodeling. Continued medial remodeling and changing phenotype of VSMCs to pro-inflammatory cells lead to the rapid proliferation of these cells, which secrete IL-8, Intercellular Adhesion Molecule 1 (ICAM-1), Vascular cell adhesion protein 1 (VCAM-1), chemokine (C-X-C motif) ligand 1 (CXCL1), and various metalloproteinases. The mentioned factors increase the migration of VSMCs and aggravate inflammation, especially by mobilizing neutrophils (through CXCL1) and enhancing monocyte binding to VSMC *via* VCAM-1 and ICAM-1, a continuous trend that contributes to the progression of ISR [25].

#### 5. THE ANTI-PLATELET APPROACH TOWARD ISR: A PROMISING SOLUTION

Introduction of new DES generations that affect the tissues surrounding the stent *via* releasing bioactive agents has led to significant success of PCI, and various factors such as growth factors and immunosuppressants are used in DES *via* attachment to the stent surface or through a carrier [41]. For

instance, sirolimus is among the mentioned factors, which has been one of the first factors successfully applied in DES technology. It binds FK506 binding protein 12 (FKBP12) that is upregulated in neointimal smooth muscle cells, inhibiting the mammalian target of rapamycin (mTOR) and ultimately leading to cell cycle arrest and prevention of restenosis [20]. The antiplatelet treatment has been particularly considered in recent years and evaluated by various clinical studies. Comparison of long- and short-term dual antiplatelet therapy regimens, including aspirin and clopidogrel, has shown that the former significantly reduces mortality and adverse events (including myocardial infarction) in patients with ISR who are again subject to PCI [42]. Another effective therapeutic regimen is the triple antiplatelet regimen with phosphodiesterase III inhibitor, namely cilostazol, the efficiency of which has been shown in the improvement of angiographic results after DES implantation in recent years [43-46]. Although this regimen is still controversial, the ability of cilostazol to increase cAMP (that inhibits VSMCs growth) along with the upregulation of p53 and p21 factors increasing apoptosis in VSMCs as well as the capacity of this drug to accelerate endothelial regeneration is likely to account for higher efficacy of the regimen [47]. Inhibitors of P2Y12 platelet receptor (including clopidogrel, prasugrel, and ticagrelor) are also used to treat patients with ISR. The investigation of ticagrelor effect on pigs showed that compared to clopidogrel and prasugrel, this drug decreases endothelial dysfunction and NIH, improving endothelial function following DES implantation [48]. In comparison with clopidogrel, ticagrelor significantly increases endothelial progenitor cells in patients with the acute coronary syndrome [49], a finding that is likely to account for the ability of ticagrelor in the improvement of endothelial regeneration. On the other hand, ticagrelor has a higher capacity than clopidogrel in the treatment of patients with ISR who show high platelet reactivity [50]. The above findings indicate the success of antiplatelet therapies in dealing with ISR, which also emphasizes the role of platelets in the pathogenesis of ISR. Study of the effect of patients' genetic differences in their response to such treatments is an interesting point that may be valuable in future research activities. Previously, several single nucleotide polymorphisms in genes involved in platelet function have been shown to be associated with different platelet reactivities [51]. Alternatively, genetic variations in cyclooxygenase-1 (cox-1) gene, as well as P2Y12 and P2Y1 platelet receptors, may be the main causes of resistance to aspirin and clopidogrel, respectively [52]. Another genetic variant which affects patients' response to clopidogrel is different variants of the cytochrome P450 (CYP) 2C19 isoenzyme (which is responsible for metabolism of clopidogrel) and its different genetic variants are associated with resistance to clopidogrel [53]. These variants include different gain of function and loss of function allelic variants. The gain of function allelic variants (such as CY2C19\*17) is associated with decreased risk of cardiovascular events, increased bleeding risk and better response to clopidogrel therapy [54] while the loss of function allelic variants (such as CYP2C19\*2) is associated with reduced response to clopidogrel therapy and increased risk of ISR [55, 56]. Consequently, investigation of genetic factors affecting platelet reactivity, which have also the potential to cause resistance to antiplatelet therapy, can indirectly help improve antiplatelet

let therapies in the treatment of ISR. Also, further research can determine whether or not these genetic variants have any possible prognostic value. Studies before indicated the association of high platelet reactivity with stent thrombosis incidence [57]. On the other hand, high platelet reactivity is an independent factor which can predict adverse events in ISR patients [58]. Previously some studies showed increased plasma levels of platelet-derived growth factor (PDGF) and beta-thromboglobulin ( $\beta$ -TG) with increased mean platelet volume in patients treated with PCI who developed ISR after the intervention [59, 60]. These findings, in addition to confirming platelet role in ISR pathogenesis, indicate the value of laboratory assessment of platelet reactivity in monitoring ISR patients and determining their prognosis.

## 6. DISCUSSION AND FUTURE PERSPECTIVES

The use of DES instead of BMS has led to a dramatic decrease in the incidence of ISRs [61]. Nonetheless, BMS stents are still used and even the new generation DES stents has not completely prevented the incidence of ISR in patients [26], which imposes high costs on the healthcare system. For this reason, it is essential to study the pathophysiology of ISR. Basically, NIH is the main factor of ISR occurrence [62]. In recent years, several studies have pointed the role of inflammatory cells, including monocytes, macrophages, neutrophils, T-cells and the like in ECM remodeling, migration, and proliferation of generally quiescent VSMCs. In this study, we further referred to the role of platelets in inflammation and reviewed the ability of these cells to secrete different chemokines to recruit and induce the activity of immunological mediators (Table 1). Inhibiting platelet activation and release of granular contents or controlling platelet activity can reduce the incidence of inflammation.

## CONCLUSION

For the first time, we suggest that platelet activity may be a prognostic biomarker for the onset of stent restenosis so that it could predict the incidence of ISR. It is reasonable to monitor platelet activity because it is not expensive and is almost applicable everywhere. Nowadays, we can evaluate and monitor platelet activity by different methods from basic bleeding time test to professional assessment of platelet aggregation by aggregometry methods. Finally, based on extensive study of ISR pathophysiology and the development of new generations of DES, it seems that the advancement of anti-inflammatory therapies could lead to a further decrease in the incidence of ISRs in the near future. Until then, we strongly recommend our colleagues to review the platelet activity of stent implantation candidates before and after the procedure to determine the prognostic value of platelet activity as a possible prognostic biomarker.

## LIST OF ABBREVIATIONS

|            |   |                                     |
|------------|---|-------------------------------------|
| CD4T Cell  | = | Cluster of Differentiation-4 T Cell |
| CXCL-1     | = | Chemokine (C-X-C motif) Ligand 1    |
| GPIIb      | = | Platelet Glycoprotein Ib Alpha      |
| GPIIb/IIIa | = | Platelet Glycoprotein IIb/IIIa      |
| ICAM-1     | = | Intercellular Adhesion Molecule 1   |

|              |   |  |
|--------------|---|--|
| IGF-2        | = | Insulin-like Growth Factor 2                   |
| IL-1a        | = | Interleukin-1a                                 |
| IL-4         | = | Interleukin-4                                  |
| IL-6         | = | Interleukin-6                                  |
| LFA-1        | = | Lymphocyte Function-associated Antigen 1       |
| Mac-1        | = | Macrophage-1 Antigen                           |
| MAP kinase   | = | Mitogen-Activated Protein Kinase               |
| MCP-1        | = | Monocyte Chemoattractant Protein 1             |
| MMP-1,3,9    | = | Matrix Metalloproteinases-1,3,9                |
| PDGF         | = | Platelet Derived Growth Factor                 |
| PI3Kinase    | = | Phosphatidylinositol-4,5-bisphosphate 3-Kinase |
| TGF- $\beta$ | = | Transforming Growth Factor Beta                |
| VCAM-1       | = | Vascular Cell Adhesion Molecule 1              |
| VSMC         | = | Vascular Smooth Muscle Cell                    |

## AUTHORS' CONTRIBUTIONS

N.S. conceived the manuscript and revised it. H.H. and S.M.S.P. wrote the manuscript and prepared the table and figure.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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