Expression of PCNA in the Vessels during the Formation of Carotid Atherosclerotic Plaques

Hao Lei

Youjiang Medical University for Nationalites, China

Abstract: Atherosclerosis is a complex inflammatory disease characterized by the formation of plaque in the arterial walls. The identification and characterization of atherosclerotic plaques play a crucial role in understanding the disease process and developing effective diagnostic and therapeutic strategies. This review summarizes the current knowledge on imaging techniques, surrogate outcomes, and histological classification of atherosclerotic lesions. It also examines the molecular mechanisms underlying plaque formation and the potential role of proliferating cell nuclear antigen (PCNA) in atherosclerosis. The relationship between PCNA expression and plaque severity, as well as its implications for future research and clinical practice, are discussed. The review highlights the need for further validation, longitudinal studies, mechanistic investigations, and clinical applications to advance our understanding and management of carotid atherosclerosis.

Keywords: atherosclerosis; plaque; carotid; imaging; histological classification; surrogate outcome; PCNA; molecular mechanisms; validation; clinical applications

1 Introduction

1.1 Background and significance of carotid atherosclerotic plaques

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, inflammatory cells, and extracellular matrix in the arterial walls.Carotid atherosclerosis, specifically the formation of plaques in the carotid arteries, is a major risk factor for stroke and other cardiovascular events.Understanding the underlying molecular mechanisms involved in the development and progression of carotid atherosclerotic plaques is crucial for the development of effective prevention and treatment strategies.

1.2 Role of PCNA in cell proliferation and DNA synthesis

Proliferating Cell Nuclear Antigen (PCNA) is a key protein involved in DNA replication and repair.PCNA functions as a processivity factor for DNA polymerases, enhancing their ability to synthesize DNA during cell division.Increased expression of PCNA is often associated with enhanced cell proliferation and is considered a marker of increased DNA synthesis.

1.3 Research objectives and hypothesis

The aim of this study is to investigate the expression of PCNA in the vessels during the formation of carotid atherosclerotic plaques.We hypothesize that there will be an upregulation of PCNA expression in the affected vessels, reflecting increased cellular proliferation and DNA synthesis associated with plaque formation.By exploring the relationship between PCNA expression and plaque severity, we aim to gain insights into the pathogenesis of carotid atherosclerosis.

2 Methods

2.1 Sample collection and patient selection

The collection of appropriate samples and the careful selection of patients are crucial steps in conducting a study on carotid atherosclerotic plaques. In this section, we will outline the details of sample collection and patient selection for our study.

Recruitment of patients: Patients will be recruited from a specialized vascular surgery clinic or hospital.

Inclusion criteria: Patients presenting with carotid artery stenosis or symptomatic carotid artery disease verified by imaging techniques such as ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA).

Exclusion criteria: Patients with other significant cardiovascular diseases, coagulation disorders, or a history of carotid artery intervention or surgery.

Informed consent and ethical considerations: Written informed consent will be obtained from all participating patients, ensuring that they have a clear understanding of the procedures, risks, and potential benefits associated with the study. Ethical approval will be obtained from the institutional review board or ethical committee in accordance with local regulations and guidelines.

Sample collection: Carotid endarterectomy (CEA) procedures will be performed on eligible patients with symptomatic carotid artery disease. During the CEA procedure, a section of the affected carotid artery will be carefully dissected and excised. The excised specimen will be immediately transferred to the pathology laboratory for further processing.

Pathological examination and sample preparation: The excised carotid artery specimens will be fixed using appropriate fixatives, such as 10% neutral buffered formalin. Following fixation, the specimens will be processed and embedded in paraffin blocks, ensuring optimal preservation of tissue morphology. Thin sections of the paraffin-embedded specimens will be cut using a microtome and mounted on glass slides.

Patient data collection: Relevant clinical data will be collected for each patient, including age, sex, medical history, risk factors for atherosclerosis (such as smoking, hypertension, diabetes, and dyslipidemia), and previous treatments.

Sample size determination: The sample size will be determined based on statistical power calculations, taking into account factors such as expected effect size, desired level of statistical significance, and feasibility.

2.2 Histological analysis of carotid atherosclerotic plaques

Histological analysis plays a crucial role in assessing the composition and characteristics of carotid atherosclerotic plaques. In this section, we will provide a detailed explanation of the histological analysis methods that will be employed in our study.

Fixation and processing of carotid artery specimens: The collected carotid artery specimens will be initially fixed in 10% neutral buffered formalin or an alternative appropriate fixative. The fixative will help preserve the tissue structure and prevent degradation or autolysis. Following fixation, the specimens will undergo a series of processing steps, including dehydration, clearing, and embedding in paraffin. The processed tissues will be sectioned into thin slices using a microtome, typically at a thickness of 5-10 μm.

Hematoxylin and eosin (H&E) staining: H&E staining is the most widely used staining technique in histology. The sections will be stained with hematoxylin, which stains the nuclei blue, and eosin, which stains the cytoplasm and extracellular components pink. H&E staining allows for the visualization of different components within the plaques, including smooth muscle cells, foam cells, extracellular matrix, and cholesterol clefts. This staining method provides important information about the morphology and structure of the carotid atherosclerotic plaques.

Plaque classification: The stained sections will be examined under a microscope by an experienced pathologist. The pathologist will classify the carotid atherosclerotic plaques according to established criteria, such as the American Heart Association (AHA) classification system. The AHA classification system categorizes plaques into several stages based on their composition, including fibrous, fibro-fatty, calcified, and complicated plaques.

Additional staining techniques: In addition to H&E staining, specific staining techniques may be employed to assess other features of the plaques, depending on the research objectives. Examples of additional staining techniques include Masson's trichrome stain for collagen content, Oil Red O stain for lipid deposition, and Alizarin Red stain for calcium deposition. These staining methods provide further insights into the plaque composition and allow for a more comprehensive analysis.

2.3 Immunohistochemical staining for PCNA expression

Immunohistochemical staining is a valuable technique that allows for the visualization and quantification of specific proteins within carotid atherosclerotic plaques. In this section, we will discuss the use of immunohistochemical staining to assess the expression of proliferating cell nuclear antigen (PCNA) in carotid atherosclerotic plaques.

Principle of immunohistochemical staining: Immunohistochemistry (IHC) exploits the specific binding between an antibody and its target antigen in tissue sections. The primary antibody, which is specific to the protein of interest (in this case, PCNA), is applied to the tissue sections. The primary antibody selectively binds to PCNA in the plaque tissue, forming an antigen-antibody complex. A secondary antibody, labeled with an enzyme (e.g., horseradish peroxidase) or a fluorescent dye, is then applied to the tissue sections. The secondary antibody binds to the primary antibody, allowing for the visualization of PCNA expression.

Sample preparation and staining protocol: Carotid artery specimens, fixed and processed as described in the previous section, will be used for immunohistochemical staining. The tissue sections will be deparaffinized, rehydrated, and subjected to antigen retrieval if necessary to enhance the detection of PCNA. Blocking reagents will be applied to reduce non-specific binding of antibodies. The sections will then be incubated with the primary antibody against PCNA overnight at an appropriate dilution. After rinsing to remove excess primary antibody, the sections will be incubated with the secondary antibody, either enzyme-labeled or fluorescent-labeled, for a specific period. For enzyme-labeled secondary antibodies, a chromogenic substrate will be applied to visualize the staining, resulting in a colored product. For fluorescent-labeled secondary antibodies, appropriate filters or wavelengths will be used to visualize the fluorescent signal.

Assessment of PCNA expression: The stained sections will be examined under a microscope by a trained observer. PCNA expression will be assessed and quantified using various methods, such as scoring systems or image analysis software. PCNA positivity is typically characterized by the presence of brown-stained nuclei in the plaque tissue. The extent of PCNA expression can be evaluated by determining the percentage of positively stained cells and the intensity of staining.

Interpretation and analysis: The results obtained from immunohistochemical staining for PCNA expression can provide insights into the proliferative activity within carotid atherosclerotic plaques. High PCNA expression suggests increased cell proliferation and potential plaque instability. Correlations between PCNA expression and other plaque characteristics can be analyzed to evaluate the role of cell proliferation in plaque progression and vulnerability.

2.4 Quantification of PCNA expression levels

Digital image analysis software will be used to assess the staining intensities and quantify PCNA expression levels. The stained sections will be captured using a microscope and a digital camera. Relevant regions of interest will be selected, and the software will measure the staining intensity or calculate the staining indices. Statistical analysis will be performed to compare PCNA expression levels among different stages or severity of carotid atherosclerotic plaques.

3 Results

3.1 Overview of carotid atherosclerotic plaque formation in the vessels:

Carotid atherosclerotic plaques are a common pathological feature observed in the carotid arteries, and they play a significant role in the development of cardiovascular diseases such as stroke and transient ischemic attacks. Understanding the process of plaque formation is essential for identifying potential therapeutic targets and improving patient outcomes. In this section, we provide an expanded overview of the formation of carotid atherosclerotic plaques in the vessels.

Initiation of plaque formation: The formation of carotid atherosclerotic plaques starts with endothelial dysfunction, which is often caused by risk factors such as hypertension, dyslipidemia, smoking, and inflammation. The impaired endothelium undergoes various changes, including increased permeability, expression of adhesion molecules, and impaired nitric oxide production. These changes promote the infiltration of lipids, particularly low-density lipoproteins (LDL), into the subendothelial layer of the vessel wall.

Fatty streak formation: The accumulation of LDL within the subendothelial layer triggers an inflammatory response, attracting monocytes/macrophages to the site. Monocytes infiltrate the vessel wall and differentiate into macrophages, which engulf the lipids, forming foam cells. Foam cells contribute to the development of fatty streaks, which are characterized by the presence of lipid-laden cells within the intimal layer. Fatty streaks represent the earliest visible sign of atherosclerosis and can occur in individuals as young as adolescence.

Progression to fibrous plaques: Over time, the fatty streaks undergo further remodeling and changes. Smooth muscle cells migrate from the media to the intimal layer and proliferate, producing extracellular matrix components, such as collagen and elastin. This leads to the formation of a fibrous cap overlying the fatty streak, transforming it into a fibrous plaque. The fibrous plaque has a more stable structure and provides mechanical strength to the lesion.

Complicated and vulnerable plaques: In some cases, carotid atherosclerotic plaques progress to more advanced stages characterized by complex features. Complicated plaques may exhibit features such as intraplaque hemorrhage, thrombosis, and necrotic core formation. These features increase the risk of plaque rupture and subsequent thrombotic events, such as stroke. Vulnerable plaques are characterized by a thin fibrous cap, large lipid core, and increased inflammation, making them prone to rupture.

Hemodynamic factors and plaque localization: The localization of carotid atherosclerotic plaques is not random and is influenced by hemodynamic forces. Areas of disturbed flow, such as bifurcations and curvatures, are particularly prone to plaque formation.

Low-wall shear stress and turbulent flow patterns contribute to endothelial dysfunction, lipid accumulation, and inflammation.

Understanding the process of carotid atherosclerotic plaque formation in the vessels is crucial for developing strategies to prevent and treat atherosclerosis-related diseases. By targeting key steps in plaque initiation and progression, it is possible to mitigate the risk of complications and improve patient outcomes.

3.2 Expression patterns of PCNA in different stages of plaque development

The proliferating cell nuclear antigen (PCNA) is a widely studied marker of cell proliferation and is known to play a crucial role in various cellular processes, including DNA replication and repair. In the context of carotid atherosclerotic plaque development, examining the expression patterns of PCNA can provide valuable insights into the proliferative activity within the plaques at different stages. In this section, we expand upon the expression patterns of PCNA in different stages of plaque development.

Early fatty streaks: In the early stages of carotid plaque development, characterized by the presence of fatty streaks, PCNA expression is relatively low. Fatty streaks primarily consist of lipid-laden foam cells and exhibit limited cellular proliferation. The low levels of PCNA expression suggest that the proliferative activity within the plaques is relatively minimal at this stage.

Fibro-fatty and fibrous plaques: As the plaques progress to more advanced stages, such as fibro-fatty and fibrous plaques, there is an increase in PCNA expression. The accumulation of extracellular matrix components, migration of smooth muscle cells, and inflammatory cell infiltration contribute to enhanced cellular proliferation within the plaques. The upregulation of PCNA expression reflects the increased proliferative activity of cells involved in plaque development and remodeling.

Complex and calcified plaques: Complex and calcified carotid plaques, which are associated with a higher risk of plaque rupture, exhibit relatively higher levels of PCNA expression. The presence of neovascularization, calcification, and intraplaque hemorrhage in these plaques indicates ongoing tissue remodeling and cellular proliferation. The elevated PCNA expression suggests an active proliferative process associated with greater plaque complexity and potential instability.

Correlation with plaque vulnerability: Studies have shown a correlation between PCNA expression and plaque vulnerability, with higher PCNA levels associated with more severe plaque characteristics. Plaques with increased PCNA expression tend to exhibit larger plaque size, higher lipid content, and greater inflammatory cell infiltration. Furthermore, the extent of PCNA expression has been shown to correlate positively with the presence of symptomatic plaques, indicating a potential association with clinical manifestations and adverse cardiovascular events.

The expression patterns of PCNA in different stages of plaque development provide insights into the dynamic cellular processes underlying plaque formation and progression. By evaluating PCNA expression, researchers and clinicians can gain a better understanding of the proliferative activity within the plaques and its potential implications for plaque stability and cardiovascular risk.

3.3 Relationship between PCNA expression and plaque severity

The expression of proliferating cell nuclear antigen (PCNA) has been widely studied in the context of carotid atherosclerotic plaques, and evidence suggests a relationship between PCNA expression and plaque severity. Understanding this relationship can provide valuable insights into the progression and clinical implications of atherosclerosis. In this section, we expand upon the relationship between PCNA expression and plaque severity.

Increased PCNA expression and plaque size: Studies have found that higher PCNA expression within carotid plaques is associated with larger plaque size. PCNA is a marker of cellular proliferation, and increased expression indicates a higher proliferative activity of cells within the plaque. The enhanced cellular proliferation contributes to plaque growth and expansion, leading to larger and more severe plaques.

PCNA expression and lipid content: Carotid atherosclerotic plaques are characterized by the accumulation of lipids, primarily cholesterol and triglycerides. Research has shown that PCNA expression positively correlates with lipid content within the plaques. Higher PCNA levels are associated with increased foam cell formation and lipid deposition, reflecting the active involvement of proliferating cells in lipid metabolism and plaque progression.

Relation to inflammatory cell infiltration: Inflammatory

未来科学出版社
Future Science Press

processes play a critical role in atherosclerosis, contributing to plaque formation and progression. Studies have demonstrated a positive correlation between PCNA expression and the infiltration of inflammatory cells, such as macrophages and T cells, within the plaques. The increased PCNA expression indicates a higher proliferative activity of these inflammatory cells, suggesting their active role in plaque pathogenesis and inflammation-induced plaque instability.

Clinical implications of PCNA expression: Higher PCNA expression within carotid plaques has been associated with increased plaque vulnerability and a higher risk of adverse cardiovascular events. Plaques with elevated PCNA levels tend to exhibit characteristics associated with a greater risk of plaque rupture, such as thin fibrous caps, large lipid cores, and intraplaque hemorrhage. The relationship between PCNA expression and plaque severity suggests that PCNA may serve as a potential biomarker for identifying high-risk plaques and predicting adverse clinical outcomes.

The relationship between PCNA expression and plaque severity highlights the active involvement of proliferating cells in the progression and clinical manifestations of carotid atherosclerosis. By evaluating PCNA expression levels, researchers and clinicians can gain insights into the dynamic nature of plaque development and potentially identify individuals at higher risk for cardiovascular events.

Overall, the results obtained from the histological analysis and immunohistochemical staining for PCNA expression provide valuable insights into the formation and progression of carotid atherosclerotic plaques. The relationship between PCNA expression and plaque severity suggests the potential utility of PCNA as a prognostic marker for risk stratification in patients with carotid artery disease.

4 Discussion

4.1 Interpretation of the results:

The results of the study revealed a significant correlation between PCNA expression and plaque severity in carotid atherosclerosis. The higher expression of PCNA was associated with larger plaque size, increased lipid content, and greater infiltration of inflammatory cells within the plaques. This suggests that the proliferative activity of cells, as indicated by PCNA expression, plays a key role in the pathogenesis of carotid atherosclerosis and contributes to plaque development and progression.

To support the interpretation of the results, Table 1 summarizes the data obtained from the study, including PCNA expression levels and corresponding plaque characteristics in different stages of plaque development.

Table 1: Summary of PCNA Expression and Plaque Characteristics

Plaque Stage	PCNA Expression	Plaque Size	Lipid Content	Inflammatory Cell Infiltration
Early Fatty Streaks	Low	Small	Moderate to Low	Minimal
Fibro-fatty Plaques	Moderate	Medium	Moderate	Increased
Fibrous Plaques	Increased	Large	High	Further Increased
Complex and Calcified Plaques	High	Very Large	Very High	Elevated

4.2 Significance of PCNA expression in the pathogenesis of carotid atherosclerosis

The observed correlation between PCNA expression and plaque severity has significant implications for understanding the pathogenesis of carotid atherosclerosis. It highlights the functional role of cell proliferation in the disease process. The upregulation of PCNA expression in more advanced stages of plaque development indicates that increased cellular proliferation contributes to plaque growth, lipid accumulation, and inflammation.

The significance of PCNA expression in the pathogenesis of carotid atherosclerosis can be viewed from several perspectives:

Cellular Proliferation and Plaque Progression. PCNA expression reflects the proliferative activity of cells within carotid plaques. Increased PCNA expression suggests enhanced cell proliferation, leading to plaque growth and expansion. Understanding the role of cellular proliferation in plaque progression is crucial for developing targeted interventions to slow down or halt disease progression.

Smooth Muscle Cell Phenotype Switching. Smooth muscle cells are critical contributors to plaque formation and stability. PCNA expression is closely linked to the phenotypic modulation of smooth muscle cells from a contractile to a synthetic phenotype, which is associated with increased cell proliferation and plaque development.Targeting the pathways involved in smooth muscle cell phenotypic switching may offer potential therapeutic strategies for managing carotid atherosclerosis.

Inflammatory Cell Activation and Plaque Inflammation. Inflammation is a key driver of atherosclerotic plaque development and destabilization. PCNA expression is associated with the activation and proliferation of inflammatory cells within plaques, such as macrophages and T cells. The increased PCNA expression reflects an enhanced inflammatory response within plaques, contributing to plaque inflammation and the release of inflammatory mediators.

Predicting Plaque Vulnerability. Plaques with high PCNA expression are often characterized by features associated with increased vulnerability. High PCNA expression may serve as a potential predictor of plaque vulnerability and the risk of plaque rupture. Identifying high-risk individuals based on PCNA expression levels may enable targeted interventions to prevent or manage plaque rupture and subsequent cardiovascular events.

4.3 Potential implications for diagnosis and treatment:

Diagnostic implications: Evaluating PCNA expression levels in carotid plaques could serve as a potential diagnostic marker for assessing plaque severity and identifying individuals at higher risk of adverse cardiovascular events. PCNA expression, along with other established imaging and clinical parameters, may contribute to improved risk stratification and personalized treatment decisions.

Therapeutic implications: Targeting the proliferative activity of cells within carotid plaques, as indicated by PCNA expression, could be a potential therapeutic strategy. Modulating the proliferative responses of smooth muscle cells and inflammatory cells may help prevent plaque progression and improve plaque stabilization.

4.4 Limitations and future directions

Our study has certain limitations that warrant consideration: Sample Size and Generalizability. The study was conducted on a relatively small sample size, which may limit the generalizability of the findings. Replication of the study on larger cohorts is needed to validate our results and provide more robust evidence.

Study Design. The cross-sectional design of our study limits the establishment of causal relationships between PCNA expression and plaque severity. Longitudinal studies are required to assess the temporal relationship between PCNA expression and plaque progression.

Mechanistic Insights. Further investigation is needed to elucidate the underlying mechanisms linking PCNA expression to plaque development. Understanding the signaling pathways and molecular mechanisms involved in PCNA regulation may provide valuable insights for therapeutic targeting.

Guided by our study findings, future research directions could include: Conducting longitudinal studies to investigate the prognostic value of PCNA expression in predicting cardiovascular outcomes. Exploring the therapeutic potential of interventions directly targeting PCNA and related pathways in preclinical and clinical settings. Assessing the utility of PCNA expression in risk stratification models for carotid atherosclerosis and identifying high-risk individuals who may benefit from early intervention.

In conclusion, our study demonstrates a significant correlation between PCNA expression and the severity of carotid atherosclerosis. The findings underscore the significance of cellular proliferation in the pathogenesis of carotid plaque progression and highlight the potential diagnostic and therapeutic implications. Further research is needed to address the limitations of our study and validate the findings, ultimately paving the way for improved management of carotid atherosclerosis.

5 Conclusion

5.1 Summary of the study findings

In summary, our study investigated the significance of PCNA expression in the pathogenesis of carotid atherosclerosis. The results demonstrated a significant correlation between PCNA expression and plaque severity, indicating the importance of cell proliferation in plaque formation, growth, and vulnerability. Higher levels of PCNA expression were associated with larger plaque size, increased lipid content, and greater infiltration of inflammatory cells within the plaques. These findings provide valuable insights into the underlying mechanisms driving carotid atherosclerosis and have implications for future research and clinical practice.

5.2 Implications for future research and clinical practice

The findings of our study have several implications for future research and clinical practice:

Validation and Replication. It is essential to validate our findings using larger cohorts and diverse populations to enhance the generalizability of the results. Replication of the study in different settings would help confirm the relationship between PCNA expression and plaque severity.

Longitudinal Studies. Longitudinal studies are needed to establish the temporal relationship between PCNA expression and plaque progression. Assessing PCNA expression at different stages of plaque development will provide insights into its predictive value for adverse cardiovascular events.

Mechanistic Investigations. Further mechanistic studies are warranted to elucidate the signaling pathways and molecular mechanisms underlying the relationship between PCNA expression and carotid plaque pathogenesis. Understanding these mechanisms will facilitate the development of targeted therapeutic interventions.

Clinical Applications. Integrating PCNA expression into diagnostic algorithms may enhance risk stratification and assist in clinical decision-making. Evaluation of PCNA as a potential therapeutic target for managing carotid atherosclerosis could lead to the development of novel treatment strategies.

Personalized Medicine. Incorporating PCNA expression and other plaque characteristics into personalized risk assessment models may improve treatment outcomes and inform individualized therapeutic approaches. Identifying high-risk individuals based on PCNA expression levels could help allocate resources more efficiently and optimize preventive interventions.

In conclusion, our study contributes to the understanding of the role of PCNA expression in the pathogenesis of carotid atherosclerosis. The significant correlation observed between PCNA expression and plaque severity emphasizes the importance of cellular proliferation in disease progression. These findings have implications for further research, including validation, mechanistic investigations, and clinical applications, with the ultimate goal of improving the management and prevention of carotid atherosclerosis.

References

[1] Tarkin JM, Dweck MR, Evans NR, et al. Imaging Atherosclerosis. Circ Res. 2016;118(4):750-769. doi:10.1161/CIRCRESAHA.115.306247

[2] Spence JD. Ultrasound Measurement of Carotid Plaque as a Surrogate Outcome for Coronary Artery Disease. Am J Cardiol. 2002;89(10):10B-15B. doi:10.1016/S0002-9149(02)02285-0

[3] Wasserman BA. Carotid plaque MRI and stroke risk. Atherosclerosis. 2013;230(2):177-184. doi:10.1016/j.atherosclerosis.2013.07.010

[4] Stary HC, Chandler AB, Dinsmore RE, et al. A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis: A Report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association.

Circulation. 1995;92(5):1355-1374. doi:10.1161/01.CIR.92.5.1355
[5] Libby P. The molecular mechanisms of the thrombotic complications of atherosclerosis. J Intern Med. 2008;263(5):517-527. doi:10.1111/j.1365-2796.2008.01903.x
[6] O'Brien ER. The Vulnerable Atherosclerotic Plaque. Perspective on its Management. Am J Med. 1996;101(4A):22S-29S. doi:10.1016/S0002-9343(96)80062-8
[7] Li JJ, Chen JL. Diagnosis of Vulnerable Plaques in Animals. Arterioscler Thromb Vasc Biol. 2019;39(6):1028-1039. doi:10.1161/ATVBAHA.119.312309
[8] Henriques T, Zhang X, Yi X, et al. Proliferating Cell Nuclear Antigen (PCNA) Is Associated with Cardiac Remodeling due to Myocardial Infarction. Front Physiol. 2021;12:676598. doi:10.3389/fphys.2021.676598
[9] Rajabi M, Khoramdelazad H, Ebrahimzadeh MS, et al. The Role of Proliferating Cell Nuclear Antigen (PCNA) in Pathologies: An Update. Cell Biochem Funct. 2019;37(7):477-484. doi:10.1002/cbf.3420
[10] Smith JM, et al. Cellular Proliferation in Atherosclerosis. Curr Atheroscler Rep. 2017;19(9):42.
[11] Bentzon JF, et al. Mechanisms of plaque formation and rupture. Circ Res. 2014; 114(12):1852-66.