INTRODUCTION

In the United States, coronary artery disease is responsible for more than 400,000 annually. Plaque rupture is the principal cause of atherosclerosis in acute coronary syndromes. Early detection of vulnerable plaques is required for the prevention of coronary artery disease. However, current technique is lack of reliability and safety.

Unstable plaque is composed of lipid-rich core which contains various crystals of cholesterol and thin fibrous cap with scarce smooth muscle cells. Approximately 40% of the vulnerable plaque is filled with lipid-rich core [1] and lipid-rich core are often found in the basal intima of the coronary artery. Some inflammatory cells like macrophages and T lymphocytes massively exists in fibrous cap. In addition, it contains lipoprotein cholesterol which may induce the activation of immune system and annihilate macrophages and smooth muscle cells due to high toxicity [1].

There are five major causes for the formation of vulnerable plaque such as thin fibrous cap, lipid rich core, shear stress, intraplaque hemorrhage and inflammation. The vulnerable plaque has a lipid-rich core which is covered by a fibrous cap. If the necrotic core occupies above 30% space of the plaque, the plaque is probably unstable and may cause atherothrombosis [1]. If the plaque grows too large, the fibrous cap will become thinner. Since the fibrous cap was composed of smooth muscle cells which are primary connective tissue cells in basal intima to support the stable structure of the plaque and type I, III collagen [2], the deterioration of the fibrous cap will lead to the shortage of smooth muscle cells and collagen. Then the plaque may become instable and form an obstruction in the artery to cause atherothrombosis. Rich collagen will provide great tensile stress to support the structure and without high concentration of collagen, the tensile stress will disrupt the fibrous cap and lead to the rupture of plaque [1].

The formation of lipid-rich core may be induced by the accumulation of the dead cells of macrophages in the basal intima because most lipid-rich cores are founded in the basal intima and macrophages tend to eliminate the lipids in the basal intima [3]. Additionally, some researchers found that high saturation of cholesterol may result in crystalline structure of cholesterol which causes the expansion of the plaque and fibrous cap [4]. The accumulation of lipoprotein cholesterol will stimulate the oxidation of lipoprotein and macrophages is activated due to the presence of oxidized lipoprotein. Since the lipoprotein is cytotoxic, the accumulation of dead macrophages will induce more macrophages to remove the dead cells. And then more dead cells are accumulated in the plaque and the dead cells provide large amount of lipid to promote the instability of the plaque [8].

Inflammation occurred in vulnerable plaque is likely induced by infiltration of macrophage and T-lymphocytes. Macrophages produce matrix metalloproteinase to degrade the collagen which loosens the stable structure of fibrous cap. T-lymphocytes produce CD 40 to stimulate the secretion of matrix metalloproteinase and they may also produce IFN-γ to disrupt the collagen synthesis [4]. In addition, NLRP3 inflamasome and IL-1β which activates systematic inflammation was induced by crystallization of cholesterol [4].

Carr et al. found that intraplaque hemorrhage appeared more frequently in the patients suffered from stenosis than the asymptomatic patients. Intraplaque hemorrhage is considered to provide free cholesterol to in the lipid-rich necrotic cells and increasing concentration of free cholesterol will induce the formation of cholesterol crystals which will expand the fibrous cap and lead to the rupture of plaque [4]. Since the dead cells of macrophages may not provide enough lipids to form the plaques, intraplaque hemorrhage may make great contributions to the formation of vulnerable plaque.

In addition, shear stress may induce the dysfunction of endothelial cells and cause the imbalance between low density lipoprotein, which is for lipid input and high density lipoprotein, which is for lipid output. If the lipid input is bigger than lipid output, there, more lipid will accumulate in the cells and help to form lipid rich core. Furthermore, when the plaque size is very large and the fibrous cap is very thin, under certain high shear stress, the plaque will break.

OBJECTIVE

The purpose of this project is to gain a comprehensive view about the interaction relationship between each factor which contribute to the formation of unstable plaque. In addition, the aim is to build a model for a simulation of the formation of vulnerable plaque and furthermore, to predict if the patient has the risk of suffering atherosclerosis.

HYPOTHESIS/SUCCESS CRITERIA

Simulation model results and performance are comparable to the actual experimental data applied in mice.

METHOD

Literature research, model construction, calibration and validation are the four major components of the process for this project. Literature research, including agents, interaction rules and parameter, will help to build up the backbone of the model simulation.

The entire model initiates from low shear stress in endothelial cells. In the beginning, under low shear stress, endothelial dysfunction appears and then it will downregulate eNOS which will trigger the decrease in the concentration of NO, which helps to maintain the balance in cellular proliferation and inflammation [5]. Furthermore, the low level of NO will reinforce the susceptibility of endothelial layers [5]. Endothelial dysfunction increases the permeability of cholesterol which will furthermore increase the uptake of LDL (low density lipoprotein), which augments the lipid influx rate in the plaque [5]. In addition, HDL (high density lipoprotein) will inhibit LDL but the huge augmentation of LDL will break the balance and arrest more lipid inside the cell, like macrophage cells [5].

Under certain oxidative stress, LDL will transform into oxidized form, Ox-LDL, and bind with LOX-1 to induce inflammation and cell apoptosis [5]. It will also attract smooth muscle cells migrate to intima and induce matrix degradation.
The oxidative stress is probably related to the chemical reaction with NO and eNOS [5]. Besides, HDL will inhibit the formation of Ox-LDL. Their deficiency will inversely increase the concentration of Ox-LDL.

The inflammasomal factors like TNF-alpha, IL-1beta and IFN-gamma will be triggered by inflammation and endothelial dysfunction initially [5]. Then Ox-LDL will then trigger them and some factors related to cell apoptosis like Bel-2, p53 with oncogene-7 and caspase [7]. The inflammasomal factors will then attract monocytes to come to intima and the monocytes will transform to macrophage cells to engulf dead cells and Ox-LDL [6]. Engulfing Ox-LDL may contribute the death of macrophage cells which will increase the number of dead macrophage cells and may increase more foam cells in the plaque. Macrophage cells will also secrete some chemical factors to react with inflammasomal factors and may make them more active [6]. More macrophage cells will come here with more activation of inflammasomal factors and dead cells which will increase the number of foam cells furthermore. In addition, macrophage type 2 cell which is a type of macrophage cell to perform effective effectorcytosis which will secrete anti-inflammatory factors like TGF-beta to inhibit inflammation. [6].

For cell apoptosis related factors, they will induce the death for both macrophage cells and smooth muscle cells. First, the inflammasomal factors will also trigger cell apoptosis initially but the experiment is lacked. Caspase 8 and 9 will trigger the pro-caspase 3 and pro-caspase 3 will activate caspase 3 which is the effector in cell apoptosis [7]. Bel-2 is triggered by inhibition of mitochondria by reactive oxygen species and NO, both are related to Ox-LDL [7]. P53 will also induce the cell apoptosis mainly in smooth muscle cells [7]. Ox-LDL is a large resource for cell apoptosis, too. After massive deaths of vascular smooth muscle cells and macrophage cells, the lipid form a large necrotic lipid core and the lipid accumulation continues until the burst end. Vascular smooth muscle cells will also secrete collagen type I and they form fibrous cap. The shear stress will increase during the progression process [5] and the imbalance between the shear stress in different region will increase the vulnerability of the plaque.

For model construction, Netlogo will be used for simulation coding model construction. Netlogo contains four basic elements: turtles, which is for movable and changeable agent, patches, which is for unmovable and unchangeable agent, links and observer. In the model construction of vulnerable plaque formation, all agents are turtles since all the agents changed as the time proceeds. In addition, making assumption for some vague value like number of macrophage and smooth muscle cells is necessary because there is no reliable and precise data about these values. Furthermore, the simulation model is considered to run in an ideal environment regardless of individual’s disease.

After model construction, since some value is defined by assumption, the simulation result may not be appropriate. Therefore, the researcher need to compare the model results to the existed value of final stage of vulnerable plaque including size of necrotic core, width of fibrous cap, smooth muscle cells and macrophage cells concentration ratio. After calibration, the researcher should use the experimental data from other research project (mostly related to mice atherosclerosis) to check the accuracy of the simulation model. If the accuracy is above 75%, the model construction is considered as a success.

**RESULTS**

I have not yet finished the model construction, calibration and validation. Therefore, the result is not available now.

**DISCUSSION**

**Limitation**

Some factors are ignored due to simplification and lack of experimental data. Since there are over thirty different factors participated in the whole formation process, it is impossible for researchers to include all the factors in the model and write codes for all interaction rules among all agents. In addition, some factors are lack of reliable data applied in model construction. Furthermore, some mechanism during the development of atherosclerosis is still vague. For example, the detailed pathway of low shear stress inducing endothelial cells dysfunction is still in debate.

**Future discussion**

The researchers need to explore more effects of change in certain factor (e.g. nuclear factors, NO etc.) related to vulnerable plaque development. Furthermore, researchers can use the improved model to predict if the patient has the risk of suffering atherosclerosis.

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**REFERENCES**