Event-Tracking Stochastic Model Reveals Dynamics of Atherosclerotic Plaque

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Short Abstract — Atherosclerosis is a disease of arterial walls that leads to heart attacks, strokes and other adverse events caused by the rupture of plaques composed mostly of monocyte-derived cells (MD cells). Here we develop a direct, event-tracking stochastic model for studying plaque formation and dynamics. The model reveals the history for each cell entering the plaque region, describes their accumulation process, and points to the most influential cell event rates among those which can be altered by medical treatment. We show that development of an atherosclerotic plaque can be slowed and reduced by quantitatively controlled reduction of the monocyte influx.

Keywords — monocyte-derived cells, atherosclerotic plaque, rolling, adhesion, transendothelial migration, influx, egress.

I. Introduction

THERE has been an ongoing effort in understanding the processes involved in atherosclerosis. The inflammatory mechanisms of atherosclerotic plaque formation have been experimentally described [1,2]. The mechanisms which revers the atherosclerotic process are less understood, and begin to be experimentally studied [3]. Both the plaque formation and reduction processes lack rigorous quantitative descriptions. No model of atherosclerotic plaques can be found in literature.

In [4] we introduced the event-tracking approach to model adhesion under flow. Here we use this method for tracking monocytes' transmigration into atherosclerotic plaque, their differentiation to MD cells, their (potential) proliferation, apoptosis, necrosis and egress, thereby modeling plaque dynamics in atherosclerosis. Our model progresses by time steps dictated by the time intervals between consecutive cell events. Reconstructing the stochastic nature of the cell events allows for identification of critical points of the process, which decide about the fate (development, stabilization, reduction) of the plaque. The model is in good agreement with experimental observations [5]. We present histories of individual cells, cell accumulation in the transmigrated, proliferated and MD states, and conditions for slowing and reduction of plaques by deriving cell accumulation as a function of cell event rate for those influential rates which can be altered by available treatments.

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II. Results

The model is based on experimental observations of the cellular events involved [1,2] and measured rates of their occurrence [6-15]. Our diagrams show individual cell histories and changes in plaque accumulation under not treated and treated conditions studied. We find that

- 97.2% of transmigrated cells partially or fully transform into MD cells and die by apoptosis (95.5%) or necrosis (1.7%), while the remaining cells egress,
- under constant cell events rates the plaque eventually stabilizes at a constant size characteristic for those rates,
- reducing the arrest-to-transmigration rate by 50% (90%) reduces the plaque size by 46.6% (88.3%),
- reducing the free-to-rolling or rolling-to-arrest rates by 50% (90%) reduces the plaque size by 50.0% (89.9%),
- the egress rates can be considered less influential since they need to be increased 10 (100) times above experimentally observed values to reduce the plaque size by 39.7% (87.8%).
- the state of the disease at the time new constant rates are applied is not a factor for plaque stabilization; after imposing new rates, the plaque will grow or shrink to reach the stable size characteristic for this set of applied rates.

III. Conclusion

Our study shows that atherosclerotic plaque burden can be reduced and stabilized, mainly by reducing monocyte influx as proposed by [3]. We hope that our work will initiate experimental studies on dependence of plaque accumulation on cell events rates.

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