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IN SILICO EXPLORATION OF EARLY STAGE ATHEROSCLEROSIS THROUGH STOCHASTIC MODELLING

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Atherosclerosis (AS) is an arterial disease that initiates in the intima and compromises the patency of arteries, being the principal cause of heart attack, stroke and gangrene of the extremities, and responsible for 50% of all mortality in the USA, Europe and Japan[1]. Managing AS is challenging, and animal model studies must be interpreted cautiously, due to different metabolic and immunology responses compared to Humans. Nonetheless, computer models can provide appropriate virtual environments to test the action of treatments, while accounting for the high complexity of AS pathogenesis[2]. In this direction, we propose the use of an Agent-Based Model (ABM) in order to simulate complex cellular phenomena in intima layers, and virtually anticipate how early AS processes could be controlled (Fig 1).

The agents defined were the most relevant entities involved in atheroma formation (Fig 1). Their attributes are given in Table 1. As for the rules that governed these agents, we assumed the penetration of low-density lipoprotein (LDL) in the intima layer. LDL could oxidize at a rate of *1.5% per day*, creating LDLOX. Macrophages (MC) turned into foam cells (FC) due to both level and time persistence of LDLOX, higher than *160ng/ml* and *150days*, respectively. Above 80ng/ml, LDLOX activated the production of auto-antibodies (AB) that were able to destroy the agent. Decrease of LDLOX was also affected by interactions with FC and MC. Endothelial (EC) and the smooth muscle cell (SMC) agents were also included. While EC marked the position of FC formation, SMC had an important role in the creation of the atheroma. The ABM created was used to study the dynamic processes triggered in three cases: (1) normal levels of LDL (950-970 ng/µl), (2) hypercholesterolemia (1900-2000ng/µl of LDL) and (3) hypercholesterolemia with statin drugs. Statins were simulated as new agents able to destroy LDLOX, and activated by a critical threshold of LDLOX of *160ng/ml*.The agent disappeared when LDLOX passed below the threshold. Due to the stochastic nature of the model, we obtained different responses while repeating the same simulation case, and each case was repeated 20 times, standing for the creation of 20 "virtual patients" per case.

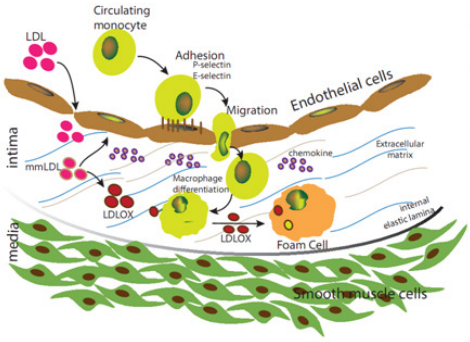

Figure 1. Biological concept involved in early atherosclerotic stage.

Table 1. Agents and Attributes defined in the ABM.

Agents (spheres)	D(µm)	Initial quantity of Agents	Max. Speed (µm/h)	Half life (in days)	Boundaries
LDL	1.4 [5]	Normal (605) or Hypercolesterol (1249)	1	-	periodic
LDL-ox	1.4 [5]	0	1	-	periodic
MC	20 [6]	10	0.5	200[4]	close
EC	20	200	0	-	close
FOAM	25	0	0	-	close
SMC	20	400	1 [3]	200 [4]	periodic
AB-AO	1.4 [5]	0	1	-	close

In normal patients, LDLOX was always below the threshold that leads to the formation of FC (Fig. 2A), being this simulation case our reference homeostatic behavior. In hypercholesterolemic patients, the LDLOX concentration exceeded the threshold (Fig 2B1), leading to an increased number of FC (Fig 2B2) in the intima until levels similar to those reported in [2]. Statins agents blocked the progression of LDLOX and limited FC creation to maximum four agents, illustrating correctly the action of these drugs. The significant variability between 20 patients shows the powerful use of this tool in biological and pharmacological approaches were interpretations are only possible based upon statistical results. Calculations with knowledge of cholesterol levels in blood, can be used to monitor the effect of changes in nutritional habits. The model also allows the introduction of more entities and rules for clinical trial simulations.

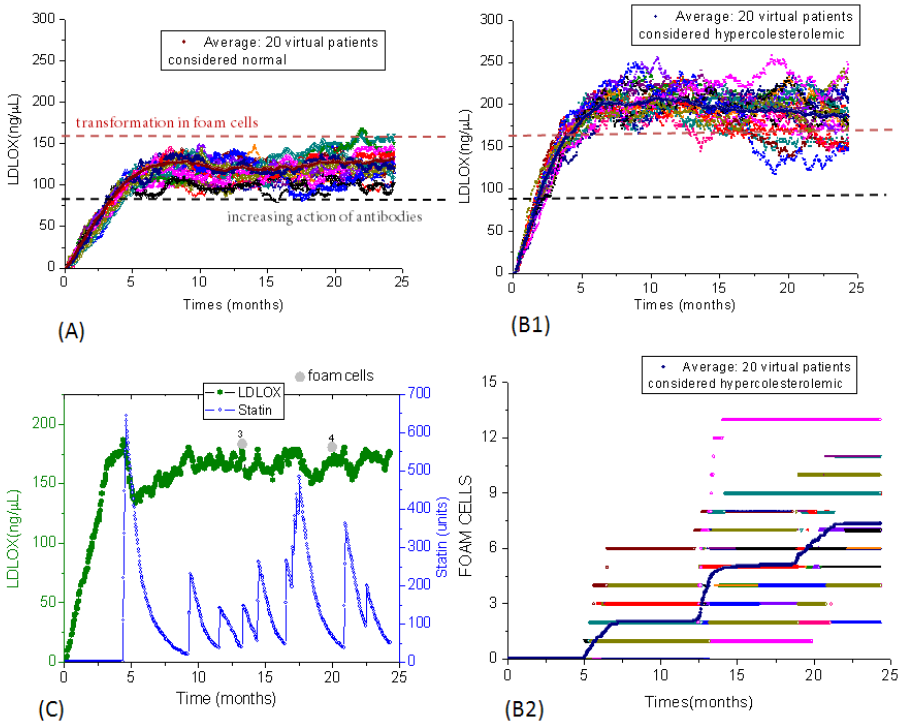

Fig. 2 Simulation results over 2 years, for 20 (A, B) and one individual (C) virtual patients. (A) LDLOX developed for normal patients was not sufficient to create FC. (B1) LDLOX developed with hypercolesterol lead to (B2) formation of FC due to insufficient work of AB. (C) Virtual administration of statins decreased LDLOX concentration and reduced the probability of FC creation.

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