# FIBRINOGEN, A MULTIFUNCTIONAL PROTEIN

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Fibrinogen is a plasma protein with three pairs of polypeptide linked together by disulfide bonds, with globular domains at each end and in the middle connected by alpha helical coiled-coil rods[1].

Calcium ions are determinant in the maintenance of the fibrinogen structure[2] and its three polypeptides are encoded by three genes located on chromosome 4q28,[3].

Fibrinogen is a multifunctional protein that participates in haemostasis mechanism either by its conversion to insoluble fibrin polymer or by forming bridges responsible for platelet aggregation. Additionally has adhesive and inflammatory functions through specific interactions with other cells[4] and the fibrinogen increased synthesis continue been proved since its finding during inflammation which it became nominated as an acute phase protein[5]; also behaving as a hemorheological factor promote week bindings with erythrocytes forming the respective aggregates likely rouleaux with different shape and dimensions[6-9].

It has been suggested that men with B beta fibrinogen -455 G/A polymorphism have also associated erythrocyte hyperaggregability[10] which did vanish in those healthy subjects with normal genotype[11]. It is also reported defective cases of fibrin polymerization resulting from abnormal fibrinogen conversion to fibrin common designed by dysfibrinogenemia with also positive influence on erythrocyte aggregation[12]. It was shown in a group of subjects with atherosclerotic risk factors a statistically significant association between the erythrocyte adhesiveness/aggregation values and the high plasma fibrinogen levels commonly obtained in inflammatory conditions[13]. The authors demonstrated the usefulness of the erythrocyte adhesiveness/aggregation test to detect the presence of the acute phase of inflammation. Inhibition of erythrocyte aggregation prevents and reduce cardiac thromboembolic risk[14].

However pathological red blood cell (RBC) aggregation may reduce capillary perfusion and oxygen transfer to tissues causing ischemia, local metabolic acidosis, degeneration of vascular wall and tissue infarction.

Angiographic studies indicate that high fibrinogen levels are associated with vascular occlusion[15] and the plasma fibrinogen level is

2nd Century AD – Galen or Claudius Galen of Pergamum was a Greek physician and he was the first to demonstrate that arteries carry blood throughout the body.

1771 – William Hewson, British anatomist, discovered the fibrinogen when working on coagulation

significantly associated with myocardial infarction and stroke[16] and it is considered as a major cardiovascular risk factor[17,18]. Fibrinogen haplotypes with single nucleotides polymorphisms in fibrinogen gamma and alpha genes are associated with variation in risk of myocardial infarction[19].

The Prime Study[20] has provided epidemiological data about haemostatic variables such as factor VII, PAI-1 and fibrinogen and evidence for the role of the last two in the pathogenesis of coronary heart disease. Our group[21] observed a significant relationship between the lower values of erythrocyte aggregation in patients at the hospital discharge after a transmural myocardial infarction and the higher cardiovascular events during the following 24 months. In a long-term evaluation (36 months) on a group of transmural acute myocardial infarction survivors, the erythrocyte aggregation values at hospital discharge may be considered as an independent predictor of recurrent cardiovascular events in this kind of patients[22].

Recently, it was identified by large-scale proteomic analysis the association between fibrinogen gamma and the hypercoagulable state of pancreatic cancer. This got the authors to consider the fibrinogen as a potential tumor marker in pancreatic cancer[23]. In general view, the process of tumor dissemination seems to be dependent of the coagulation system implicated in the tumor cells spreading onto the vascular network bed, in isolated lung preparations, in the presence of additional platelets and fibrinogen[24]. The deposition of fibrin (ogen) related material was observed in and around solid tumors[25,26]. There are recent highlights about some of the tumor–associated regulatory genes with the disorders in which there is a proliferate inflammatory response[27].

Beside no evidence for RBCs adhesion to the vascular endothelial cell, at normal physiological conditions, the erythrocyte express CD36 (a receptor for thrombospondin) and during the coagulation process the erythrocytes are entrapped into the fibrin, enhancing platelet recruitment and activation[28-30].

While for platelet the fibrinogen binding site is well established; namely a membrane bound glycoprotein GP IIb/IIIa (or $\alpha_{IIb}\beta_3$ integrin,)[31,32], for erythrocytes its binding site is still unknown.

Some *in vitro* studies were done maintained the fibrinogen concentration constant and adding vaso-active molecules (for example acetylcholine) to blood samples, modifying erythrocyte aggregation[33-42]. From a fluorescence study[43] also conducted by our group, alterations of fibrinogen molecule conformations were obtained in the presence of β-estradiol, which may explain the impairment of the erythrocyte aggregation previously verified

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