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Iron-induced fibrin formation may explain vascular pathology in Alzheimer's disease

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To the Editor

In their review article Serý *et al.* [6] have presented compelling arguments in favour of the role of vascular mechanisms in the development of Alzheimer's disease (AD). These arguments are in line with a recent series of publications questioning the prevailing concept of amyloid beta-induced neurodegeneration. Already in 2009 Pimplicar published a paper reassessing the amyloid hypothesis in AD [4]. More recently another important paper was published, in which the author has indicated that therapeutic targeting Abeta brain deposits had no significant effect in AD patients [5]. In the last decade of this century, a number of papers appeared that offered alternative explanations of the molecular mechanisms of AD that are related to cardiovascular diseases (CVD). It is well known that the hallmark of CVD is the intravascular formation of persistent fibrin deposits, or thrombi. Under the conditions of normal hemostasis, fibrin is gradually albeit completely removed by a powerful blood fibrinolytic enzyme system. It is known, however, that in the pathologic situations, such as coronary and/or cerebral thrombosis, fibrin clots are refractory to the thrombolytic dissolution [2].

We have recently shown that, when compared to thrombin-generated clots, the iron-induced fibrin has a radically different structure and morphological appearance as documented by scanning electron microscopy [1]. A characteristic feature of this novel form of fibrin (*parafibrin*) is its complete resistance to the proteolytic degradation. Thus, it may be argued that the formation of parafibrin in the cerebral circulation may be an important factor contributing to AD pathology. Apparently, unfolding of fibrinogen polypeptide chains and its scrambled refolding induced by iron potentiates and/or mimics amyloid deposits in the brain, and in this way contributes to AD pathology. This concept is supported by the findings of Strickland and his group, who have shown that persistent fibrin deposits contribute to neuro-inflammation [3]. In conclusion, we believe that the information presented above supports arguments presented by Serý *et al.* [6] that deserve further attention.

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