Are platelets more than a model of brain neurons?

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For many years, the brain was considered as a closed system protected by the blood-brain barrier (BBB), where only the hormones produced by the body can mediate the interplay between the brain and the blood. Indeed, hormones, crossing the BBB and binding to specific receptors on the brain cells, regulates neuronal and synaptic plasticity and neurogenesis. In this context, the crosstalk between brain and blood cells was thought unlikely under physiological conditions. More recently, this picture changed: several evidence suggest that the platelets, the smallest blood cells, may facilitate communication between the blood and the brain.[1]

No doubt, platelets and neurons are different cells:[2] they have different embryological origin as neurons derive from the neuroectoderm and platelets from mesoderm; neurons are resident cells with very poor regenerative capacity, while platelets are circulating cells with a reasonable turnover, with a life span of 8-10 days; neurons are the fundamental units of the brain and nervous system, and are responsible for carrying information throughout the human body, whereas platelets play a role in hemostasis, thrombosis, inflammation, immunity and tissue regeneration.[3] However, growing evidence in the past decade supports the notion that circulating platelets and brain neurons are closely intertwined and share common features.

First, neurons and platelets realize a functional network of interconnected cells, and exchange paracrine bioactive messengers to fully accomplish their function. These essential metabolites are contained in specific granules both in neurons and in platelets (α-granules and dense granules) and released upon activation.[4] Second, some proteins that are present in neurons with specific neuronal function, are also highly expressed in platelets with physiological relevance.[5] Striking example of proteins shared between neurons and platelets are the neurotransmitter serotonin and transporter/enzymes involved in its metabolism,[6,7] the neurotrophic factors reelin,[8] Brain-Derived Neurotrophic Factor (BDNF),[9] the amyloid precursor protein (APP)[10] and its metabolites amyloid Aβ peptides.[11] Since platelets lack a nucleus, these proteins may mainly derive from platelet precursors, the megakaryocytes, or be translated from small amount of residual mRNA, or internalized from the bloodstream. In the latter case, it should be argued that platelets hike molecules throughout the body thus allowing the redistribution of bioactive modulators. The reason of the unusual presence of neuronal proteins in platelets is not known, but the practical consequences are evident. It has been shown, in fact, that neurological disorders in which these proteins are dysfunctional (mood disorders, autism spectrum disorder, depression, Parkinson and Alzheimer disease) have also a counterpart in platelet dysfunction.[12,13] Epidemiological and genetic studies showed that patients with neurodegenerative and neuropsychiatric traits displayed enhanced platelet hyper-reactivity, as suggested by the increased aggregability, expression of platelet αIIbβ3 and P-selectin, and percentage of platelet/leukocyte aggregates. In addition, a higher MPV (mean platelet volume), platelet distribution width (PDW) and/or platelet-to-larger cell ratio (P-LCR) have been detected in subject with depression, anxiety disorder, patients affected by Parkinson and Alzheimer diseases.[12,13]

A genetic overlap of platelet parameters with neurodegenerative-psychiatric disease has been recently sug-

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gested. In a very elegant study, Tirozzi *et al*. showed an association between MPV and genes, as *ARHGEF3*, *KALRN* and *IQGAP2*, previously related with depression, Alzheimer Disease, schizophrenia and Parkinson Disease; they suggested a potential coagulation, megakaryocyte development and platelet production pathway as common link between platelet abnormality and neuropathological dysfunction.[14]

More interestingly, platelets and their released factors may directly participate in the modulation of brain plasticity. In recent years, the use of platelet products in different medical applications, ranging from neurodegenerative diseases to stroke, and the beneficial effect of platelet-rich plasma in animal models of neurodegenerative diseases is well consolidated. In a mouse model of Parkinson's diseases, intranasal administration of human platelet lysates as well as plasma enriched in platelet secretome displayed a neuroprotective effect in the substantia nigra and striatum.[15,16] Similarly, in a mouse model of Alzheimer's disease, chronic intranasal administration of plasma enriched in platelet secretoma reduced neuropathologic hallmarks, improved cognitive functions and decreased amyloid Aβ peptides deposits and tau hyperphosphorylation.[17]

It has been proposed that under pathological conditions, platelets can directly recognize the neuronal damage,[18] accumulate in the brain along the vasculature, and by secreting their content, regulate inflammation and stimulate neuronal functions and synaptic plasticity.[19] The presence of platelets within the zone rich in neural stem and progenitor cells has been found and associated with a reduced number of apoptotic cells in the damaged area,[20] suggesting the critical relevance of platelets in the lesion repair. In support of this hypothesis, the injection of platelet-lysate improved behavioral deficits and decreased infarct size after stroke. In a mouse stroke model, platelet-lysate enhanced a neuroprotective effect by promoting neuronal stem cell proliferation, angiogenesis, gliogenesis and neurogenesis in the subventricular zone (SVZ).[21] *In vitro* studies provided evidence that platelet-lysate treatment promoted the survival without affecting the proliferation or differentiation of neural precursor cells.[20] On the basis of these data, platelets might actively contribute to these processes only in pathological conditions. In effect, under physiological conditions activated platelets are not able to influence *ex vivo* neurogenesis in the SVZ.[22] By contrast, secretome of activated platelets increased the neurosphere number generated by hippocampal dentate gyrus (DG) cells. Similarly, in a murine model, running increased platelet activation and promoted the proliferation of neural precursor cell in the DG without affect the neurogenesis in SVZ.[22,23] Intriguingly, platelet depletion abolished the neurogenesis induced in the DG by running paradigm. Platelets might then modulate neurogenesis in specific brain areas in relation to pathological and physiological conditions.

Despite that, the use of platelet products in different medical applications (ranging from stroke to neurodegenerative diseases) is of particular interest in recent years, however, how platelet-brain cell communication occurs remains to be established. Both soluble proteins and extracellular vesicles released by activated platelets may be considered good candidates.

Heterochronic parabiosis experiments provided evidence of the presence of "anti-aging" or "pro-aging" factors in blood of young and old mice, respectively. Katsimpardi *et al*. showed that a grow factor highly concentrated in platelets (GDF11)[24] had great neurogenesis potential,[25] supporting a platelet-centric model in the blood-brain connection.

The possible key role of extracellular vesicles platelet-generated (PMP) in this interplay has been proposed based on: the parallelism found between the miRNAs detected in PMP and those expressed in the brain from Alzheimer disease patients;[26] the identification of specific platelet miRNAs among those candidate as biomarkers of multiple sclerosis;[26] the *in vivo* neurogenic and angiogenic effects induced by PMP in adult rats after cerebral infarction.[27]

Following these considerations, we can assert that: yes, platelets are more than a model of neurons! We can here emphasize that platelets play a crucial role that is not limited to hemostasis and thrombosis but goes far beyond them.[3,13]

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