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Abstract

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Document type : Article de périodique (Journal article)

Référence bibliographique

Goubau, Christophe ; Buyse, Gunnar M ; Van Geet, Chris ; Freson, Kathleen. The contribution of platelet studies to the understanding of disease mechanisms in complex and monogenetic neurological disorders.. In: Developmental Medicine and Child Neurology, Vol. 56, no.8, p. 724-731 (2014)

DOI : 10.1111/dmcn.12421
The contribution of platelet studies to the understanding of disease mechanisms in complex and monogenetic neurological disorders

CHRISTOPHE GOUBAU1,2 | GUNNAR M BUYSE2 | CHRIS VAN GEET1,2 | KATHLEEN FRESON1

1 Center for Molecular and Vascular Biology, University of Leuven, Leuven; 2 Department of Child Neurology, University Hospitals Leuven, Leuven, Belgium.

Correspondence to Kathleen Freson, Center for Molecular and Vascular Biology, KU Leuven, Campus Gasthuisberg, C&N1, Herestraat 49, Box 911, 3000 Leuven, Belgium.
E-mail: kathleen.freson@med.kuleuven.be

Platelets, known for their role in primary haemostasis, prevent excessive bleeding after injury. The study of platelets has, therefore, traditionally focused on bleeding disorders. It has recently become evident, however, that platelet research can contribute to unravelling the disease mechanisms that underlie neuropathological disorders that have a subtle subclinical platelet phenotype. Platelets and neurosecretory cells have common gene expression profiles and share several biological features. This review provides a literature update on the use of platelets as easily accessible cells to study neurological disorders. We provide examples of the use of different platelet-based tests to understand the underlying pathophysiological mechanisms for both complex and monogenetic neuropathological disorders. In addition to the well-studied regulated granule secretion and serotonin metabolism, more recent studies have shown that defects in transcription factors, membrane transporters, G-protein signal transduction, and cytoskeletal proteins can be investigated using platelets to gain information on their role in neuropathology.

Platelets are best known for their function in primary haemostasis, where they prevent excessive blood loss at sites of vascular damage by the formation of a stable platelet-fibrin aggregate.1 Platelets are small anucleate cells that originate from megakaryocytes in the bone marrow. They circulate in a non-adherent resting state and become activated after vascular damage when subendothelial adhesive proteins become exposed. Activated platelets secrete the contents of their alpha and dense granules into the surrounding blood to induce secondary stimulation and to activate other platelets. Interestingly, mainly related to the presence of these secretory organelles, platelets are thought to share some morphological and functional features with neurosecretory cells.2 We have previously described how both cell types contain similar types of granules loaded with their specific signalling molecules and proteins that are secreted upon activation, a process that seems, at least in part, to be conducted by a common molecular machinery.3 A structural resemblance has also been noted, as closely interacting platelets seem to mimic the stable synaptic structure between neurons.4

Using platelets as model cells to study neuropathology is a concept that has been noted by several researchers since the early 1960s (see Table I).5–9 There are many studies providing evidence to propose blood platelets as a model of bioaminergic neurons.10 Similarities between platelets and neurons have been found to be particularly important with respect to serotonin metabolism,11 but this model can also be extended to other neurotransmitters such as dopamine,9,12 gamma-aminobutyric acid (GABA), and glutamate.11 These similarities may be due to the common embryonic origin (ectoderm) of these two very different cell types.14,15

Changes in platelet functions were first observed in complex neurological disorders such as schizophrenia, migraine, Parkinson disease, autism, and Alzheimer disease.5–9 Furthermore, many psychotropic drugs have been found to alter platelet functions.16,17 In biological psychiatry, the platelet model has, therefore, been proposed by numerous research groups as a method to improve (1) our knowledge of basic pathophysiological mechanisms underlying some psychiatric diseases, (2) the treatment of these diseases, and (3) the study of new psychotropic drugs. Based on the knowledge of the cellular and molecular similarities between platelets and neurons, and because platelets are easily accessible cells that can be
isolated in a resting basal state and subsequently activated in vitro with several agonists enabling the functional study of several signalling cascades, platelets have been used as a tool to gain novel insights in the underlying molecular and biological defects of several monogenetic neurological disorders.18

This review provides an update on the use of different functional and morphological platelet studies in several well-known complex and monogenetic neurological disorders. It is beyond the scope of this article to provide a full literature review, but we have summarized the main findings here. The findings show that there is indeed a relation between neuropathology and platelet abnormalities, and also illustrate the complexity and diversity of this relationship. It is obvious that further insights are needed to understand the latter aspects.

### PLATELET STUDIES IN THE UNDERSTANDING OF COMPLEX NEUROLOGICAL DISORDERS

Platelets are one of the most researched biological markers in psychiatry.19 Platelets and neurons secrete and respond to neurotransmitters and share many of the same secretory pathways and transporters for neurotransmitter uptake and packaging.10-13 On the basis of this knowledge, a few mainly complex neurological disorders have been studied for many years using platelets, although these patients never present with even a (subtle) subclinical platelet phenotype (Table I). A search of the PubMed, Embase, and Science Direct databases showed that schizophrenia and migraine were the first neuropathological disorders to be linked to mild platelet abnormalities, but no precise findings were detected for one specific molecular pathway. Later on, more specific platelet abnormalities related to the monoamine oxidase (MAO) and serotonin metabolism were described for Parkinson disease and autism respectively. Defects for the role of platelets in relation to inflammatory reactions were specifically detected in Alzheimer disease. Despite these evident links between platelets and neurons, it is currently not possible to give a relevant meaning to the scientific findings that are often variable and not characterized by direct relationships. Therefore, extensive studies are needed before neurotransmitters in platelets can ever be used as biomarkers for the diagnosis of complex neurological disorders. A summary of the representative platelet studies for some of these complex diseases is presented in Table I and briefly discussed below.

### Schizophrenia

Different platelet characteristics including MAO activity,20,21 serotonin release and uptake,9,22,23 GABA metabolism,24 and other phenotypes have been studied in patients with schizophrenia with variable outcomes.25-31 There is still no clear state or trait platelet markers for schizophrenia that can be unequivocally used to detect vulnerability to the illness, predict therapeutic response, define clinical diagnostic entities, or follow the course of the illness. However, platelet markers are of use to monitor psychopharmacological effects (e.g. the effect on MAO activity21) and study the fundamental mechanisms related to pathophysiology. More studies are required to establish true functional relationships between platelet variables and different subtypes of schizophrenia. Improved platelet testing could be possible if genetic factors for schizophrenia are discovered via the emerging next generation genetic approaches.

### Migraine

Migraine was suggested to be a platelet-related disease as far back as 1968.6 Many platelet-related markers that were suggested as being related to schizophrenia were also studied for migraine.32-41 Again, none of these platelet phenotypes is useful as a direct diagnostic biomarker for migraine. It seems that activated platelets participate in the pathogenesis of the disorder, but the nature of this activation is still unknown. Recently, increased platelet activity has been described during migraine attacks related to serotonin release, and antiplatelet medication seems to have a favourable effect in migraine.32 Further studies are needed to characterize the relation(s) between increased platelet activity and migraine, especially in relation to ongoing genetic studies that will discover candidate risk genes.

### Parkinson disease

Parkinson disease is a neurodegenerative disorder resulting from the death of dopamine-generating cells in the substantia nigra,32 but the cause of this cell death is unknown. Motor symptoms are treated with dopamine agonists and MAO type B inhibitors. Platelets also possess mitochondrial MAO type B.43 Similar to the major form of MAO in the human brain, this enzyme actively oxidizes substrates such as tyramine, dopamine, and phenylethylamine.44 In addition to some basic studies related to dopamine uptake45 and granule morphology,46 most platelet studies focused on changes in platelet MAO-B activity in patients with Parkinson disease.35-49 Platelet MAO-B is also expected to be useful in monitoring the anti-parkinsonian activity of such drugs, because of their ability to inhibit brain MAO-B. The plasma levels of their metabolites may be an index of MAO-B activity found in the platelet and brain.

### Autism

Autism is a neurodevelopmental disorder characterized by impaired communication, impaired social interactions, and repetitive interests and behaviour.50 Platelet activity was decreased in infantile autism.51 The most consistent
finding is the platelet hyperserotonemia related to this disease.52,53 The serotonin transporter that is required for the reuptake of serotonin in the central nervous system is also present in the platelet plasma membrane and mediates uptake of plasma serotonin from the platelet cytosol.54 After its uptake, serotonin can either be stored in the platelet dense granules or degraded by the enzyme MAO-B.53 However, there is no consistent biochemical finding as both uptake and release of serotonin by platelets as well as serotonin plasma levels were found to be altered in patients with autism throughout the different studies. To our knowledge, there is also no direct association described between altered serotonin levels and variants in genes that regulate the serotonin metabolism for autism cases.

Interestingly, the importance of genetic factors for autism has been highlighted by different epidemiological studies and by the fact that the relative risk of first degree relatives is about 100-fold higher than the risk in the healthy population, while the concordance in monozygotic twin is about 60%.55 Cytogenetic abnormalities were found in a small subgroup of patients with autism. Recently, it was shown that idiopathic patients with sporadic autism carrying a de novo chromosomal translocation near NBEA, SCAMP5, or STXBP6 have platelets with a significantly smaller dense core granule compared with normal platelets.56,57 Gene silencing of NBEA, SCAMP5, and STXBP6 in mouse beta-TC3 cells resulted in a two-fold increase in stimulated secretion of large, dense core vesicles that resemble the platelet dense granules. Further studies are needed to link these findings with serotonin metabolism and to understand the yet unknown role of these proteins in autism and platelet physiology. In the future, more gene candidates for autism are expected from the next generation of genetic approaches, and the combination with platelet studies will be important for developing our understanding of alterations in serotonin metabolism and granule secretion for autism spectrum disorders.

### Table I: Overview of platelet studies in complex neurological disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of PubMed hits</th>
<th>Main findings related to defects in platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>558</td>
<td>Diverse studies showed changes related to Platelet size and volume, Prostaglandin E1 and cAMP pathway, MAO metabolism, Platelet aggregation and dense granule secretion, Phospholipase A2, Serotonin metabolism, Arachidonic acid and cox activity, Dopamine metabolism, GABA metabolism, Platelet auto-antibodies</td>
</tr>
<tr>
<td>Migraine</td>
<td>368</td>
<td>Diverse studies showed changes related to MAO metabolism, Prostaglandin E1 and cAMP pathway, Platelet dense and alpha granule secretion, Platelet aggregation, Platelet auto-antibodies, NO pathway, Arachidonic acid and cox activity, Dopamine metabolism, Serotonin metabolism, Platelet morphology</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>141</td>
<td>Studies showed mainly changes related to the MAO-B metabolism, but also to Dopamine metabolism, Platelet morphology</td>
</tr>
<tr>
<td>Autism</td>
<td>110</td>
<td>Studies showed mainly changes related to the serotonin metabolism, Haploinsufficiency of NBEA, SCAMP5, and STXBP6, defect in regulated secretion of dense core granules and electron microscopy showed abnormal dense cores in platelet granules</td>
</tr>
<tr>
<td>Alzheimer</td>
<td>326</td>
<td>Studies showed mainly changes related to a role of platelets in inflammation</td>
</tr>
</tbody>
</table>

A PubMed, Embase and Science Direct database-related search (performed on 30th November 2013) was performed using the terms ‘platelets’ AND ‘name of disorder’ (e.g. ‘schizophrenia’, as given in the first column). The number of resulting hits is reported in the second column (year of first publication), while the main platelet defects that were published are listed in the third column with representative publications. cAMP, cyclic adenosine monophosphate; MAO, monoamine oxidase; GABA, gamma-aminobutyric acid; NO, nitric oxide.

### Alzheimer disease

Alzheimer disease is the most common form of dementia worldwide.58 It is characterized by the accumulation of extracellular beta amyloid plaques and intracellular tau tangles as well as gliosis, neuronal cell death, and inflammation.59–61 Interestingly, platelets contain a high concentration of amyloid precursor protein (APP) and express alpha-, beta- and gamma-secretases that are responsible for generating the beta amyloid peptide.62–64 A number of laboratories independently described alterations in the APP metabolism or concentration in platelets of patients with Alzheimer disease.65,66 Activated platelets play an important pro-inflammatory role67 and participate in the proteolytic processing of APP into beta amyloid peptide as well as in the release and deposition of these proteins;68–72 and increased levels of activated platelets are seen in patients with Alzheimer disease.70 In addition, the microtubule-associated Tau protein is also present in platelets,73 together with the Tau kinase GSK3B (glycogen synthase kinase) that has been shown to be overactive in patients with Alzheimer disease.74,75 Platelets can be considered to be a suitable model for Alzheimer disease, and the current scientific interest on this model is very high because many disease concepts are controversial and still under investigation.

### PLATELET STUDIES IN THE UNDERSTANDING OF MONOGENETIC NEUROLOGICAL DISORDERS

Platelet functional and morphological studies have also been used to characterize monogenic neurological disorders for which patients mainly present with a subclinical platelet phenotype.18 We will discuss some well-
documented examples of proven genetic defects related to different cellular pathways (Table II). In contrast to the studies related to complex neurological disorders, the detailed study of genotype–platelet phenotype relations are now possible and these studies have brought novel insights into disease mechanisms.

**Defects in transcription factor FOXG1**
Transcription factors are essential regulators of gene expression during platelet development from megakaryocytes in the bone marrow, as well as during neuronal differentiation and proliferation that is essential for the development of the central and peripheral nervous system. Genes for some transcription factors, such as the forkhead box G1 (FOXG1) gene, are expressed in both platelets and neurons. FOXG1 encodes a transcriptional repressor that is important for prenatal development of the ventral telencephalon by integrating several brain signalling centres. Postnatally, FOXG1 promotes postmitotic neuronal cell survival. In humans, intragenic mutations and gene deletions leading to FOXG1 haploinsufficiency cause a neurodevelopmental disorder originally described as the congenital variant of Rett syndrome, but recently redefined as FOXG1 syndrome. These patients typically have postnatal microcephaly, developmental delay and intellectual disability, dyskinetic movement disorders, and stereotypic hand movements together with corpus callosal hypogenesis. No increased clinical bleeding tendency has been reported in these patients, but it was recently shown that platelets from these patients have decreased responses to epinephrine and abnormal granules.77 These data suggest a non-transcriptional role of FOXG1 in the amplification of intracellular signal transduction after initial platelet activation.

**Defects in membrane transporters AQP7 and ATP1A3**
Aquaglyceroporin 7 (AQP7), which belongs to the evolutionary conserved family of aquaporins, is a membrane protein that facilitates the transport not only of water but also of glycerol. AQP7 is expressed during perinatal development in the mouse brain. Aquaporin family members AQP1 and AQP6 are associated with synaptic vesicles and participate in their swelling, implying a possible role for aquaporins in neuronal granule secretion. We recently published a report on three unrelated children with intellectual disability and a mild platelet secretion defect that is homozygous for the AQP7 G264V variant. Homozygous carriers of this mutation have enlarged and more rounded platelets with centrally localized granules that result in a reduced release of granule content when platelets are stimulated with a weak agonist such as

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### Table II: Overview of functional and morphological platelet alterations in patients with monogenetic neurological disorders

<table>
<thead>
<tr>
<th>Disease phenotype</th>
<th>Causative gene (OMIM number)</th>
<th>Platelet function (aggregation/ATP secretion)</th>
<th>Platelet morphology (electron microscopy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcription factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Rett syndrome variant</td>
<td>FOXG1 (MIM164874)</td>
<td>Decreased PFA100, reduced platelet ATP secretion and aggregation response to epinephrine only84</td>
<td>Enlarged and rounder platelets, alpha granules with heterogeneous content and fewer dense granules84</td>
</tr>
<tr>
<td>Membrane transporters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia with platelet defects and risk for mental disability</td>
<td>AQP7 (MIM602974)</td>
<td>Reduced ATP dense granule secretion after ADP stimulation and reduced platelet aggregation to epinephrine84</td>
<td>Enlarged and rounder platelets, more centrally localized granules84</td>
</tr>
<tr>
<td>Alternating hemiplegia of childhood</td>
<td>ATP1A3 (MIM182350)</td>
<td>Reduced aggregation to epinephrine, normal ATP secretion84</td>
<td>Dense granules with an abnormal polygonal dense core80</td>
</tr>
<tr>
<td>G-protein signalling proteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albright’s hereditary osteodystrophy</td>
<td>GNAS (MIM139320)</td>
<td>Gsalpha platelet hypofunction (aggregation/inhibition test), reduced formation of cAMP92</td>
<td>Normal</td>
</tr>
<tr>
<td>Trisomy 18p with severe mental disability, endocrine dysfunction and bleeding</td>
<td>ADCYAP1 (PACAP) (MIM102980)</td>
<td>Gsalpha platelet hyperfunction (aggregation/inhibition test), increased formation of cAMP after stimulation of VPAC1 with PACAP95</td>
<td>Reduced amount of alpha and dense granules95,96</td>
</tr>
<tr>
<td>Granule trafficking protein</td>
<td>VPS33B (MIM608552)</td>
<td>Reduced platelet aggregation response to adenosine diphosphate and arachidonic acid97</td>
<td>Absence of alpha granules and increased dense granules97</td>
</tr>
<tr>
<td>Arthrogryposis, renal dysfunction and cholestasis syndrome with cerebral malformations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoskeletal protein</td>
<td>FLNA (MIM300017)</td>
<td>Reduced platelet aggregation, secretion, glycoprotein VI signalling, and thrombus growth after collagen stimulation. Reduced platelet adhesion to von Willebrand factor under flow103,105</td>
<td>Enlarged alpha granules, and an abnormal fragmentation of the cytoplasm103,105</td>
</tr>
</tbody>
</table>

ATP, adenosine triphosphate; ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; PFA, platelet function analyser; PACAP, Pituitary adenylyl cyclase-activating peptide; VPAC1, Vasoactive intestinal polypeptide receptor 1.
Epinephrine. Immunostaining showed AQP7 co-localization with dense granules, and it seemed to be released after strong platelet activation.

The ATP1A3 gene encodes the alpha-3 isoform of the Na+/K+ channel that maintains electrochemical gradients across cell membranes. ATP1A3 mutations in humans have been linked to a disease spectrum comprising rapid onset dystonia parkinsonism (or dystonia-12, DYT12) and alternating hemiplegia of childhood (AHC). AHC is characterized by cognitive impairment, repeated transient episodes of hemiplegia and bilateral hemiplegia or quadriplegia disappearing on going to sleep, and by other paroxysmal disturbances such as dystonic attacks, abnormal ocular movements, and autonomic disturbances. Recently, patients with AHC with ATP1A3 mutations were shown to have defective dense granule platelet morphology and delayed release of dense granules after mild platelet stimulations with epinephrine.60 Starting from this proteome, a proteomic analysis by 2DIE using platelets revealed a lysosomal defect with increased catepsin-dependent apoptosis related to APT1A3 deficiency.

**Defects in G-protein signal transduction players Gsalpha and PACAP**

Many platelet stimulatory agonists bind G-protein-coupled receptors and mediate signalling through heterotrimeric G-proteins. Many of these signal transduction genes are ubiquitously expressed. The G-protein Gsalpha that regulates intracellular cyclic adenosine monophosphate (cAMP) formation is ubiquitously expressed and a broad clinical phenotype is associated with a defect in this protein. The Gsalpha subunit is coded by the imprinted gene cluster GNAS1 that not only gives rise to Gsalpha, but also to several other transcripts, antisense transcripts, and non-coding RNAs. Genetic and epigenetic abnormalities of the GNAS1 cluster can result in Albright’s hereditary osteodystrophy (AHO), pseudohypoparathyroidism types la (PHP1a) and Ib (PHP1b) and pseudopseudohypoparathyroidism (PPHP). A variable degree of platelet Gsalpha hypofunction, as measured by the platelet aggregation-inhibition test, is seen in these patients. As an AHO phenotype consisting of a combination of intellectual disability, short stature, round face, subcutaneous calcifications, obesity, and/or brachydactyly is rather non-specific and common, this platelet-based Gs hypofunction test now delivers the first screening tool for patients with evidence for AHO before applying complex (epi)genetic GNAS studies.

The pituitary adenylyl cyclase-activating peptide (PACAP) has been conserved remarkably during evolution and is mainly expressed in the nervous system. PACAP exerts its actions via three G-protein coupled receptors: one PACAP-specific (PAC1) receptor and two receptors (VPAC1 and VPAC2) shared with the vasointestinal peptide (VIP). PACAP plays an important protective role in nervous system diseases, such as focal cerebral ischemia, traumatic brain injury, schizophrenia, anxiety disorders, Parkinson disease, and Alzheimer disease. Neurons, platelets, and megakaryocytes express the Gs-coupled VPAC1 receptor. Two unrelated patients with a partial trisomy 18p containing three copies of the PACAP gene have increased PACAP concentrations in plasma. These patients showed multiple neurological symptoms (epilepsy, hypotonia, intellectual disability, tremor, and psychotic, hyperactive behaviour) and had a spontaneous and trauma-related bleeding tendency with mild thrombocytopenia. The reduced platelet aggregation is related to the elevated basal cAMP levels in the patients’ platelet cells with platelet Gs hyperfunction, and the VPAC1-mediated Gs signalling was shown to inhibit megakaryocyte maturation and platelet formation. This is a completely new disease mechanism that has been discovered via platelet studies.

**Defects in the granule trafficking protein VPS33B**

Vascular protein sorting-associated protein 33B (VPS33B) is a protein that in humans is encoded by the VPS33B gene. Vesicle-mediated protein sorting plays an important role in segregation of intracellular molecules into distinct organelles. Patients with arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome have autosomal recessive VPS33B mutations. They also suffer from cerebral malformations, deafness, congenital heart disease, diabetes, dysmorphic features, and a bleeding diathesis mainly after surgery or treatment with aspirin. It was shown that VPS33B is essential for alpha granule biogenesis and patients have enlarged platelets with strongly reduced numbers of alpha granules. Platelets typically present with reduced aggregation responses.

**Defects in cytoskeletal structure protein FLNA**

During platelet formation, megakaryocytes first undergo a dramatic rearrangement of the cytoskeleton that results in long, branching cytoplasmic extensions, called proplatelets, which fragment at their end to finally form platelets. Organelles and specific platelet granules need to be transported along these proplatelet extensions over sizeable distances before being loaded into the nascent platelets, which resembles the transport along the neuronal axons into the synapse where vesicle exocytosis occurs. Microtubules, actin filaments, and other cytoskeletal proteins are essential in this process. Cytoskeletal proteins such as filamin A (FLNA) or actin are abundantly present in platelets, important not only during their formation but also contributing to their structure and shape change after activation. Filamins stabilize actin filament networks. Mutations in the FLNA gene cause a spectrum of disorders, including brain malformations with periventricular nodular heterotopia as the most frequent phenotype. FLNA is also the predominant isoform expressed in platelets, and patients with filaminopathy A typically have thrombocytopenia and defective platelet adhesive functions.
related to neurological disorders. This results in novel insights in disease mechanisms through the unravelling of the biological functions of novel disease-causing genes as well as their specific role(s) in pathogenesis. In addition, platelets have been shown to be helpful for screening the mode of action of some psychotropic drugs.

Despite the evident links between platelets and neurons, the different platelet-based studies performed in complex neuropathological disorders could not pinpoint a clear single biomarker. Since there is often evidence of more than one impaired factor, combining those different factors into an array could help us produce a more comprehensive profile. An alternative way to address the concern of heterogeneity could be to subcategorize the complex diseases according to, for example, their genetic profile or treatment response. However, this would require further analysis to identify such markers, which are currently still largely unknown. Diagnosis is being standardized and will undergo a revolution in the coming years with the application of new generation DNA typing. This, in turn, will help to improve diagnosis and also the ability to ‘personalize treatment’ for the individual patient.

Many genes are commonly expressed in platelets and neurons, as highlighted for the monogenetic disorders discussed in this review. Taking advantage of the ease in obtaining platelets from patients, these cells have already been proven to be useful for large-scale expression studies such as in platelet transcriptomics and proteomics for pathophysiological investigations and signalling pathway analysis.106

CONCLUSION

Activated platelets are best known for their role in primary haemostasis, and traditional platelet research has focused on isolated thrombopathies caused by the imbalance between bleeding and thrombosis. Interestingly, platelets and neurons resemble each other in many respects. Similar neurotransmitter pathway regulators such as serotonin receptors and transporters, but also GABA and glutamate signalling pathways are present in both platelets and neurosecretory cells. Both cell types contain similar secretory granules that release their content upon stimulation. Moreover, platelets are easy to isolate in a non-active state and can be activated in vitro with specific agonists to study, specifically, different intracellular pathways and granule secretion. As a consequence, platelet studies have been performed in patients with various rare monogenetic and more common complex neuropathological disorders to gain insights into disease mechanisms and to obtain knowledge that is important for megakaryocyte and platelet biology.

ACKNOWLEDGEMENTS AND FINANCIAL SUPPORT

Supported by research grants G.0490.10N and G.0B17.13N from the FWO-Vlaanderen (Belgium) and by GOA/2009/13 from the Research Council of the University of Leuven (Onderzoeksraad KU Leuven, Belgium). GMB and CVG are Senior Clinical Investigators of the FWO – Vlaanderen.

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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