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About

Alexandra is a British Heart Foundation Post-doctoral Research Fellow working in the School of Clinical and Experimental Medicine and an integral member of the Birmingham Platelet Group. Alexandra has a strong background in haemostasis and signal transduction. Her main research interests are signalling events regulating megakaryocyte development and platelet formation.

Qualifications

PhD Biology of Blood Cells , Université Denis-Diderot Paris VII, France

MSc Biology of Blood Cells , Université Denis-Diderot Paris VII, France

BSc(Hons), Life Sciences, Université de Créteil Paris XII, France

Biography

Alexandra earned her PhD degree at Université Denis-Diderot, Paris VII, France, investigating the role of MAP Kinases in platelet adhesion and activation under the supervision of Dr. Marijke Bryckaert at the Centre of Cardiovascular Research of Lariboisiere, INSERM Paris. She immigrated to England in 2007 to do post-doctoral work in the laboratory of Professor Steve Watson in the Institute of Biomedical Research at the University of Birmingham. Her main project is the investigation of signalling events regulating megakaryocytopoesis, megakaryocyte migration and platelet formation.

Alexandra has several peer-reviewed publications in leading scientific and biomedical research journals. She has written a book chapter on megakaryocyte migration. She has been also a speaker at national and international conferences on platelets and megakaryocytes.

Research

Megakaryocytes are large cells found in the bone marrow that release platelets into the circulation. The primary physiological function of platelets is to plug holes in damaged blood vessels. Too few platelets can result in excessive bleeding following injury, whereas too many platelets can cause unwanted thrombi that block the blood supply to vital organs. Megakaryocytes must therefore maintain a healthy concentration of platelets in the blood. Megakaryocytopoiesis is a multi-step process that includes development and maturation of megakaryocytes from haematopoietic stem cells (HSCs) in the osteoblastic niche; migration of megakaryocytes from the osteoblastic to the vascular niche; and formation of proplatelets and release of preplatelets and platelets into the vasculature. Megakaryocytes differentiate from HSCs in the bone marrow, primarily under control of the cytokine thrombopoietin.

We have shown that megakaryocyte development and platelet formation are regulated by a family of proteins that contain a protein sequence known as an ITIM. Elucidating the relative contributions of the various ITIM to the modulation of megakaryocyte and platelet activation has important implications to our understanding of mechanisms that govern platelet formation, which is of direct relevance to hemorrhagic, thrombotic and cardiovascular disorders.

Alexandra's main research interest is the investigation of signalling events involved in the process of megakaryocyte migration. She demonstrated that megakaryocytes are able to migrate in response to the chemokine SDF1-a on fibronectin through a tyrosine kinase-regulated pathway that involves the tyrosine phosphatase CD148 and both Src and Syk family kinases (SFKs) as well as PLCg2. However, the two major surface proteins, integrin aIIbb3 and GPVI/FcRg, are dispensable for this movement. In addition, platelet formation in mice that have been made thrombocytopenic using a specific antibody is severely delayed in the absence of PLCg2, but not in the absence of aIIbb3 or GPVI/FcRg. These findings, together with the previous studies on PECAM-1-deficient megakaryocytes, have led to propose a new model that governs movement of megakaryocytes in the bone marrow and platelet formation that involves receptor activation of PLCg2 through Src and Syk family kinases.

In parallel to this work, with Dr Yotis Senis, the functional roles of the novel platelet ITIM receptor G6b-B and the structurally related platelet tyrosine phosphatases Shp1 and Shp2 in megakaryopoiesis is being investigated in order to elucidate The molecular mechanisms of how ITIM receptors regulate megakaryocyte function.

Other activities

- Member of the Biochemical Society
- Member of the British Society for Haemostasis and Thrombosis

Publications

Despouy, G., Bastie, J.N., Deshaies, S., Balitrand, N., Mazharian, A.,Rochette-Egly, C., Chomienne, C. & Delva, L. (2003) Cyclin D3 is a cofactor of retinoic acid receptors, modulating their activity in the presence of cellular retinoic acid-binding protein II.**J. Biol. Chem. 278: 6355 - 6362.** 278: 6355 - 6362.

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Mazharian, A., Thomas, S.G., Dhanjal, T., Buckley, C. & Watson, S.P. (2010) Critical role of Src-Syk-PLCg2 signalling on megakaryocyte migration and thrombopoiesis. **Blood**, 116:793 - 800.

Mazharian, A., Gheavert, C., Zhang, L., Massberg, S. & Watson, S.P. (2011) Dasatinib enhances megakaryocyte differentiation but inhibits proplatelet formation. **Blood,** 117:5198 - 5206.

Wang, Y.J., Mazharian, A., Mori, J., Bem, D., Finney, B., Heising, S., Gissen, P., White, J.G., Berndt, M.C., Gardiner, E.E., Douglas, M.R., Campbell, D.R., Watson, S.P. & Senis, Y.A. Macrothrombocytopenia and severe GPVI deficiency in mice lacking the ITIM receptor G6b-B, **Science Signalling**, under review.

Review

Severin, S., Ghevaert, C., Mazharian, A. (2009) The mitogen-activated protein kinase signalling pathway: role in megakaryocyte differentiation. **J. Thromb. Haemost.** 8: 17 - 26.

Book Chapter

Mazharian, A. Assessment of megakaryocyte chemotaxis/migration, in “Platelets and Megakaryocytes Volume 3”, Gibbins, J. and Mahaut-Smith, M., Humana Press, in press

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