

The role of platelets in metastasis of solid tumours

Blood platelets are circulating anuclear cell fragments that originate from megakaryocytes in bone marrow. They represent the second most abundant “cell type” in blood, and have well defined roles in haemostasis, thrombosis and wound healing. More recently platelets have emerged as central players in the immune response, with local and systemic roles in growth and metastasis of solid tumours.

In primary carcinomas, secreted growth factors and cytokines contributed by the tumour micro-environment induce epithelial-mesenchymal transition (EMT), a transient and reversible process that promotes cell motility, invasion, and dissemination of cancer cells. Subsequently, tumor cells travel through the bloodstream before arresting and extravasating in a new microenvironment (secondary site). There is mounting evidence for the role of platelets in this process. Reduced platelet counts have been associated with decreased metastasis formation in various mouse models (Bakewell et al. *PNAS*, 2003; Camerer et al. *Blood*, 2004). Platelets have been shown to bind to and form a physical barrier which insulates the metastatic cells from natural killer cell-mediated lysis (Nieswandt et al. *Cancer Res*, 1999; Palumbo et al. *Blood*, 2005) limits their exposure to shear stress, and promotes their adhesion to the endothelium (Erpenbeck et al. *Blood*, 2010; Gay et al. *Nat Rev Cancer*, 2011). Recent research (Labelle et al, *Cancer Cell* 2011, Egan et al, *PLoS ONE*, 2011) has further shown that show that these platelet-tumor cell interactions induce pro-survival and pro-angiogenic signaling and are sufficient to prime tumor cells for subsequent metastasis through intracellular signaling events. Concurrently, tumour cells signal to platelets, subverting their phenotype and function to facilitate tumour survival and growth. Indeed, changes in “tumor-educated” blood platelet RNA is proposed as a promising diagnostic test for metastatic cancer (Best et al. *Cancer Cell*, 2015).

Platelet-derived TGF β and direct platelet-tumor cell contacts synergistically activate the TGF β /Smad and NF- κ B pathways in cancer cells, resulting in their transition to an invasive mesenchymal-like phenotype and enhanced metastasis in vivo. Inhibition of NF- κ B signaling in cancer cells or ablation of TGF β 1 expression solely in platelets protects against lung metastasis in vivo. Thus, cancer cells rely on platelet-derived signals outside of the primary tumor for efficient metastasis. However, platelets contain a plethora of growth factors, cytokines and other platelet-derived factors could potentially be involved in the promotion of a metastatic phenotype.

In 2015, Dr Linden led the installation of only the second mass cytometer in the Southern hemisphere at The University of Western Australia. This unique facility allows, for the first time, simultaneous assessment of phenotype, entire signaling networks and function in heterotypic platelet-tumour aggregates (as well as unbound platelets and tumour cells) on a cell-by-cell basis. Under supervision, the candidate will use this technology to assess the interaction of platelets and their secretions on several tumour cell lines to characterize the cell-cell signaling events responsible for EMT. They will evaluate the effectiveness of specific inhibition of candidate pathways of platelet activation in preventing EMT.

Other details: The principal supervisor for the project is Dr Matthew Linden. If you would like additional information regarding this project, please email matthew.linden@uwa.edu.au or call (+61 8) 9346 1050.

If you have questions about how to apply to become a PhD student at UWA, please email pghelp@postgraduate.uwa.edu.au or call (+61 8) 6488 2807.