

## Emerging protagonists in cancer metastasis: An oath of allegiance by platelets

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The global burden of cancer is burgeoning at steady rate on account of genetic insults (5-10%), as well as an increasing prevalence of unhealthy and preventable lifestyle risk factors (90-95%) such as smoking, alcohol, stress and sedentary habits.<sup>1</sup> More recent mortality data suggests that, in 2012, 8.2 million cancer deaths were registered globally.<sup>2</sup> Annual death toll, besides, is estimated to heighten, by 2030, to 13.1 million.<sup>3</sup> Mortality trend attributes 90% of cancer-associated deaths to metastasis, a perturbing phenomenon in oncological medicine that endows cancer with the propensity to dodge immunological hijacking, pervade and survive circulatory territory, and reproduce within distinct cellular lineages (distant organ systems) through complex cellular and molecular signals.<sup>4</sup> Indeed, metastasis-assisted mortalities have reached pandemic proportions. Regrettably, the underlying molecular pathways harmonizing the dissemination of primary tumour to remote tissues of the body remain to be uncovered.

Metastasis represents the sequential and successful transfiguration of tumour cells to encroach established nearby (primary) and distant (secondary) tissues integrity, stochastically by compromising their genetically scripted cellular behaviour. Genetically speaking, the high vulnerability of genetic mutations and aberrant epigenetic regulations (such as loss of p53, the tumour suppressor protein) are critical for cancer cells to envision aggressive metastatic prospect.<sup>5</sup>

Recent advances in bio-molecular techniques and extensive molecular and cellular digging have brought the diverse role of platelets (thrombocytes) in aiding cancer metastasis much in the limelight.<sup>6</sup> Platelets are dynamic regulators of haemostasis. They are small, non-nucleus cellular fragments of megakaryocytes generated in the bone marrow. As a dominant player in haemostasis entity, their primary response to injured endothelium is attainment of adhesion to exposed sub-endothelial collagen, platelet activation and degranulation and platelet aggregation to attenuate haemorrhage.<sup>7</sup>

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Platelets, now widely accepted, are capable of multimodal task beyond their well-appreciated part in haemostasis and thrombosis. They have been outlined to behave as a bridge between benign and malignant tumour, transmuted the pro-metastatic tumour to highly aggressive metastatic cancer. They faithfully ease the tumour cells to breach cellular boundaries by successively limiting tumour cells to vascular compartment, escaping immunological checkpoints and potentiating invasiveness and eventually colonizing distant tissues. A key component is the release of 'biological vomitus'; bioactive molecules from platelets which, importantly, includes the mitogenic and angiogenic factors. Both mentioned factors are designed to enhance cellular and vascular proliferation, respectively with succeeding cancer expansion over wide area of the body.<sup>8</sup>

Tumour microenvironment ('pro-metastatic niche') represents an early and imperative step in the progression of cancer by optimizing cellular environment in favour of tumour dissemination. For effective rooting, the molecular exchange of courtesies between the host and tumour cells must be constructive. Platelets have been revealed to synchronize tumour microenvironment by engaging granulocytes (leukocytes) using chemokine signaling mechanisms, marking the initiation of platelet contribution towards malignant transformation. It has been further remarked that, whereas tumour cells have ample biomolecules, tumour cell per se might not be efficient to attract granulocytes; making platelets of central importance to 'pro-metastatic niche'.<sup>9</sup>

The transitional interval of tumour cells in vascular compartment commences their first encounter with platelets. Tsuruo et al. proposed, in their review, that the vascular longevity of tumour cells is indispensable for successful haematogenous seeding of cancer since they are vulnerable to extinction, owing to extreme straining of blood flow and immunological destruction. In vitro experimental studies have emphasized that platelet activation and aggregation is pivotal to cancer budding. Furthermore, their activation and aggregation is mainly procured by biologically active molecules expressed on tumour cells surface such as tissue factor (TF) and P-selectin ligands (adhesion molecules). Worthy of note is the subsequent formation of 'platelet shield' (platelet cells-cancer cell adhesion) surrounding cancer cells that is central to immune evasion; impeding natural killer cells

mediated tumour lysis and potentiating attachment to vascular endothelium.<sup>9,10</sup>

Growing body of evidence suggests that actively induced experimental thrombocytopenia significantly attenuates metastasis. A study by Camerer et al. used platelet deficient (genetically knocked out) mice and reported viable reduction in experimental metastasis load (94%). Another surfacing fact is the platelet releasate, emphatically platelet microparticles. Tumourigenesis is a complex molecular process and crucial to it are genetic mutations that allow cancer cells to undergo proliferation incessantly. A research study documented that such molecular signals could be derived from platelet microparticles. Beyond aberrant cellular growth, platelet microparticles confer cancer cells with the ability of highly orchestrated anti-apoptotic activity; maintaining their everlasting survival.<sup>11,12</sup>

Neovascularization (Angiogenesis) is a requisite for tumour survival and metastatic expansion. The cocktail of bioactive (pro-angiogenic) factors are encapsulated by platelets such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF) and insulin-like growth factor (IGF), whereby they contribute to the development of tumour burden. Also, platelets have been linked to induce the pro-angiogenic factor expression by tumour cells.<sup>13-15</sup>

The archetypes of cellular entities, notably cancer stem cells, perhaps in opposite to other non-tumourigenic tumour cells have potential to engender new tumour and metastasis phenotype. Accumulating evidences have demonstrated that tumour cells are composed of assorted cell group involving cellular subtypes with self-sufficiency in regeneration. Platelets also play a key role in assisting aforementioned group of tumour cells. Labelle and his colleague mentioned morphological modifications consistent with epithelial to mesenchymal transition (EMT) in experimental platelet conditioned mouse colon (MC38GFP) and breast carcinoma cell (Ep5) lines. Additionally, these findings were further tested for enhanced tumour invasiveness and appeared positive.<sup>9</sup>

In conclusion, metastasis is a highly coordinated process and is compounded by the cascade of molecular and cellular events. Early cognizance of tumour with metastatic disposition is crucial for the foundation of adaptable therapies to minimize the risk of metastasis associated mortality. Platelets and their delivered substances are emerging as active regulators, mobilizing cancer stability and

substantial metastasis. Rather, they have become evident as new diagnostic, prognostic and therapeutic markers in the discipline of bio-molecular oncology. Identification of 'Mechanistic heterogeneity' of platelets to endorse cancer advancement is a growing concern which calls for additional experimental studies. Nevertheless, many such findings will help us in devising novel therapies to target precise molecular signature steps mediating cancer cell adhesion, migration and proliferation; metastasis.

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