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Molecular Aspects in Platelets Physiology and Tumorigenesis: A Review

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ABSTRACT:
Platelets are the small, bioactive, anucleate; discoid cellular fragments in the human body have an extraordinary capacity for morphological change and powerful secretion properties. Platelets having the important roles in hemostasis and possessed other regulatory functions in normal physiology such as angiogenesis, wound healing, antimicrobial action.The importance of platelets on the hallmarks of cancer and it can influence multistep development of tumorigenesis and thrombocytosis influence invasiveness of malignant cells, inducing Epithelial-Mesenchymal transition through cross linked with NK cells, macrophages etc. Platelets dysfunction mechanism and tumorigenesis provide us new era for research of several pathophysiologic events.

Purpose: To review the literature on role of platelets in tumorigenesis.

Materials & Methods: An electronic search on different search engines for relevant articles published from January 2001 to 2019.

Results: Only 15 publications were searched and each articles shows platelets has a strong relationship with tumour formation and progression of cancer.

Conclusion: Few studies show platelets have role in tumour formation some show metastasis and some show that platelets works through neutrophils and interesting finding coming up that anti-platelets therapy have the preventive role in cancer formation.

KEYWORDS: Platelets, Tumorigenesis, Hall marks of Cancer, Epithelial-Mesenchymal transition, Growth factors, Angiogenesis, Apoptosis, Circulating Cancer Cells, Metastasis, Neutrophil extracellular traps, Cancer Immunity.

I. INTRODUCTION

Platelets are the small, bioactive, anucleate; discoid cellular fragments in the human body have an extraordinary capacity for morphological change and powerful secretion properties. Platelets play important roles in hemostasis and possessed other regulatory functions in normal physiology such as angiogenesis, wound healing, antimicrobial action.The importance of platelets on the hallmarks of cancer and it can influence multistep development of tumorigenesis and thrombocytosis influence invasiveness of malignant cells, inducing Epithelial-Mesenchymal transition through cross linked with NK cells, macrophages etc. Platelets dysfunction mechanism provide us new era for research of pathophysiologic event.

II. REVIEW OF LITREATURE

Platelets in Tumour Development:

Platelets releasates: This are the products released after platelets activation (1,2) which are induced by the platelets agonist of thromboplastin receptors, proteases activated receptors-1 (PAR1) and (PAR4) (3), promotes and proliferate of MCF-7 and MDA-MB231 in breast cancer. Angiogenesis happens through phosphoinositide 3-kinase/ protein kinase C (PI3K/PKC) pathways (4). Another agonist like adenosine diphosphate (ADP) via P2Y12 and P2Y1 receptor influenced the growth of ovarian cancer and pancreatic cancer (4,5). Recent study shows there is positive co-relation between P2Y12 and malignancy (6).

Platelets Influence Tumor Growth:

Platelets have a numbers of growth factors stored in their alpha (a) granules (7–9, 10). They are present in the tumor microenvironment outside of the vasculature where they can come into direct contact with the malignant cells (11, 12).When activated, they secrete transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and platelet derived growth factor (PDGF) (13, 14). These factors not only induce tumor growth, but also promote angiogenesis and tumoral neo-vascularization (15).Recently, platelet-derived

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micro-RNA has been identified as an important regulator of tumor development (16).

(TGF-β1) promotes the growth of primary ovarian cancer in murine model (17) and down-regulation of this factor with platelets blocking with TGF-β1antibody inhibits proliferation in ovarian cancer cell (18).

Platelets induce hepato-cellular carcinoma growth (19) by suppressing the expression of Krüppel like factor 6 (20).

Platelets derived micro-RNA has recently been identified as a regulator of tumour development which target mt-Nd2 and Snora75, modulates mitochondrial function and inhibits tumour growth (21).

Platelets and Cancer Metastasis

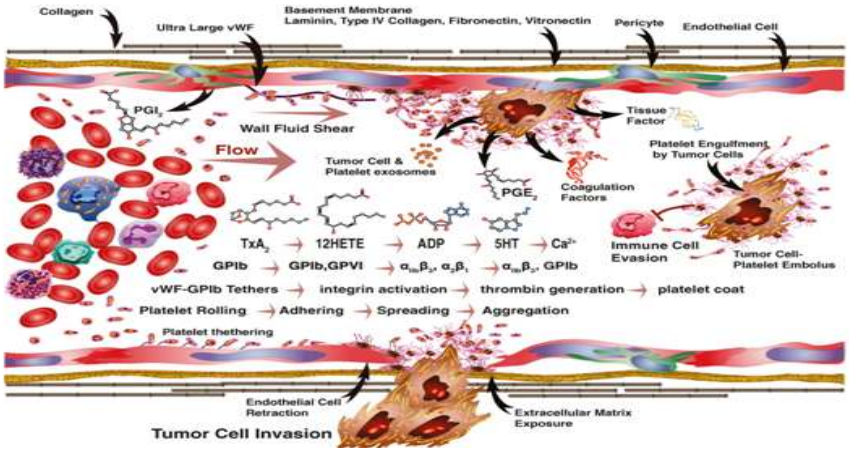
90% of death occurs due to metastasis of cancer (22). Inhibition of platelets activations can inhibits cancer metastasis (23,24). Cancer cell must detach from primary tumour and invade into circulation during metastasis. In this condition tumour cells encounter immune cells and fluid shear stress. This shear force can sensitize to TNF related apoptosis-inducing ligand (TRAIL)-induced apoptosis in prostate and colon cancer (25).

Platelets-cancer interaction promotes EMT (epithelial mesenchymal transition) in tumour cells and enhances the rate of tumour extravasation in vivo through TGF-β and NF-κB pathways (26, 27). Platelets micro-particles (PMPs) which are available in the blood, transport mi RNA and many other factors promoting EMT. E-cadherin and claudin downregulates by EMT of mi RNA 939 in PMPs and targeting the 3/ UTR regions genes (28). High expression of Tissue factor (TF) which is a transmembrane receptor may associate with cancer metastasis (29). TF also enhances platelets recruitment and tumorsphere formation (30). Platelets derived growth factor (PDGF) released from platelets stimulate Cyclooxygenase (COX)-2 expressions and induce the EMT markers (31).

Anoikis is a programmed cell death induced by cell detachment (32). CTC are the small number of cancer cells invade into circulation system through intravasation process. Anoikis resistance is required for CTC survival and colonization in distant organs. Platelets interaction protects cancer cell from Anoikis (33). RhoA-(myosin phosphate targeting subunit 1) MYPT1-protein phosphate (PP1) mediated Yes associated protein 1 (YAP1) dephosphorylation and translocation of nucleolus in induced by the platelets, resulting in apoptosis resistance (34). Apoptosis signal regulating kinase 1 (Ask1) is a stress-responsive mitogen activated protein kinase kinase kinase (MAP3K) in the Jun N-terminal kinases (JNK) and p38 pathways (35). If Ask1 deficiency takes place in Platelets, tumour metastasis is aggravated (36).

Acid Sphingomyelinase (Asm) is secreted protein which released from platelets induces the production of Ceramide which activate the ∞5β1 integrin on melanoma cells and promotes metastasis in vivo (37).

Platelets activation and adhesion depend upon integrin signaling (38), ∞2β1, ∞5β1, ∞6β1, ∞IIbβ3, ∞vβ3 are bind preferably to collagen, fibronetin, laminin, vitronectin and fibrinogen respectively (39). Platelets ∞6β1 mediates the platelets cancer interaction by binding metalloproteinase (ADAM) 9 on the tumour cell. Deletion of integrin ∞6β1on platelets reduces lung metastasis (40). Experiments on knockout mouse show that β3 integrin causes cancer bone metastasis (41). Fig 1.



Courtesy: David G. Menter, Platelets and cancer: a casual or causal relationship: revisited.Cancer Metastasis Rev. 2014; 33(1)

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Cancer Promotes Platelets Activation

Platelets and cancer cell interaction is directional and cancer has a typical role in platelets generation and activation. Thrombosis and thrombo-embolism fivefold increased in cancer patients (42). Cathepsin K (CAT K) up regulated in different cancer (43) and platelets aggregation is induced by CAT K in a dose dependant manner via proteolytically activated receptors (PAR) 3& 4. Osteoprotegrin, parathyroid hormone related protein sonic hedgehog and TGF-β are produced which induce the downstream signaling pathways in breast cancer (44).

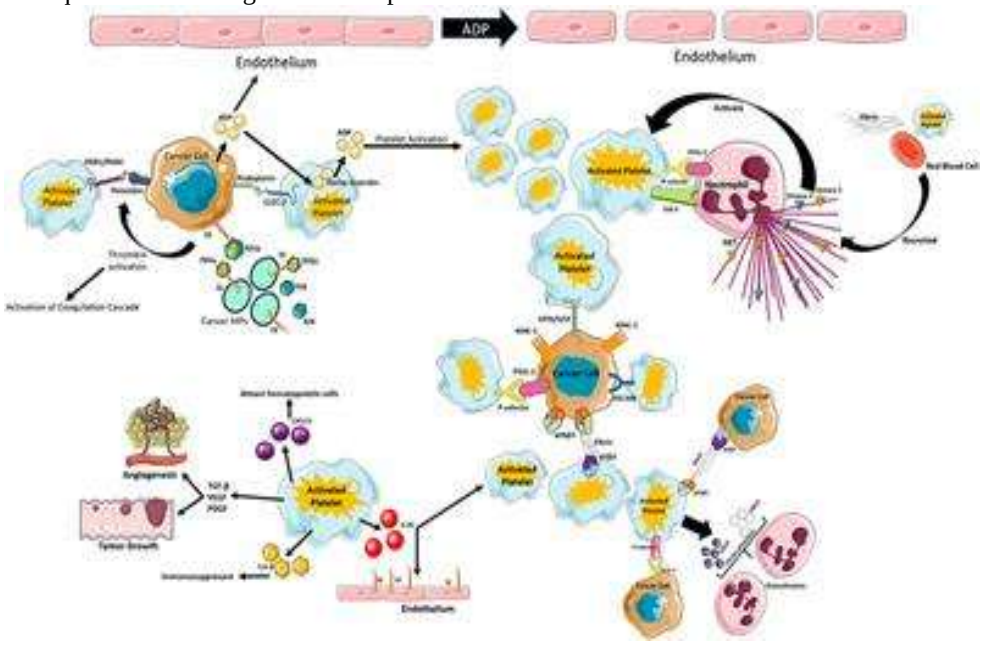
The malignant association with thrombosis is one of the most common features of cancer patients and worse prognosis and survival rate (45).The tumour cell induced platelets aggregation (TCIPA) correlated to higher metastatic potential (46) and so many mechanisms involved in platelets activation and TCIPA (47).

Colon, prostate and breast cancer cells bind platelets FcγRIIa and induce dense granule secretion in the platelets (48). Different types of cancer like squamous and germinal express podoplanin which binds to platelets expressed CLEC-2 and induce platelets activation (49).

Platelets and Anti-tumour immunity

On the time of tumour progression a small number of cancer cell invade into circulation from going to primary site to distal site, these small cells are known as Circulating Tumour Cell (CTC) (50). CTC overcome the shear-force induced damage and also attacks from immune cells. NK cells are very much potent for antitumour activity (51). Depletion of NK cells significantly increase cancer metastasis in mouse (52). It has been well established that binding of platelets protects CTC from NK cells (53). Platelets derived MHC class I and TGF-β released from platelets inhibits the anti-tumour activity of NK cells (54,55).

P-selectin is an adhesion molecule which expressed on the surface of the endothelial and activated platelets (56) and cancer cell bind to platelets P-selectin through TCIPA and form aggregates themselves from blood circulation and hide from NK cells (57). Figure 2



Courtesy:Ana Luisa Palacios et. al. Platelets, Thrombo-Inflammation, and Cancer: Collaborating With the Enemy. Front. Immunol.2019

Platelets and NET formation

Neutrophils have well established two functions a) pathogen engulfment b) anti-microbial substance secretion (58) but nowadays it is identified of a new function of neutrophils i.e. neutrophils extracellular traps (NETs) (58). The NET are results of neutrophil's chromatin and granular content being expelled from the nucleus to form web-like structure and entrap and kill pathogens (58,59). Recent study suggested that NETs may have the role in tumour progression, metastasis and cancer related thrombosis (60). Activated platelets P-selectin trigger NET formation through P-selectin glycoprotein ligand-1(PSGL-1) (61,62). Platelets TLR4 can also trigger NETosis and histones 3 and 4 released during this process can in turn activate platelets in a continuous loop (60,63). The extracellular DNA in

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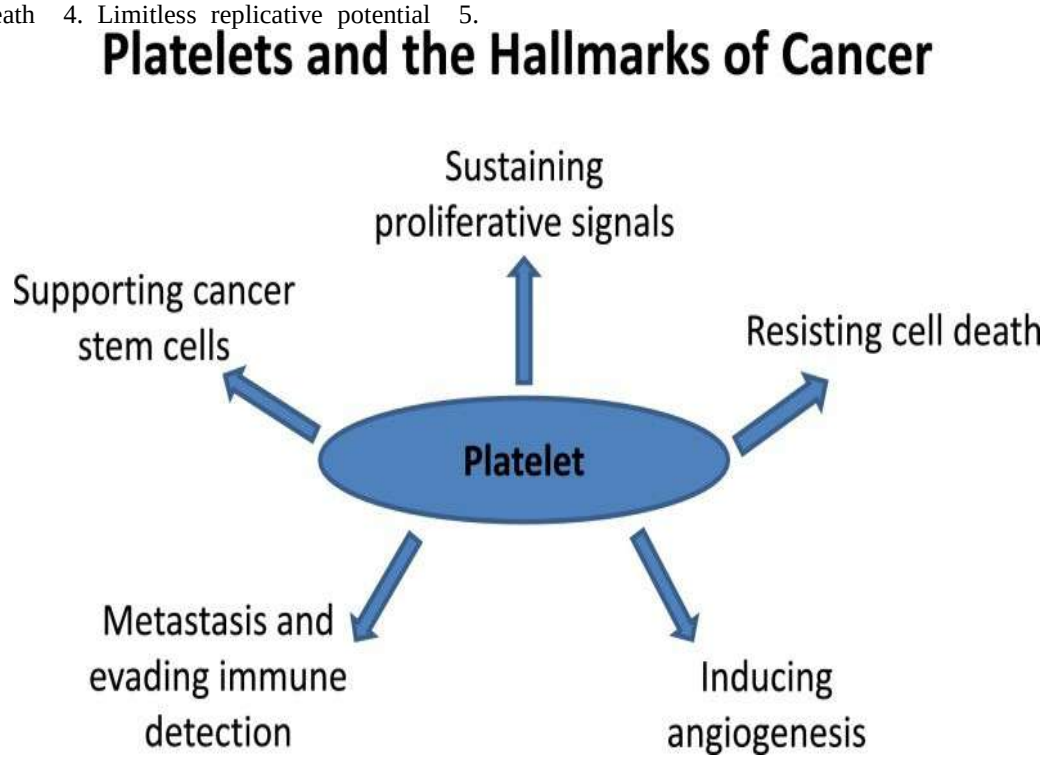
the NETs is capable of binding and activating coagulation factor XII and activates platelets directly (64).

Platelets and the Hallmarks of Cancer

Cancer is multistep complex diseases in 2000 Hanahan and Weinberg defined 6 hallmarks of cancer: 1. Self sufficiency in growth signal 2. Insensivity to growth inhibitory signal 3. Resisting cell death 4. Limitless replicative potential 5. Sustained angiogenesis and 6. Metastasis (65). In 2011 list was updated with cellular and micro-environment alteration, genomic instability, dysregulation of cell energetic, avoidance of immune destruction and tumour promoting inflammation (66). Many of these hallmarks resemble the inflamed state placing the platelets within the interface with thrombosis, inflammation and cancer (67). Figure 3



Sustaining Proliferative Signal

Tumorigenesis is the process where both changes in tumour cell and the tumour microenvironment (TME) take place. Janowska-Wieezorek et al. (68) showed platelets derived micro-particles stimulate mitogen activated protein kinase in lung carcinoma cell line and stimulate cell proliferation.A549 lung carcinoma cell led to expression of matrix metalloproteinases (MMPs) and invasion through matrigel.

Resisting Cell Death

Platelets had the ability to change the apoptotic activity in different modes. Platelets induce MMP-9 expression and activation in colon and breast carcinoma cell line leads to increased remodeling of extracellular matrix and released of growth factor from the extracellular and decrease apoptotic signal (69). Through platelets and platelets lysates reduce apoptosis in leukemia cell line. Contents of platelets micro-particles inhibit intrinsic apoptosis through mitochondrial uncoupling and independent of autophagy (70).

Inducing Angiogenesis

Tumour cell proliferate in rapid progression and neovascularization support adequate blood supply for necessary nutrients and removal of waste substances and oxygen supply to the rapid growing tumour cells. Platelets have the ability to deliver proangiogenic factor to the tumour cells and also stimulate them to express (71). Platelets are the chief source of vascular endothelial growth factor (VEGF) (72, 73), Platelets derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) each promotes tumour cellular growth (74, 75). In colorectal cancer patients reported with increased stored level of VEGF, PDGF and Platelets factor 4 in platelets (76). Increased level of platelets microparticles in plasma is seen in solid tumours and hematological malignancies (77). Highest levels of platelets microparticles are found in stage IV diseases in

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gastric cancer and significantly correlated with metastatic diseases (78). In -vitro and in –vivo studies revealed that platelet microparticles can also promote proliferation and survival of endothelial cells, vascularization in both healthy and diseased states as well (79,80).

Metastasis & Evading Immune Detection

Metastasis is the very important subject for cancer prognosis and it increased the cancer related mortality. Platelets present surround the tumour cells and protect from immune surveillance (81). The platelet protect tumour cell in circulation from neutral killer (NK) cell thus in contribute in cancer metastasis (81,82). Platelets also play a vital role in osteolytic bone metastasis in breast cancer.Boucharaba et al suggested that platelet derived lysophosphatidic acid (LPA) can support and stimulate metastatic breast cancer cells (83).

Supporting Cancer Stem Cells

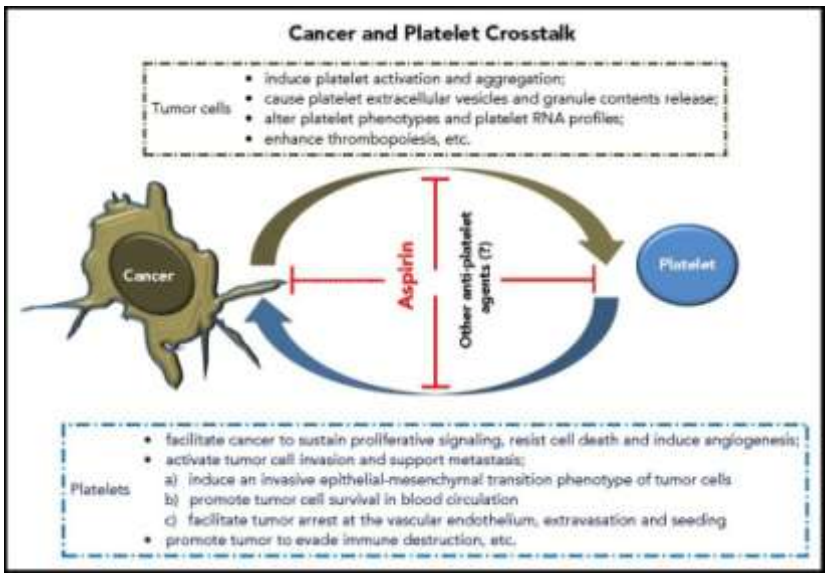
Hallmark of Cancer not support cancer stem cell but it is very much crucial for tumorigenesis and colonization at the distant sites. Labelle et al reported that platelets co-cultured with Ep5 breast carcinoma cells for 24 hours induced a cancer stem cell gene signature in the Ep5 cells (84). Higher level of platelets count in blood increased the mortality of various cancers including gynecological malignancies, malignant mesothelioma, lung, renal, gastric, colorectal and breast cancers (85-92).

Transcription Factors and Hematopoiesis

During megakaryopoiesis and platelets formation megakaryocytic lineage derivation is mediated by a series of transcription factors. Runt-related transcription factor 1 (RUNX1) is very important for the entire Hematopoiesis. In case of (RUNX1) haploinsuffiency thrombocytopenia, platelets dysfunction along with acute leukemia manifestation takes place (93). RUNX1 mutations also impact on different types of cancers. RUNX1 alone or in cooperation with the Ets transcription factor to promote PSA expression in prostate cancer (94).

NSAIDs, COXIBs and Cancer

NSAIDs and COXIBs both are effectively inhibit cancer formation and progression (95). Aspirin covalently inactivates COX-1 more selectively than COX-2 but it has Gastro-Intestinal toxicity effect (95). Population and clinical studies indicate that regular intake of aspirin and various other NSAIDs reduce the risk and incidence of various cancers (96-102). Prospective cohort studied by Nurses' Health Study 82,911 women and (103) 47,363 male health professionals (104) showed that regular long-term use of aspirin significantly reduced incidence of cancer. Fig. 4



Courtesy: Xiaohong Ruby Xu et. al, Cancer and platelet crosstalk.Blood2018 | Vol. 131,No. 16

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CONFLICT OF INTEREST

The authors have no financial conflict of interest.

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