in pre-metastatic niche formation are derived from the bone marrow. Analysis of the molecular mechanisms has revealed that both secreted soluble factors and membrane vesicles derived from both primary tumour and its stromal cells are key players in bone marrow cell mobilization during pre-metastatic processes [37].

1.4. SURVIVAL IN CIRCULATION

After intravasation the vast majority of circulating tumour cells (CTCs) is rapidly destroyed [35]. Platelets, cancer associated fibroblasts and macrophages have an important role during this phase, because they help CTCs to evade the immune system and make extravasation easier, through the following mechanisms: (1) tumour cell-induced platelet aggregation and thrombus formation (primary tumour cells express thrombin to activate specific membrane receptors on platelets) protects CTC from shear stress, (2) help to evade immune system, because: (a) physically shelters them from cytotoxicity of NK cells, (b) platelet-derived TGF-β reduce the inhibiting NK cell activity, (c) while platelet-derived VEGF may inhibit the maturation of dendritic cells, which are major antigen-presenting cells in the immune system; (3) sticking CTCs to blood vessels via specific proteins, (4) releasing degradative enzymes and angiogenic growth factors to facilitate CTCs migration and to support secondary tumour neoangiogenesis (through platelet-derived TGF-β and PDGF) (some of these processes are depicted on Figure 1.3). Aggregates of CTCs surrounded by platelets and thrombus, can be easily trapped by the capillary beds because of their size [35]. **Application of anticoagulants (heparin) for metastatic CRC patients might act against formation of clot around thrombus with CTC-platelets complexes and therefore prevent trapping of CTC and their extravasation and metastases formation.** As mentioned above, metastatic cancer cells might also fuse with macrophages or cancer associated fibroblasts, which are beneficial for their survival in circulation and/or extravasation [18–19, 34, 35].

Some endogenous factors (TNF-α, epiregulin, IL-6, and inflammatory mediators) can increase survival of CTCs in the blood, while others (of chemokine gradients CXCR4, CCR4, CCR7, and CCR9) influence their migration.

In case of colorectal cancer the development of liver metastasis has been significantly related to presence of CD133[19]/CD54[20]/CD44[21] immunopositive circulating tumour cells

[19] CD133 antigen, also known as prominin-1, is a glycoprotein that in humans, he precise function of CD133 remains unknown, it has been proposed that it acts as an organizer of cell membrane topology, CD133 is expressed in haematopoietic stem cells, endothelial progenitor cells, glioblastoma, neuronal and glial stem cells, various paediatric brain tumours, as well as adult kidney, mammary glands, trachea, salivary glands, uterus, placenta, digestive tract, testes, and some other cell types.

[20] CD54 or ICAM-1 (Intercellular Adhesion Molecule 1) cell surface intercellular adhesion molecule continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Upon cytokine stimulation, the concentrations greatly increase. After activation, CD54 (on endothelial cells) binds to LFA-1 on leukocytes and stimulates lymphocyte transmigration into tissues.

[21] CD44 cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration.