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Review

Circulating tumor cell-blood cell crosstalk: Biology and clinical relevance

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SUMMARY

Circulating tumor cells (CTCs) are the seeds of distant metastasis, and the number of CTCs detected in the blood of cancer patients is associated with a worse prognosis. CTCs face critical challenges for their survival in circulation, such as anoikis, shearing forces, and immune surveillance. Thus, understanding the mechanisms and interactions of CTCs within the blood microenvironment is crucial for better understanding of metastatic progression and the development of novel treatment strategies. CTCs interact with different hematopoietic cells, such as platelets, red blood cells, neutrophils, macrophages, natural killer (NK) cells, lymphocytes, endothelial cells, and cancer-associated fibroblasts, which can affect CTC survival in blood. This interaction may take place either via direct cell-cell contact or through secreted molecules. Here, we review interactions of CTCs with blood cells and discuss the potential clinical relevance of these interactions as biomarkers or as targets for anti-metastatic therapies.

INTRODUCTION

For a successful outgrowth of tumor cells at a distant metastatic site, several critical steps and obstacles need to be overcome. This multistep process, known as the metastasis cascade, includes and requires cancer cells to escape their primary site, circulate in the bloodstream as circulating tumor cells (CTCs), the arrest and extravasation of these cells through vascular walls into the parenchyma of distant tissues, and finally adaptation and outgrowth at distant sites (Talmadge and Fidler, 2010). Once CTCs reach and settle in a distant organ, they are called disseminated tumor cells and together with CTCs are recognized as the seeds of metastasis (Aguirre-Ghiso, 2018).

During these steps, the tumor cells encounter different microenvironments, each consisting of different hurdles to the tumor cells. Since an increase in the number of CTCs detected in the blood of cancer patients is associated with worse prognosis, understanding the mechanisms and the interactions behind the survival of the CTCs in the blood is of utter importance. One critical step is the survival of CTCs within the circulation (Alix-Panabières and Pantel, 2021). This involves surviving the shear forces within the vessels but also the evasion of immune surveillance by the numerous blood cells within the blood (Ganesh and Massagué, 2021; Luo et al., 2018), as documented by the fact that the blood from cancer patients contains cell DNA fragments released from tumor cells (Ganesh and Massagué, 2021; Nanou et al., 2020).

Numerous studies of various tumor entities have shown that the number of detectable CTCs in the blood of patients is negatively associated with survival in both early- and late-stage settings (Alix-Panabières and Pantel, 2021). Since CTCs are considered the seeds of metastasis, their detection and molecular characterization in early stages is of high clinical relevance. However, detecting CTCs in early stages of cancer is still a challenge because the CTC counts are much lower than in advanced metastatic disease (Cristofanilli et al., 2019). Still, CTC analyses in the adjuvant setting of breast cancer patients with apparently localized disease (i.e., no clinical or radiological sign of overt distant metastases) have shown that the detection of CTCs at primary diagnosis was correlated with metastatic relapse (Bidard et al., 2018; Rack et al., 2014; Riethdorf et al., 2017). Moreover, blood samples were also analyzed after initial adjuvant therapy (e.g., chemotherapy) and the detection of CTCs 2 or 5 years after initial cancer diagnosis was correlated to progression-free and overall survival (Sparano et al., 2018; Trapp et al., 2019). Further molecular characterization of patient-derived CTCs combined with different mouse models might help to reveal targets of specific therapies to prevent metastasis onset.

Here, we discuss recent data indicating that, during the process of dissemination in the blood, CTCs interact with a large number of different hematopoietic cells, such as platelets, neutrophils, and monocytes/macrophages (Figure 1; Table 1), but also endothelial cells and cancer-associated fibroblasts (CAFs). These interactions have shown to be permissive or even necessary for CTC survival in blood. These interactions can take place as direct cell-cell interplay, especially within a heterotypic CTC cluster, or indirectly via molecules that change the phenotype of the interacting cells. By manipulating the cell function of the surrounding normal cells, cancer cells can survive this hostile environment and facilitate the extravasation of CTCs to distant sites. In addition, we also discuss the potential biological strategies for anti-metastatic therapies based on the known interactions of tumor cells with hematopoietic cells.

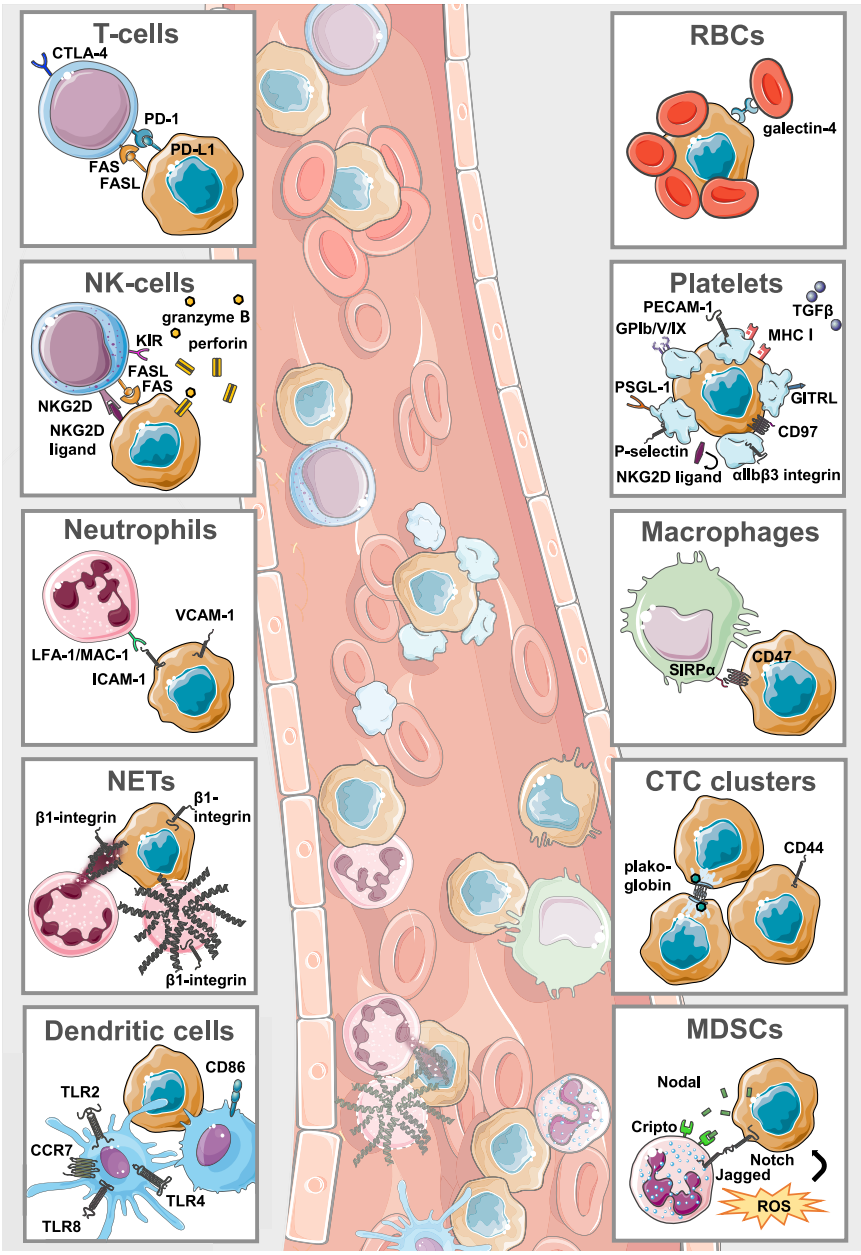

Figure 1. CTC-immune cell interactions in the peripheral blood

This figure depicts an overview of the different direct interactions between CTCs and the respective blood cells, with a focus on the main molecules involved in these interactions. T cells can interact with CTCs by the inhibitory molecules CTLA-4 and PD-1, as well as the FAS-FASL axis, which is also involved in CTC-NK cell interactions. Furthermore, NK cells exert their cytotoxicity toward CTCs by expression of KIR and NKG2D receptors. Upon ligand binding, cytolytic proteins granzyme B and perforins are released, which ultimately leads to the cell death of CTCs. CTCs can express adhesion molecules VCAM-1 and ICAM-1, the latter is known to bind to LFA-1/MAC-1 receptors on neutrophils resulting in attachment to the endothelial membrane, transendothelial migration, and extravasation of the CTCs. NK cells that have undergone NETosis can furthermore bind to CTCs through the expression of β1-integrin on both NETs and CTCs. Macrophages are able to directly interact with CTCs via SIRPα and CD47, which protects CTCs from phagocytosis. Within the blood stream, platelets are known to protect CTCs from shear forces and shield them from being detected by immune cells. They can confer MHC class I molecules onto CTCs and help shed them their NKG2D ligands, which prevents them from being recognized by NK cells. The expression of CD97, GITRL, PECAM-1, GPIb/V/IX, PSGL-1, P-selectin, and αIIbβ3 integrin, as well as the release of TGF-β is furthermore beneficial for the survival of the tumor cells. Recently, it has been shown that also RBCs can interact with CTCs via galectin-4. Apart from immune cells, CTCs can also form homotypic clusters among each other, which are known to harbor an increased metastatic potential compared with single CTCs. The previously described interaction molecules between CTCs are plakoglobin and CD44. While cDCs show an upregulation of TLR2, TLR4, TLR8, and CCR7 when CTC counts are elevated in cancer patients, pDCs have an increased expression of CD86. MDSCs interact with CTCs through increased Nodal signaling and subsequent ROS formation, resulting in activation of Notch signaling in the CTCs. This figure was created with smart.servier.com.

CTCs, HETEROTYPIC, AND HOMOTYPIC CTC CLUSTERS

CTCs have been detected in the peripheral blood of most types of carcinomas and they have been associated with dismal prognosis (Alix-Panabières and Pantel, 2021). CTCs in the blood can occur as both single cells and as CTC clusters (multicellular CTC aggregates). Single CTCs can be detected in patients even with premalignant diseases, such as intraductal papillary mucinous neoplasm and ductal carcinoma *in situ*, indicating that a fraction of malignant cells acquire the ability of early tumor dissemination at very early premalignant stages of the disease (Franken et al., 2012; Franses et al., 2018; Poruk et al., 2017). The number of CTCs varies greatly depending on the tumor type, stage, and treatment response of patients. Even in metastatic patients the number of CTCs is still rather low and is undetectable in a large proportion of patients. This can be partially explained by the rather small blood volumes usually analyzed and the great heterogeneity of the tumor cells and thus lack of analytical sensitivity of many assays, especially those using marker-dependent enrichment methods (Alix-Panabières and Pantel, 2021). Moreover, the presence of CTCs in the blood stream of cancer patients not only correlates with a poor prognosis but can also be used to monitor the therapy response and collect tumor material for molecular and functional analyses (Alix-Panabières and Pantel, 2021).

Table 1. Summary of direct and indirect CTC-blood cell interactions and their consequences

Cell type	Interacting molecule on CTC	Interacting molecule on host cell	Consequence	Authors
Direct interactions				
CTC clusters				
	CD44	–	higher metastatic propensity of the clusters	Kapeleris et al. 2020; Liu et al., 2019
	Plakoglobin	–	higher metastatic propensity of the clusters	Aceto et al. 2014; Goto et al. 2017
Platelets				
	CD97	–	platelet activation and granule secretion, release of ATP, and evasion of CTCs off the blood stream; promotes metastasis	Ward et al. 2018
	–	integrins (αIIbβ3)	form a "shield" around CTCs, protecting them from the physical stress in the blood stream	Zhang et al. 2009
	–	P-selectin	"	Coupland et al. 2012; Qi et al. 2015
	–	PSGL-1	"	Gong et al. 2012
	–	GPIb/V/IX	"	Barnes et al. 2012
	–	PECAM-1	"	Labelle and Hynes 2012; Palacios-Acedo et al. 2019
	–	GITRL	NK cell inhibitory ligand	Lorenzo-Herrero et al. 2018
Neutrophils				
	VCAM-1	–	enhanced metastasis formation	Szczerba et al. 2019; Park et al. 2021
	ICAM-1	Mac-1	attach of neutrophils to CTCs, arrest of the tumor cells to the blood vessels, transendothelial migration and extracellular matrix remodeling; extravasation and metastasis formation	Spicer et al. 2012
	ICAM-1	LFA-1	"	Filippi 2019
NETs				
	β1-integrin	β1-integrin	CTC adhesion to NETs	Najmeh et al. 2017
Red blood cells				
	–	galectin-4	activation of signalling cascade(s)	Helwa et al. 2017; Hernández-Hernández et al. 2006
Macrophages				
	CD47	SIRPα	limits macrophage removal of HSCs	Mohme et al. 2016
NK cells				
	loss of MHC class I	KIRs	NK cell-induced killing of tumor cells	Lorenzo-Herrero et al. 2018; Morvan and Lanier 2016
	FAS	FASL	activation of caspase-dependent apoptosis in CTCs	Que et al. 2021
	NKG2D ligands	NKG2D	NK cell-mediated immune pressure	Lo et al. 2020; López-Soto et al. 2013
	ULBP1	NKG2D	immune evasion	Hu et al. 2020

(*Continued on next page*)

Table 1. *Continued*

Cell type	Interacting molecule on CTC	Interacting molecule on host cell	Consequence	Authors
T cells				
	PD-L1	PD-1	immune evasion	Hofman et al. 2019; Mazel et al. 2015
	FASL	FAS	immune evasion	Gruber et al. 2013
	–	CTLA-4	immune evasion	Arnoletti et al., 2022
Indirect interactions				
Platelets				
	–	TGF-β	platelet-induced CTC immune-escape	Leblanc and Peyruchaud 2016; Orellana et al. 2015
Neutrophils				
	IL-8	CXCR1/2	increase in Mac-1 expression on neutrophils, shear-resistant binding of neutrophils and ICAM-1-expressing tumor cells	Huh et al. 2010; Dong et al. 2005
NK cells				
	–	granzyme B, perforins	apoptosis in the target cell	Brodbeck et al. 2014
Red blood cells				
	β-globin	–	promotes cell survival during blood-borne dissemination and may have a potential role in mediating sequestration of reactive oxygen species	Zheng et al. 2017

Both clinical and experimental data have indicated that the biological and clinical relevance could be different between single CTCs and CTC clusters. In most, but not all studies, the presence of clusters in clinical samples is an independent prognostic marker (Wrenn et al., 2021). However, to our knowledge, the largest prospective-retrospective study on 594 metastatic breast cancer patients indicated that it is the number of CTCs, regardless of "cluster status," that causes the dismal prognosis (Paoletti et al., 2019). Furthermore, certain treatment regimens can cause a release of CTC clusters without causing an increase in metastases formation (Mohme et al., 2017; Ortiz-Otero et al., 2021). Nevertheless, CTC clusters may additionally have other negative consequences for patient outcome by causing cerebral infarctions and lung emboli (Feinauer et al., 2021; Hong et al., 2016). Furthermore, several different mouse models using both mouse cancer cell lines and patient-derived xenografts have been used to show the higher metastatic potential of clusters compared with single CTCs (reviewed in Wrenn et al., 2021). Aceto et al. (2014) showed that CTC clusters are cleared much faster from the circulation. Thus, CTC clusters may be trapped in smaller capillaries because of their physical properties. But also, their increased expression of certain adhesion markers, such as plakoglobin (Aceto et al., 2014; Goto et al., 2017), as well as stemness markers, such as CD44 (Kapeleris et al., 2020; Liu et al., 2019), could explain the higher metastatic propensity of the clusters.

Although clusters with over 20 cells have been reported in patients, most CTC clusters consist of between 2 and 6 cells (Wrenn et al., 2021). These CTC clusters can be composed of only CTCs (homotypic clusters) or admixtures of CTCs and other cells (heterotypic clusters) (Aceto, 2020; Wrenn et al., 2021). The heterotypic clusters can be composed of different types of white blood cells (WBCs) (such as neutrophils, lymphocytes, natural killer [NK] cells, and macrophages) or platelets (Aceto et al., 2014). Different types of clusters can be detected even within one patient's blood, indicating a big adaptability of CTCs to ensure survival. CTCs also interact with non-hematopoietic cells. Duda et al. (2010) used a lung cancer mouse model and showed that CTCs have a survival advantage if the CTCs formed heterotypic clusters with fibroblasts. This interaction also increased the efficiency of lung metastasis formation as the depletion of fibroblasts resulted in reduced metastasis, implying an important role of fibroblasts for CTC survival and metastatic capacity. In a zebrafish model, it was shown that CTCs and circulating (c)CAFs remain in a tight association during circulation and aid early dissemination (Liu et al., 2017). Similarly, Arnoletti et al. (2018) showed that CD105- and CD14-positive fibroblast cells are essential for *ex vivo* CTC cluster formation in pancreatic and cholangio-carcinoma patients. Recently, Sharma et al. (2021), identified circulating CTC-cancer-associated fibroblasts (cCAFs) heterotypic clusters in both early- (M0, 4.8%) and late-stage (M1, 10%) breast cancer patients. Furthermore, spontaneous and xenograft mouse models showed that CTC-cCAFs clusters have a higher metastatic potential than homotypic CTC clusters (Sharma et al., 2021). In the following sections, the importance of CTC interaction with hematopoietic cells are discussed in more detail (Figure 1; Table 1).

In summary, although CTC clusters are much more rarely seen compared with single CTCs, their presence has been associated with higher metastatic potential in animal models (Cheung et al., 2016; Liu et al., 2019; Taftaf et al., 2021) and in most of the studies indicated worse prognosis in patients compared with single CTCs (Aceto et al., 2014; Hou et al., 2012). In this regard, the interaction within the clusters with different blood cells and CAFs seems to be crucial for both CTC survival and for extravasation and outgrowth at distant sites. However, equally important are decisive interactions with single CTCs for metastasis occurrence.

INTERACTIONS OF CTCs AND MYELOID CELLS

The cellular elements of the blood are derived from hematopoietic stem cells (HSCs) in the bone marrow. HSCs are pluripotent cells that divide to produce two different lineages, the lymphoid progenitor and the myeloid progenitor, which give rise to granulocytes, macrophages, dendritic cells (DCs), red blood cells (RBCs), as well as megakaryocytes (MKs) and platelets (Noetzli et al., 2019).

Platelets and MKs

MKs are large (50–100 μm in diameter) rare cells that undergo a differentiation process in the bone marrow to produce platelets. In addition, MKs also play role in bone metabolism, for example, inhibiting osteoclast function and enhancing osteoblast proliferation (Kacena et al., 2006). Platelets are small anucleated cell fragments that have a characteristic discoid shape and range from 1 to 3 μm in diameter (Machlus and Italiano, 2013). The main roles of platelets are to maintain the hemostasis of the vascular system and to promote wound healing at sites of vascular injury (Sacks et al., 2018). However, the interplay between platelets and CTCs is the most extensively studied from all the blood cells and it is well known that platelets interact with CTCs and support many aspects of their dissemination (Anvari et al., 2021).

Numerous different biological effects of interactions between CTCs and platelets have been described: (1) CTCs can induce platelet activation; (2) platelets protect CTCs from shear stress and anoikis; (3) platelets mediate immune evasion of cancer cells (extensively reviewed in Anvari et al., 2021). CTCs interact with platelets leading to their activation and aggregation; however, the mechanisms underlying this process are still to be fully characterized (Anvari et al., 2021). Ward et al. (2018) showed that CD97 expressed on tumor cells may be involved in platelets activation, leading to granule secretion, including the release of ATP, which promotes evasion of CTCs off the blood stream and that consequently promotes metastasis. Furthermore, platelets have many adhesion molecules, including integrins (αIIbβ3), selectins (P-selectin), leucine-rich glycoproteins (PSGL-1 and GPIb/V/IX), and immunoglobulin superfamily proteins (PECAM-1), that allow them to form a "shield" around CTCs, protecting them from the physical stress in the blood stream (Barnes et al., 2012; Coupland et al., 2012; Palacios-Acedo et al., 2019; Qi et al., 2015; Zhang et al., 2009). The platelet-CTC aggregation has also the effect of protecting the CTCs from anoikis. Haemmerle et al. (2017) have shown that platelets improve anoikis resistance of cancer cells by activating Yap1 signaling.

Beyond their role as a shield for tumor cells in the circulation and the protection against anoikis, platelets can help CTCs escape from major histocompatibility complex class I (MHC class I)-mediated recognition by NK cells. Placke et al. (2012a) showed that platelets coat tumor cells rapidly and, furthermore, CTCs can acquire a "pseudonormal" phenotype by the transfer of platelet-derived MHC class I containing membrane vesicles to the tumor cell surface, this causes CTCs to mimic host cells and protects them from NK cells recognition. Moreover, CTC-conjugated platelets lead to the release of chemoattractants that facilitate the recruitment of other granulocytes, including neutrophils (Kral et al., 2016). Besides direct contact, activated platelets also produce secreted factors and cytokines that can influence CTC EMT phenotype, such as an increase of TGF-β and tissue factor (Labelle et al., 2011; Leblanc and Peyruchaud, 2016). Further mechanisms of a platelet-induced CTC immune escape include the induction of shedding of NKG2D ligands, thereby reducing the activating signals for NK cells to kill the tumor cells as well as the expression of NK cell inhibitory ligands, such as glucocorticoid-induced TNF-related ligand (Placke et al, 2012b). Gained knowledge about platelet-CTC interplay has led to studies to investigate how these interactions could be druggable targets, and how the platelet-CTC connection could be inhibited to reduce metastases (Coyle et al., 2016). However, anticoagulant therapy is still not routinely implemented in the treatment of cancer patients (Lucotti and Muschel, 2020).

While the contribution of platelets to metastasis has been extensively characterized, the role of MKs is less well established. In contrast to platelets, MKs normally stay in the bone marrow and have rarely been reported to be released into blood circulation. However, while high platelet count has been correlated with poor cancer prognosis, providing a selection driver for the metastatic phenotype, circulating MKs have recently been associated with good patient survival (Xu et al., 2017; Zhu et al., 2019).

Neutrophils and NETs

Neutrophils represent the most abundant type of WBCs in both tissue and blood (Rosales, 2018). These myeloid cells are released from the bone marrow in a terminally differentiated state and serve as first responders to inflammation and infection, and thus are the first cells to arrive at the inflammatory site. It is often observed that cancer patients harbor an increase in peripheral blood neutrophils. An elevated neutrophil-to-lymphocyte ratio in peripheral blood represents an independent prognostic factor for poorer overall survival in both solid tumors and leukemia (Zhang et al., 2021). Neutrophils can, on the other hand, also suppress tumor growth and metastasis and therefore exhibit anti-tumorigenic effects. Similar to macrophages, the pro- and anti-tumorigenic effects might derive from the different polarization states neutrophils can undergo. While N1-polarized neutrophils exhibit anti-tumor effects, N2 neutrophils show a pro-tumor phenotype (Fridlender et al., 2009).

CTCs in circulation can be detected as single cells, as well as in homotypic and heterotypic clusters with WBCs as discussed earlier. In breast cancer patients, Szczerba et al. (2019) observed the presence of heterotypic clusters, characterized these CTC-associated WBCs by single-cell RNA-seq, and could show a

direct association of CTCs with neutrophils in most of the clusters. The gene expression profiles of neutrophils show elevated levels of *ARG1*, *CXCL1*, *CXCL2*, *CXCL10*, *CCL2*, *CXCR2*, and *VEGFA*, which furthermore resemble those of pro-tumor N2-like cells. Their CTC association leads to changes within the transcriptome of these CTCs and the major pathways that are induced drive their cell cycle and DNA replication. Furthermore, VCAM-1 has been validated to be a crucial protein to mediate this CTC-neutrophil interaction which ultimately leads to an increase in proliferation and overt metastasis formation (Szczerba et al., 2019).

Park et al. (2021) also identified the interaction of CTCs and neutrophils via VCAM-1. Since CTC-neutrophil interactions are rare events and difficult to capture, this group established an inertial-force-assisted droplet microfluidic chip to generate these CTC-neutrophil clusters. Using mRNA sequencing it was furthermore shown that the expression profiles of heterotypic clusters are changed, and an immune-related and cytokine and chemokine gene phenotype is induced. The key genes include *CCL4*, *CCL24*, *CCL2*, *PPBP*, and *CD69*, which are involved in recruitment of macrophages, T cell differentiation, and increased metastasis formation (Park et al., 2021).

During inflammatory responses, neutrophils are capable of transendothelial migration via three crucial steps: neutrophil rolling, adhesion, and migration (Filippi, 2019). While initial binding and neutrophil rolling is mediated through selectins, neutrophil attachment to the surface of endothelial cells and their migration also requires the expression of LFA-1 and Mac-1 on the neutrophils, as well as ICAM-1 on the endothelial cells (Filippi, 2019). Through the same interactions, neutrophils can also attach to CTCs, which leads to the adhesion of tumor cells to the blood vessels, ultimately leading to transendothelial migration and extracellular matrix remodeling. Spicer et al. (2012) identified ICAM-1 as the crucial molecule to mediate the interaction between activated neutrophils via Mac-1 and CTCs via ICAM-1, which promotes the formation of liver metastases in mouse models. These CTC-neutrophil clusters potentially lead to a facilitated binding to endothelial cells and thereby enhance their extravasation. Moreover, CTCs from melanomas entrapped in lung capillaries have been shown to secrete IL-8 to attract neutrophils, which in turn increases Mac-1 expression on neutrophils, thereby leading to shear-resistant binding of neutrophils and ICAM-1-expressing tumor cells (Huh et al., 2010). Blocking of the neutrophil IL-8 receptors CXCR1 and CXCR2 can further downregulate Mac-1 expression and thus reduce melanoma extravasation (Dong et al., 2005). Furthermore, McDonald et al. (2009) showed in an *in vivo* lung carcinoma model of liver metastases that neutrophils can enhance CTC adhesion to liver sinusoidal endothelial cells through selectin ligands containing Sialyl-Lewis X moieties on the surface of the CTCs and endothelial E-selectin.

As part of the innate immune response, neutrophils inactivate pathogens by phagocytosis and subsequent killing through proteolytic enzymes, antimicrobial proteins, and reactive oxygen species. Apart from phagocytosis, activated neutrophils are also capable of undergoing a specific form of cell death called NETosis, through which they release neutrophil extracellular traps (NETs) into the extracellular space, consisting of DNA and proteolytic enzymes resulting from degranulation (Brinkmann et al., 2004). The formation of NETs is associated with impaired vascular function, thrombosis development, and heightened inflammation in tumor-bearing mice, which could be attributed to enhanced G-CSF and IL-8 plasma levels (Alfaro et al., 2016; Cedervall et al., 2015; Demers et al., 2012). NETosis has also been correlated with enhanced metastasis formation through capturing of CTCs within these traps, thereby leading to an increase in CTC mobilization toward the endothelium and an increase in vascular permeability (Chen et al., 2021). Cools-Lartigue et al. (2013) showed, on an *in vivo* xenograft model, that circulating lung carcinoma cells can be trapped by NETs, which leads to an increase in liver micro metastasis formation. Moreover, NET formation could be inhibited by DNAse or a neutrophil elastase inhibitor, abrogating these effects. Najmeh et al. (2017) then showed that β1-integrin expression of CTCs and NETs is crucial for CTC adhesion to NETs *in vitro* and *in vivo* and that DNAses can disrupt this adhesion. NET formation can also be indirectly induced by communication via EVs originating from CTCs. Their protein cargo has been shown to induce changes in the transcriptome of these neutrophils, which result in degranulation, granule mobilization, and even modulate cluster formation (Charles Jacob et al., 2021).

Thus, work mostly in mouse models has clearly shown that the formation of CTC-neutrophil clusters leads to an enhancement of metastatic potential. Mechanistically this seems to occur through entrapping tumor cells on endothelial cells and by disrupting the endothelial barrier, ultimately leading to an extravasation of the CTCs. Likewise, ample evidence exists on NETs that entrap CTCs through the release of DNA and proteolytic enzymes, thereby also leading to attachment to the endothelium.

RBCs

RBCs are the most abundant cell type in the human body, accounting for nearly 85% of the total cell count in the average adult (Sender et al., 2016). RBCs are the functional component of blood responsible for the transportation of gases and nutrients throughout the human body and, more recently, attention has been drawn to their role in hemostasis (Alamin, 2021).

Despite their high abundance in the human body, it is surprising how little the role of RBCs in cancer has been explored. RBC distribution width (RDW), which is a measure of the variation in the volume of RBCs, has been associated with poor prognosis in many cancers, such as lung, breast, and gastric cancer. It has been suggested that an increment on immature RBCs in the circulation could the reason behind the rise in the RDW value (Hu et al., 2017).

Regarding CTCs, the expression of one of the two main hemoglobins from RBCs, β-globin, by cancer cells promotes cell survival during blood-borne dissemination and may have a potential role in mediating sequestration of reactive oxygen species (ROS) (Zheng et al., 2017). Regarding direct interaction of RBCs with tumor cells, Helwa and colleagues reported that tumor cells interact with RBCs via galectin-4, and two more independent studies have shown that RBCs membrane protein composition is altered in breast and advanced non-small cell lung cancer (Helwa et al., 2017; Hernández-Hernández et al., 2006). In addition, RBCs have been recently described to bind cell-free DNA,

which leads to innate immune activation in pathological settings, uncovering a previously unappreciated role of RBCs as critical players in inflammation (Lam et al., 2021).

Furthermore, altered states of coagulation are usually found in cancer patients. Contrary to the obsolete notion that RBCs play a minor role in hemostasis and thrombosis, there is increasing evidence that RBCs have biologically and clinically important functions in blood clotting and its disorders. Enhanced eryptosis (apoptosis-like cell death of RBCs) shortens the lifespan of circulating RBCs and confers them a pro-coagulant phenotype (Qadri et al., 2017). This phenomenon has been involved in the pathogenesis of anemia, impaired microcirculation, and increased pro-thrombotic risk in cancer patients (Lang et al., 2017). Besides, RBCs can modulate platelet reactivity directly through chemical signaling or adhesive RBC-platelet interactions (Helms et al., 2013). CTC adhesion to micro-vessel walls depends on blood viscosity, thus, RBC aggregation enables the CTCs to stably roll along the vessel wall at a lower flow rate (Xiao et al., 2017). However, the precise coagulation mechanism that increases the survival and success of tumor cells in the blood remains to be established.

Macrophages and cancer-associated macrophage-like cells

Macrophages are tissue-resident cells that differentiate from monocytic precursors and keep tissue homeostasis by coordinating the inflammatory response through the clearing and repair of damaged cells and matrices (Italiani and Boraschi, 2014). Similarly to neutrophils, macrophages can polarize toward M1- or M2-like macrophages in response to tissue microenvironmental changes (Wang et al., 2014b). In addition to different chemokine production profiles (Mantovani et al., 2004) and metabolic differences (Biswas and Mantovani, 2012), M1-like macrophages display eliminating and inhibitory functions, whereas M2-like macrophages promote cell growth and repair (Mills, 2012).

In contrast to the well-characterized tumor-macrophage interactions, the interplay of macrophages and CTCs is poorly understood. It has been reported that CTCs could be interacting with macrophages directly through CD47, which could bind to the macrophage fusion receptor SIRPα, conferring CTCs with an anti-phagocytic signal (Mohme et al., 2016). The CD47/SIRPα axis, a myeloid-specific immune checkpoint, limits macrophage removal of HSCs but can be exploited by hematologic and solid malignancies (Mohme et al., 2016).

Moreover, in 2014, Adams et al. defined an atypical population of circulating macrophages as cancer-associated macrophage-like cells (CAMLs). This population was composed by giant cells of myeloid lineage (CD14+/CD11c+), with enlarge nuclei, positive for the blood cell marker CD45 but also expressing epithelial markers, such as CK8/18 and 19 and EpCAM (Adams et al., 2014). According to their study CAMLs could interact with CTCs in the circulation by bonding to CTCs or by engulfing cells that appeared to have an epithelial phenotype (Adams et al., 2014). In addition, it has been described that CAMLs disseminate from the tumor tissue into the peripheral blood circulation in large numbers together with CTCs via transendothelial migration (Adams et al., 2014; Condeelis and Pollard, 2006). Wei et al. (2019a) have further shown that, in colorectal cancer, tumor-associated macrophages induce the EMT program to enhance the release of CTCs into the blood stream and CTC-mediated metastasis. Studies have described that macrophage-tumor cells can potentially fusion with CTCs in various cancer patients but not in healthy individuals (Clawson et al., 2015; Zhang et al., 2017). Zhang et al. (2017) reported that macrophages could acquire expression of epithelial markers (keratins and EpCAM) as well as stem cell markers (Oct4) upon phagocytosis of apoptotic cancer cells, defining the concept of "tumacrophages." These tumacrophages were consistently absent from the blood of healthy donors, suggesting a possible clinical value as a biomarker of cancer. In addition, Gast et al. (2018) described that the fusion of neoplastic cells with macrophages occurs *in vivo* and can generate hybrid cells with various combinations of phenotypes exhibiting enhanced metastatic behavior. However, it is still not clear whether all the circulating atypical cells with epithelial- and macrophage-like features arise from cell fusion or whether some of them derive from phagocytosis or other direct or indirect interactions between neoplastic cells and macrophages. Nonetheless, the published studies about atypical circulating cells with epithelial- and macrophage-specific markers strongly suggest their potentially relevant role in tumor invasion and their prognostic clinical value (Augustyn et al., 2021; Gast et al., 2018; Gironda et al., 2020; Mu et al., 2017).

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immune cells originating from the bone marrow myeloid stem cell lineage, with a strong immunosuppressive function. MDSCs interact with other immune cells, including NK cells and T lymphocytes, to regulate their function, although their mechanisms of action have not been elucidated yet (Tumino et al., 2022). In cancer patients, the amount of MDSCs found in circulation are highly increased and it has been associated with an increased number of CTCs (Elbasateeny et al., 2022; Papadaki et al., 2021). Furthermore, Sprouse et al. (2019) identified CTC-MDSC clusters in patient blood and further *in vitro* analyses demonstrated that CTC-MDSC clusters induced a pro-tumorigenic differentiation of MDSCs resulting in a pro-survival CTC activation via ROS and the Notch signaling pathway. Similar results have been shown from portal blood of pancreatic ductal adenocarcinoma patients, where *ex vivo* cultures of portal MDSCs and CTCs spontaneously formed clusters with other surrounding cells, promoting CTC proliferation and migration (Arnoletti et al., 2022).

DCs

DCs act as important mediators between the innate and adaptive immune responses. Their main role consists of antigen presentation and are therefore inducers of T cell responses in tissue. However, DCs can also be found in blood circulation, in which three distinct types of have been described so far (Veglia and Gabrilovich, 2017; Ziegler-Heitbrock et al., 2010). DCs form an heterogeneous group with regard to their hematopoietic origin and gene expression patterns and can therefore be from both myeloid and lymphatic lineage—depending on their subtype (Cabeza-Cabrerizo et al., 2021). Within the blood circulation,

two major subtypes of conventional dendritic cells (cDCs also referred to as myeloid DCs, or mDCs), namely cDC type 1 (cDC1) and cDC type 2 (cDC2) can be found, together with plasmacytoid (pDCs), which are, however, of lymphoid origin (Veglia and Gabrilovich, 2017; Ziegler-Heitbrock et al., 2010).

Due to the immune-activating nature of DCs, several studies showed that an upregulation of DCs is beneficial for survival in various cancer entities, thus making it an interesting cell type for immunotherapy as well as for cancer vaccinations (Tran Janco et al., 2015; Zhao et al., 2012). It is furthermore described that CTC positivity induces expression changes of several proteins on DCs. For example, CTC-positive breast cancer patients were found to have an increase of TLR2, TLR4, and TLR8 expression by circulating $CD11c^+$ DCs, while TLR3 expression was decreased (Green et al., 2014). In the same study, patients harboring more than five CTCs showed a significant decrease in peripheral blood cDCs producing TNF-α, IFN-α, and IL-12, and an elevated expression of CCR7 and CD86 on cDCs and pDCs, respectively, presumably causing a pro-inflammatory immune response that leads to a reduced survival in these patients (Mego et al., 2017). Furthermore, Wei et al. (2019a) have recently proven the direct interaction of circulating DCs and CTCs in the blood stream using an *in vivo* imaging flow cytometry system, which moreover revealed that CTC-DC clusters move at a lower velocity than single CTCs or DCs individually, possibly due to the enhanced size of these clusters compared with single cells. This slower movement might lead to an increased adherence to blood vessels, ultimately resulting in enhanced extravasation and metastasis formation (Wei et al., 2019a). However, to the best of our knowledge, no directly interacting molecules facilitating this new type of direct interaction between the two cell populations have been identified so far.

INTERACTIONS OF CTCs AND LYMPHOID CELLS

The lymphoid cell lineage gives rise to two different types of cells: NK cells and lymphocytes. Both cell types complement each other through antibody-dependent and -independent mechanisms and therefore together link the adaptive with the innate immune responses. NK cells play a crucial role in the prevention of cancer metastasis through constantly governing the growth of neoplasia. While the role of NK cells in metastasis prevention is rather undisputed as an increase in these cells mostly leads to a favorable prognosis, the role of lymphoid cells is not as clear. Nevertheless, both cell types are of utmost importance regarding established as well as emerging immunotherapies currently under investigation, e.g., in immune-checkpoint inhibition or adoptive NK cell therapy, which can act independently of tumor-antigens.

NK cells

NK cells, which mature and differentiate within the bone marrow and secondary lymphatic organs, such as lymph nodes, spleen, tonsils, and thymus (Abel et al., 2018), are a critical component of the innate lymphoid immune system and provide a rapid response against pathogens, such as virus-infected cells, as well as neoplasia (Scoville et al., 2017). They are typically characterized by their $CD3^-CD56^+$ expression pattern (Morvan and Lanier, 2016). There is a limited accessibility of NK cells to enter solid tissue, thus NK cells are able to eliminate highly motile CTCs especially in the blood (Dianat-Moghadam et al., 2021). Besides shear stress, they therefore represent the main threat for CTCs to survive within the blood stream and thus are considered a substantial suppressor of metastasis formation (Leblanc and Peyruchaud, 2016).

NK cells exert their cytotoxicity through a variety of different activating or inhibitory receptors. Activating receptors bind to MHC class I polypeptide-related sequence A/B (MICA/MICB) molecules on tumor cells, which subsequently activates a cytotoxic NK cell response (Dianat-Moghadam et al., 2021). In breast cancer patients, it was previously published that oncogenic miR20a downregulates MICA/B in circulating breast cancer stem-like cells, which leads to resistance to NK cell defenses and increased lung metastasis (Wang et al., 2014a). Liu et al. (2013) showed that miR-296-3p inhibits ICAM-1 expression in prostate cancer cells and knockdown of this miRNA leads to an induction of NK cell cytotoxicity, thus a decrease in CTCs and lung metastases. Inhibitory effects of NK cells also include the recognition of the so-called "missing self" by the killer cell by immunoglobulin-like receptors, which sensitize the absence of MHC class I molecules on the surface of target molecules and thus they try to escape the detection of immune cells (Lorenzo-Herrero et al., 2018; Morvan and Lanier, 2016).

The immune response mechanisms of NK cells consist of three main pathways (López-Soto et al., 2017). (1) The exocytotic release of cytolytic granules, which contain cytotoxic molecules, such as granzyme B and perforins, that subsequently induces apoptosis in the target cell. Using mouse models, Brodbeck et al. (2014) showed that perforin-dependent lysis of both solid tumors and CTCs leads to a significant decrease in metastasis formation. (2) NK cells mediate the release of IFN-γ, thereby activating further immune cells, such as dendritic cells. Other cytokines released by NK cells include different interleukins, prostaglandin E2, TNF, growth factors, and chemokines (Mohme et al., 2017; Morvan and Lanier, 2016). Their antigen-independent defense mechanisms thus act as a potent bridge between innate and adaptive immune responses and potentiate tumor inhibitory immune responses. (3) Primed NK cells express death-inducing ligands on their cell surface, such as FASL and TRAIL. Binding to their respective receptors leads to activation of caspase-dependent apoptosis in the target cell (Morvan and Lanier, 2016). Recently, Que et al. (2021) have shown that Jinfukang can induce the expression of FasL and secretion of TNF in NK cells *in vitro*, which leads to induction of apoptosis through activation of the Fas/FasL signaling pathway in a CTC cell line, showing a mechanistic link between NK cells and CTCs. *In vivo*, this leads to increased elimination of CTCs and inhibition of CTC lung metastasis.

In a recent study, Lo et al. (2020) showed *in vivo* that, while NK cells successfully eliminate single CTCs in the blood stream of mice, CTC clusters show a resistance against NK cell-mediated cytotoxicity. They furthermore showed that NK cells co-cultivated with breast cancer cells exert an increased cytotoxic activity toward those cells with a more mesenchymal rather than epithelial phenotype. Due to an increase in activating NKG2D NK cell ligands as well as downregulation of MHC class I

molecules on the tumor cells, the NK cell-mediated immune pressure is therefore increased in those cells undergoing EMT. This is in line with an *in vitro* study by López-Soto et al. (2013)), who found that NK cells have an increased activity against mesenchymal tumor cells through upregulation of NKG2D ligands on their cell surface. This is, however, in contrast to a study by Hu et al. (2020)), who postulate that EMT leads to downregulation of NKG2D ligand ULBP1, ultimately resulting in immune evasion of these CTCs.

Overall, an increased amount of NK cells is highly beneficial for survival of cancer patients (Bald et al., 2020). The cytotoxic and cytolytic activities of NK cells are thus often impaired in CTC-positive, metastatic patients in several different tumor entities (Bald et al., 2020; Mohme et al., 2017). Furthermore, the overall NK cell counts in the blood of cancer patients are often negatively correlated with the number of CTCs (Hayes et al., 2021; Navarro et al., 2015; Ye et al., 2017). However, positive correlations between NK cell counts and CTCs also have been described, and a specific subset of NK cells ($CD56^{high}CD16^{low}$) has been correlated with shorter overall survival rates (de Jonge et al., 2019). Whether the increase in NK cells is a compensation for an impaired NK cell activity or whether it is a reaction to the high tumor burden and the CTCs in circulation by upregulating the amount of NK cells still remains elusive. Moreover, restoring NK cell abundance and activity showed significant effects against metastatic spread (Bald et al., 2020; López-Soto et al., 2017), making NK cell-mediated immunotherapy a promising tool for targeting CTCs in patients.

Lymphocytes

For the successful differentiation of CTCs among a large background of PBMCs, the standard exclusion marker used for blood cells is CD45. Several studies have furthermore identified CD45-positive cells within CTC clusters; however, mostly without characterizing them (Jiang et al., 2017; Scharpenseel et al., 2019; Szczerba et al., 2019). Together with the fact that CD45-positive cells within these clusters are usually very small (~10 μm) in size, it is likely that these cells could be characterized as lymphocytes and thus are thought to commonly interact with CTCs.

T and B lymphocytes make up the adaptive immune response. While B lymphocytes have gained more and more attention in the last decade regarding their prognostic value in cancer (Fridman et al., 2021), to the best of our knowledge, no CTC-B cell interactions have been described so far. Since T cells can be categorized into many different subtypes, the immune responses exerted from these cells in relation to their association with tumor cells or CTCs also depend greatly on their environment and are not yet completely understood. In general, an increased number of CD8+ T cells seems to be beneficial for survival, whereas an increased frequency of CD4+ Tregs is often correlated with disease progression (Facciabene et al., 2012; van der Leun et al., 2020).

Positive correlations have been shown between the amount of CTCs and the number of intra- and peritumoral Tregs as well as primary tumor size in breast cancer, and CD4+ and CD8+ T cells showed negative correlations (Mego et al., 2016; Xue et al., 2018). Likewise, in NSCLC, the number of Tregs were positively correlated with CTCs, while a negative correlation was described between the number of CTCs and CD3+, CD4+, CD4+/CD8+ amounts (Ye et al., 2017). In metastatic genitourinary cancer, CTC-positive patients with PD-L1+ CTCs, and low CD4 and CD8 T cell counts, were associated with shorter overall survival (Chalfin et al., 2021).

Overall, there are very few studies available analyzing direct interactions between CTCs and lymphocytes. However, both CD4+ T helper cells and CD8+ cytotoxic T cells can directly interact with CTCs through the FAS-FASL axis or immune-checkpoint molecules, such as PD1-PDL1 and CTLA 4, which induce immunosuppressive responses, leading to enhanced survival of the tumor cells (Arnoletti et al., 2022; Gruber et al., 2013; Hofman et al., 2019; Mazel et al., 2015). The introduction of immune-checkpoint therapies has already proven to be a successful tool toward cancer treatment in solid tumors; moreover, the advantages of analyzing PD-L1 expression on CTCs are being more and more investigated as well, since upregulation can inhibit the induction of T cells (Hofman et al., 2019). Wang et al. (2019) recently showed that, upon radiation therapy, the amount of PD-L1+ CTCs increased significantly, which was associated with poorer prognosis. Despite the high amount of correlative studies available, mechanistic studies are, however, still lacking.

CONCLUSIONS AND PERSPECTIVES

Metastatic spread is a highly inefficient and complex multistep process. The immune system is the most important effector of eliminating malignant or transformed cells. Even after successful dissemination from the solid tumor, CTCs have to survive the harshness of circulation, including anoikis and the escape of immune surveillance from hematopoietic cells in the blood circulation. The identification of the mechanisms underlying these blood cell-CTC interactions is important for better understanding of metastatic spread in cancer patients and it can reveal relevant information for the development of new targeted therapeutic strategies to prevent the outbreak of overt metastasis, which usually signals incurability for most patients.

An important mechanism for CTC survival is the formation of heterotypic clusters with different cells, such as MDSCs (Sprouse et al., 2019), stromal cells like fibroblasts (Hurtado et al., 2020) and/or neutrophils (Szczerba et al., 2019), macrophages (Hamilton and Rath, 2017), and DCs (Wei et al., 2019b). Furthermore, platelets also play a role in the immune evasion by facilitating the escape of CTCs from MHC class I-mediated recognition by NK and T cells by the transfer of MHC class I onto the tumor cell surface (Placke et al., 2012a; Rodriguez-Martinez et al., 2022). In addition, platelets provide CTCs with a coating shield that helps their survival from the physical stress in the blood and from anoikis (Lucotti and Muschel, 2020). Similarly, neutrophils can also attach to CTCs, assisting their arrest to the blood vessels and eventually leading to transendothelial migration (Szczerba et al., 2019). Likewise, CTCs can be entrapped by NETs, contributing to their attachment to the endothelium. Moreover, although the biological mechanisms behind are not clear yet, neoplastic cells can associate with macrophages via cell fusion and/or phagocytosis or other direct or indirect interactions, further conferring them an increased ability to evade the immunosurveillance. Besides,

the expression of molecules, such as PD-L1, CD44, CD47, and FAS, among others, have been reported to help CTCs avoid the clearance from blood circulation (Baccelli et al., 2013; Loreth et al., 2021; Szczerba et al., 2019).

The association of CTCs with other blood cells can also result in the release of different cytokines and secreted factors that could act as chemoattractants for the recruitment of more blood cells or influencing the CTC EMT state (Labelle et al., 2011), which might contribute to immune evasion and resistance to chemotherapy. Among various potential mechanisms this could be a result of NK cells failing to recognize CTCs that have downregulation of ULBP1 during EMT (Hu et al., 2020). On the other hand, NK cells seem to have an increased ability to kill those CTCs that underwent EMT due to an altered expression of inhibiting and activating NK cell ligands (Lo et al., 2020).

The emerging knowledge on the receptor-ligand interactions between CTCs and blood cells may lead to the development of new strategies of immunotherapies in patients with solid tumors. In this context, liquid biopsy measurements may serve as a powerful tool to identify the patient who might benefit most and monitor the therapies by sequential blood tests, including the characterization of both CTCs and host cells. Prediction of therapy success and monitoring of tumor evolution shaped by therapy may lead to new concepts for personalized medicine, which may prevent metastatic progression and improve the survival of cancer patients.

The recent implementation of immunotherapies in oncology has already proven the immense power that lies within harnessing the immune system and reactivating it toward improved clearance of cancer cells. The expression of PD-L1 on tumor cells and the ability to counteract the inhibitory signals by binding to T lymphocytes can thus be reversed through the administration of anti-PD-L1/PD-1 antibodies. Many studies are already available that have quantified the expression of PD-L1 on CTCs and some studies have shown its prognostic value, which suggests the importance of further implementing CTCs into future clinical immune-oncology trials. However, the evaluation of PD-L1 expression on CTCs leads to opposing views regarding their clinical relevance. While it has been proposed that CTCs are a useful tool for tracking therapy responses, there is no clear stance in the field as to whether the expression of PD-L1 serves as a negative or positive predictive marker (Hofman et al., 2019; Indini et al., 2021). However, a recent meta-analysis showed that patients with CTCs expressing PD-L1 had a shorter survival time than patients with CTCs not expressing PD-L1 (Kong et al., 2021). Besides CTC interaction with lymphocytes, more cell types are becoming the field of current investigations.

NK cells harbor an extraordinary potential of CTC elimination and prevention of metastasis formation due to the plethora of different activating and inhibiting receptors. Furthermore, NK cells are potent activators of T cell responses. Therefore, not surprisingly, a variety of immunotherapy options are being investigated, either as an alternative or complementary to T cell immunotherapy (extensively reviewed in Dianat-Moghadam et al., 2021; Lorenzo-Herrero et al., 2018). Different NK cell therapy approaches are possible, such as increasing the amount of NK cells, which significantly reduces the number of CTCs in breast and non-small cell lung cancer (Liang et al., 2017; Lin et al., 2017; Lorenzo-Herrero et al., 2018), cytokine-based therapy to boost NK cell activity with different activating interleukins (e.g., IL-2, IL-12, IL-15, IL-18, or IL-21) (Romee et al., 2016; Wang et al., 2003), or the modulation of activating/inhibitory receptors or ligands by using different antibodies to counteract NK cell inhibition or to induce activating functions (Dianat-Moghadam et al., 2021). Furthermore, the possibility of using DCs in immunotherapy and their impact on CTC viability are currently also being explored. Kolostova et al. (2022) generated monocyte-derived DCs using leukapheresis and isolated CTCs from the same patient for maturation of the DCs, an important prerequisite for the establishment of a cancer vaccine. Moreover, in a study by Hancharou et al. (2020) it was recently demonstrated that pancreatic cancer patients who have received subcutaneous injections of DCs have shown a significant decrease in CTCs and Tregs, an increase in antigen-specific T cells, as well as enhanced overall survival.

Despite the growing number of therapy options available, there are still many unknown receptor/ligand interactions, especially occurring during CTC travel in the circulation. However, elucidating the exact molecular mechanisms is crucial for the development of future target-based drugs. Besides the current focus on immune cells, the inclusion of other circulating host cells (e.g., CAFs, CECs, RBCs, or platelets) might lead to a more comprehensive view with potential implications for the discovery of new targets and the design of future clinical trials.

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AUTHOR CONTRIBUTIONS

All authors wrote and reviewed the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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