ONCOGENES AND THE COAGULATION SYSTEM – FORCES THAT MODULATE DORMANT AND AGGRESSIVE STATES IN CANCER

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Abstract. Cancers arise and progress genetically amidst profound perturbations of the microenvironmental and systemic homeostasis. This includes the coagulation system, which is a part of the vascular milieu (niche) which remains under the control of molecular events occurring within the cancer cell genome. Thus, activation of several prototypic oncogenic pathways, such as RAS, EGFR, HER2, METSHH and loss of tumor suppressors (PTEN, TP53) alter the expression, activity and vesicular release of coagulation effectors, as exemplified by tissue factor (TF). The cancer-specific determinants of coagulopathy are also illustrated by the emerging link between the expression profiles of coagulation-related genes (coagulome) in glioblastoma multiforme (GBM), medulloblastoma (MB) and possibly other cancers and molecular subtypes of these respective tumors. The state of the coagulome is consequential for growth, metastasis and angiogenesis of established tumors, but could potentially also affect dormant cancer cells. For example, TF expression may trigger awakening of dormant glioma cells in mice in a manner involving recruitment of vascular and inflammatory cells, and resulting in lasting changes in the cancer cell genome and epigenome. Thus, coagulation system effectors could act as both targets and (indirect) inducers of genetic tumor progression, and a better understanding of this link may hold new diagnostic and therapeutic opportunities.

Introduction.

The haemostatic system represents the first and the most immediate element in the program of tissue responses to injury, and as such is a part of the biological continuum involving inflammation, angiogenesis, stromal cell recruitment, and repair [1-4]. It is increasingly clear that this succession represents more than just a temporal order of biological events, and instead reflects a coordinated web of mechanistically linked processes. In this regard, the emerging evidence suggests that the coagulation system activation not only precedes, but also to some extent regulates inflammation and angiogenesis [5-9]. There is also a growing appreciation for the fact that while haemostatic circuitry preserves the vascular integrity and patency, this molecular apparatus also ‘informs’ surrounding cells about the state of the microenvironment and about the related systemic perturbations.

Various cellular populations are molecularly equipped to receive coagulation signals, owing to their ‘sensing’ apparatus that consists of several receptors capable of binding the haemostatic system proteins. This includes tissue factor (TF), thrombin receptor (PAR-1) along with other protease activated receptors (PARs), urokinase receptor (uPAR), thrombomodulin (TM), endothelial protein C receptor (EPCR), receptors for protein S (TAM group), integrins, and growth factor receptors that can be transactivated by the coagulation system [10-14]. These molecular interactions activate intracellular signalling pathways and change the expression of several genes [15,16], including mediators of angiogenesis, inflammation and other processes relevant to cancer [10,17-19]. In this manner, the various components of the haemostatic circuitry, such as factor VIIa, Xa, thrombin, fibrin, proteins C and S and others, in conjunction

with the fibrinolytic system and platelets participate in cellular responses that extend far beyond regulation of blood liquidity.

These mechanisms are subverted in cancer in at least two important ways, namely by perpetual challenges to the vascular homeostasis posed by tumor growth, progression, angiogenesis and metastasis. An important extension of these perturbations are brought about by therapeutic interventions, including consequences of surgery, radiation, administration of chemotherapeutic and antiangiogenic agents, central venous lines and protracted immobility [20]. Collectively, these insults contribute to various forms of coagulopathy and thromboembolic disease that disproportionately affect cancer patients [21]. Indeed, thrombosis is regarded as the second leading cause of cancer related mortality [22], and a factor that independently and adversely affects therapeutic outcomes [23,24].

Coagulopathy, thrombosis and Trousseau syndrome have long been regarded as unspecific consequences of cancer-related disruption in tissue anatomy and vascular continuity, or driven by vascular hyperpermeability, inflammation, stasis, toxic side effects or other factors. This perception may have influenced the way in which cancer coagulopathy is approached from a diagnostic, therapeutic and even biological point of view, that is, mainly as a generic complication and disease epiphenomenon. There are reasons to suggest, however, that activated coagulation may possess cancer-specific properties and thereby require more biologically-based diagnostic and therapeutic consideration [10,25-28].

Oncogenic pathways and the coagulant phenotype of cancer cells

The successes and failures of virtually all cancer treatments have their sources in underlying therapeutic and biological concepts. It is generally accepted that cancers arise as a result of mutational alterations, but it continues to be debated whether those affect a set of common core signalling pathways (and amenable to repositioning of targeted agents) [29-31], or are uniquely configured in each of the emerging types and subtypes of specific cancers (necessitating precision/personalized therapy)[32,33]. A third avenue is one that proposes that genetic events ultimately shape, and cooperate with, the tumor microenvironment (niche), which therefore needs to be a part of the therapeutic paradigm [34]. The latter applies to the coagulation system, an important facet of the vascular milieu present in all cancers.

We have initially proposed that the state of the coagulation system in cancer may be influenced by oncogenic transformation [35]. This was predicated on several considerations. Thus, if coagulation system perturbations in cancer were simply an unspecific consequence of the mass effect, tissue invasion, metastasis, therapeutic interventions, or bed rest, they would be expected to correlate with the grade, but not necessarily the type of the underlying malignancy. This is, however, not the case and cancers differ greatly with respect to the risk of venous thromboembolism (VTE). For instance, pancreatic, brain and gastrointestinal cancers, as well as certain leukemias, are all associated with a relatively high risk of VTE, while skin, breast and prostate cancer are inherently far less prothrombotic [36-38]. This suggests that the specific phenotypes of cancer cells may affect the coagulation system, and do so in a differential manner, either directly, or through changes in the tumor microenvironment.

The phenotypic uniqueness of cancer cells arising in different tissues rest with two major factors: the nature of the (stem) cell of origin for a particular disease, and the configuration of mutations that activate oncogenic pathways and ultimately drive the malignant process [39]. Oncogenes affect cancer cell phenotype in a manner that impacts not only their inner workings, such as mitogenesis, but also their surroundings and systemic interactions, for example with the vasculature and the bone marrow [40]. The latter aspect of the oncogenic activity may include the state of the coagulation system, an effect that could involve all three elements of the Virchow's triad (stasis, vascular wall abnormalities, and hypercoagulability).

For example, it is well known that the overabundance and deregulation of angiogenic mediators in human cancers results in formation of aberrant vascular networks characterized by a sluggish blood flow pattern [41], hyperpermeable, procoagulant [42] and incomplete endothelial lining, as well as the exposure of subendothelial tissues and tumor masses to the circulating plasma [43]. The occurrence, magnitude and nature of these effects are different in different tumor types and thereby parallel the related oncogenic drivers, their combinations and losses of tumor suppressor mechanisms. Vascular patterns may also be a function of other permanent alterations in the cancer cell genome, epigenome and chromatin architecture, all of which could contribute to reprogramming of the cellular secretome and the profile of angiogenic factors and extracellular vesicles (EVs) released by cancer cells [40,44].

These are not merely correlative findings, and it is well documented that several dominant oncogenes, such as RAS, EGFRvIII, MET, and many other genetic lesions frequently upregulate

vascular endothelial growth factor (VEGF), the key mediator of the angiogenic circuitry [45], as well as many other proangiogenic activities [40]. Indeed, numerous, often redundant proangiogenic growth factors and angiogenesis inhibitors are regulated in this manner, along with production of extracellular matrix molecules, proteases and angiogenesis-modulating EVs harbouring a rich repertoire of bioactive mediators, as reviewed elsewhere [40,44,46].

The succession of oncogenic mutations that accompanies cellular transit through pre-malignant, indolent, benign and aggressive states is often paralleled by a corresponding progression of vascular anomalies [47,48]. Importantly, these oncogene-driven vascular changes translate into the aforementioned aberrations in haemostatic mechanisms, processes that in highly angiogenic tumors are often associated with manifest vaso-occlusive thrombosis within the tumor microcirculation and may trigger overt or subtle coagulopathy in the periphery [24,49,50]. Thus, oncogenes affect the coagulation system by triggering angiogenesis.

Oncogenic pathways also influence the recruitment of inflammatory cells, which themselves may exhibit pro-angiogenic and pro-coagulant phenotypes [51,52]. For example, myeloid cells and monocytes could release TF-containing EVs (microparticles/MPs) [53], while neutrophils may deploy extracellular chromatin traps (NET-osis) [54], or participate in other events that could add to cancer-related coagulation perturbations.

However, oncogenic pathways may also deregulate coagulation effectors more directly, through at least three different types of effects. First, certain coagulation-related genes, such as TF, which are normally expressed by various cells, either at low levels or transiently, are important regulatory targets of several oncogenic signalling pathways. This may result in abnormally high and/or constitutive expression of TF in transformed cells [8]. Second, oncogenes can trigger coagulation gene expression ectopically [55-57], that is in cancer cells originating from tissues that normally do not produce coagulation factors. Third, oncogenic and differentiation pathways may modulate biogenesis of procoagulant extracellular vesicles (EVs), including emission of TF-bearing large and small (exosome-like) microparticles that could enter biofluids and general circulation [58].

In this regard oncogenic RAS may serve as an informative paradigm. Thus, mutant KRAS oncogene was initially found to upregulate the expression, activity and EV-mediated emission of TF from colorectal cancer cells. In the same cells deletion of the *TP53* tumor suppressor exacerbated this procoagulant phenotype, as well as TF exposure and shedding [59]. Epidermal growth factor receptor (*EGFR*) and the related HER-2/ErbB2 receptor tyrosine kinase (RTK) are both upstream activators of the RAS signalling cascade [60]. It is therefore not surprising that activation, amplification or mutation of EGFR (e.g. expression of ligand independent form known as EGFRvIII), as well as overexpression of HER-2 result in the increase of TF production by glioma and carcinoma cells, respectively [61] [56].

Several oncogenes are also known to activate hypoxia response pathways and AKT signalling [60]. Consistently with this notion the loss of *PTEN* tumor suppressor resulting in AKT activation was found to drive TF upregulation and procoagulant phenotype in glioma cells especially under hypoxic conditions [62-64]. TF is also upregulated by other oncogenic kinases, such as SRC [65] and MET [66]. As indicated by elegant studies on transgenic hepatoma, MET may also regulate other regulators of the coagulation system, including plasminogen activator inhibitor 1 (PAI-1) and cyclooxygenase 2 (COX-2) [67]. In pediatric brain tumor cells the expression of TF and PAR receptors are modulated by MET, sonic hedgehog (SHH) and oncogenic microRNA (miR-520g) [68].

In acute promyelocytic leukemia (APL) where profound coagulopathy is a common occurrence, the chimeric driver gene, *PML-RAR α* , also regulates the coagulant phenotype of transformed cells, including their TF expression. This can be inferred from the effects of PML-RAR α antagonists, such as all-trans retinoic acid (ATRA), which reduce the levels of TF in APL cells relieving hemostatic complications [69]. Similarly, the *V617FJAK-2* mutation found in essential thrombocythemia (ET) is also linked with deregulated TF activity and perturbed coagulation [70].

Another process activated by oncogenic pathways and unique to cancer cells is the activation of ectopic expression of coagulation proteins. Thus, while under normal circumstances several components of the coagulation cascade are produced exclusively in the liver, and under control of vitamin K-regulated mechanisms [71], this requirement can be circumvented by cellular transformation. Indeed, production of coagulation factors VII and II has been reported to occur in

hepatocyte-unrelated cancer cells [72,73]. This is important as vitamin K antagonists are often used in thromboprophylaxis, including in cancer, and it remains uncertain whether they are effective in suppressing coagulation factor production by cells harboring mutant oncogenes.

A more direct evidence for the role of oncogenes in the ectopic production of coagulation factors stems from experiments with cancer cells engineered to express a well controlled repertoire of transforming mutations [56]. For example, in a series of GBM cell lines lacking expression of PTEN (U373, U87) the enforced overexpression of the glioma-specific oncogenic EGFR mutant gene (EGFRvIII) was found to trigger a complex rearrangement of the coagulant phenotype, including the expression of FVII, TF, PAR-1, and PAR-2. Notably, these changes rendered EGFRvIII-expressing cells not only more proficient in generating FXa in coagulation assays but also responsive to exogenous FVIIa and PAR-activating peptides in terms of expression of angiogenic and inflammatory factors such as VEGF and IL-8, respectively [56]. Similar changes were also noted in medulloblastoma cells, in which oncogenic growth factors cooperated with coagulation pathway in regulation of mediators of angiogenesis and inflammation [74]. These observations suggest that activation of oncogenic pathways contributes to both quantitative and qualitative rearrangements of the cellular coagulome and these changes may have consequences for clotting and beyond [75].

Molecular subtypes of cancer and changes in tumor coagulome.

Genetic regulation of coagulation factors in cancer cells implies that molecularly distinct subtypes of human tumors should exhibit correspondingly different coagulomes. The recent

availability of rich molecular databases collected by the The Cancer Genome Atlas (TCGA) and other profiling initiatives [32,76,77] makes it possible to examine this question *in silico*.

Indeed, molecular profiling efforts have revolutionized the very classification and definition of malignancy. For example, in spite of similar histology, location and clinical features of human glioblastoma (GBM) exists as at least four distinct molecular subgroups (proneural, neural, classical, and mesenchymal), a notion that is highly consequential for future targeted therapies, whether directed at the tumor or at the host cell compartments [32,78,79]. GBM subgroups effectively constitute different disease entities, which can be distinguished by profiles of mutational events, methylation patterns and gene expression. These features include, and are a function of, the underlying oncogenic pathways [78].

It was of considerable interest to find that molecular diversity of GBM, indeed, translates into subtype-specific features of coagulomes analysed at the mRNA level in a large cohort of tumor specimens. For example, the elevated TF and PAR-1 mRNA expression correlated strongly with the classical GBM subtype, in which upregulation and amplification of EGFR is among the most predominant characteristics [57]. This is consistent with the aforementioned *in vitro* observations, which suggested that EGFR and EGFRvIII regulate TF and PAR-1 in cultured glioma cells, both at the protein and mRNA level [56]. In contrast, in proneural GBM the expression of both TF and EGFR mRNA was relatively low, but these tumors characterized by a strong presence of stem cell markers (SOX-2) appear to express increased levels of FVII mRNA. Also in mesenchymal GBM, TF levels are lower than in the classical subtype, but, instead, these

tumors express high levels of PAI-1, uPA, uPAR, EPCR, thrombomodulin among other changes [57]. While the levels of corresponding proteins and their activities are presently unknown, it should be noted that, as expected, the levels of TF protein are non-uniformly distributed among human GBM samples, at least according to testing performed thus far (Magnus, Meehan and Rak – unpublished observation). These observations are thought provoking, as all GBMs are considered highly procoagulant, and are thought to exhibit features of intravascular thrombosis and high risk of VTE [24,49]. Whether such risk is a function of GBM subtype is presently unknown. Regardless whether this is found to be the case, it may be possible that in different patients, thrombosis could be triggered by somewhat different mechanisms and could, hypothetically, be opposed using approaches based on the coagulome of the underlying disease.

Pediatric brain tumors are usually not considered to be a source of clinically relevant thromboembolic disease [80], and therefore the role of coagulation pathway in this setting is infrequently studied [74]. It could be argued, however, that this may represent an oversight, as biological effects of the coagulation system and their oncogenic drivers in these tumors may still be relevant. In this regard, medulloblastoma (MB) represents the most common form of aggressive brain malignancies in children. MBs are associated with embryonal characteristics, and originate from the neuronal cell lineage, mostly within the cerebellum [81]. Importantly, in spite of limited histological diversity these tumors vary widely with respect to the age of onset, aggressiveness, and especially responses to therapy and prognosis [82]. Once again, in recent years the traditional description of MB has been challenged by molecular classification that distinguishes at least four molecular subgroups of the disease (WNT, SHH, Group 3, and Group 4) with vastly different clinical properties [77].

To assess whether MB subgroups entail differences in the ability of cancer cells to engage vascular system we compared their profiles of angiogenic, inflammatory and coagulation factors using the existing databases and by profiling cultured MB cells [68]. This analysis revealed marked differences in gene expression and enforced the link between oncogenic growth factor pathways and the cancer cell coagulome. For example, TF mRNA expression was preferentially elevated only in the SHH subgroup of MB, and this coincided with higher levels the proto-oncogenic MET receptor in these tumors. Interestingly, MB-derived cells co-stimulated with SHH and hepatocyte growth factor (MET agonist) exhibited a similar TF upregulation, along with altered responsiveness to thrombin and a series of unique changes in the profile of angiogenic and inflammatory factors [74]. In view of these observations, it could be argued that even in cancers not associated with clinically apparent thrombosis (like MB), coagulation system may be engaged in a consequential manner [50]. Moreover, not only the extent, but also the mechanistic nature of this interaction could be influenced by unique oncogenic circuitries that define types, subtypes and potentially individual cases of human cancers [57,74]. The implications of these relationships remain presently unexplored.

Coagulation system as modulator of tumor initiation, progression and dormancy

Arguably the coagulant phenotype of cancer cells could be viewed as one of several important effector mechanisms that link genetic progression of the disease and its biological, as well as clinical appearances in patients. This does not necessarily imply a direct proportionality between procoagulant properties and cellular, or clinical aggressiveness [83]. Rather, this is meant to suggest that deregulation of haemostatic proteins may influence the tumor microenvironment in

several pathogenetically significant ways and that many but not all of these changes are procoagulant.

Evidence to this effect includes the role of clotting factors and platelets in such fundamental processes in cancer as cellular growth, angiogenesis, metastasis, inflammation, therapeutic responsiveness and vascular comorbidities, as extensively reviewed in the recent literature [6,7,20,21,25,84-91]. Notably, pharmacological and genetic strategies targeting TF, FVIIa, thrombin, platelets and other coagulation mechanisms led to anti-tumor and anti-metastatic effects [61,92-96], which are often comparable to other ‘main stream’ targeted agents [87,93]. Moreover, anticoagulation with low molecular weight heparin (LMWH) was in several clinical studies associated with a detectable (albeit limited) survival advantage in certain cancer settings [20,97-102].

One of the less studied, but tantalizing, questions is whether coagulation system plays a role at pre-clinical, or otherwise occult stages of malignancy, such as events surrounding tumor initiation by cancer stem cells (CSCs), post-therapeutic repopulation, or tumor dormancy [61,103]. In this regard, Karpatkin first postulated that thrombin may trigger growth of dormant cancer cells [104], a notion of considerable importance given microscopic prevalence of ostensibly transformed cells in the adult and elderly population [105]. Contact with soft fibrin has also been proposed as a milieu that may enrich for CSCs [106].

It could be speculated that dormant cells could be awakened by tissue injury or repair responses such as clotting and inflammation. In this regard it is intriguing that injuries such as head trauma were reported to increase the risk for brain tumor formation later in life [107]. Similarly, higher frequency of colorectal cancer was recently described in certain (albeit not all) forms of thrombophilia, especially in association with the homozygous mutation of the Factor V Leiden [108]. Of note in this context are well controlled and elegantly executed studies of Palumbo and colleagues who demonstrated that in a mouse model where colon cancer originates on the background of inflammatory bowel disease, coagulation factors, such as fibrinogen are an essential part of the disease pathogenesis. In this setting the leukocyte binding domain of fibrinogen (Fib γ 390-396A) was required for tumor formation, a finding that suggests a link between coagulation and inflammation [109]. This is also important because in this model cancer cells are not introduced externally, but are formed endogenously in mice subjected to the pro-inflammatory protocol of azoxymethane and dextran sodium sulfate exposure, and thereby the related processes likely induce (transform) colonic epithelium to form a full blown adenoma [25,109]. It remains unclear whether the nexus of inflammatory and coagulant events is mainly a part of the supportive niche for CSCs transformed by another mechanism (mutagenesis), or whether host responses are responsible for the transformation process.

During the long natural history of adult human cancers these possibilities do not have to be mutually exclusive. As mentioned earlier, several human tissues contain morphologically transformed but dormant cells, and such cells can also be found in the bone marrow of patients in remission after clinically effective anticancer treatment [105,110-112]. Exit from such a

quiescent state represents an important and potentially targetable event in the onset and progression of the malignant disease [110].

In this regard, we observed that certain human glioma cell lines exhibit a remarkable (permanent) dormant phenotype in mice. These cells also express extremely low levels of TF and negligible procoagulant activity. These properties dramatically change upon expression of the oncogenic EGFRvIII in these cells, a change that renders them TF-positive, procoagulant and highly aggressive [56]. Notably, introduction of similar levels of TF by transfection, but in the absence of EGFRvIII-dependent transformation, also interrupted the dormant state of indolent glioma, but did so in a delayed and less aggressive manner. In this case, TF-expressing glioma cells entered into a transitory latent state, after which tumors emerged in the majority, but not all, of injected mice, and no earlier than within 2-4 months post injection.

Interestingly, within 1-3 weeks after inoculation of control and TF-transfected glioma cells their surrounding microenvironment *in vivo* underwent a profound histological rearrangement. Thus, the injection sites containing TF-high cells (but not those inoculated with TF-low control counterparts) became infiltrated with blood vessels and inflammatory cells, especially CD11b⁺ myeloid cells and F4/80⁺ macrophages. This occurred months before the tumor onset could be observed clinically and by bioluminescent imaging, and suggested that host cells could act as triggers and mediators of the TF-dependent exit of indolent cancer cells from their dormant state [113].

In order to determine whether this delayed tumor onset represents a stable phenotype of these cells, tissues were recovered re-established in culture and re-injected into secondary recipients. Surprisingly, in this case TF-high tumors emerged rapidly, indicating a stable change in the cellular phenotype that occurred in vivo in addition to the initial TF expression. This was underscored by differences in the gene expression profile between TF transfected cells and their tumor-derived isogenic counterparts (PT cells). Strikingly, the latter cells also exhibited permanent changes in their genome and epigenome that were, clearly, not a function of TF expression but arose within the TF-dependent procoagulant and inflammatory microenvironment. Thus, PT cells exhibited gene copy number variations, as indicated by SNP analysis, and had a profoundly altered DNA methylation profile.

These observations suggest that while TF may have a role in regulating cellular properties due to signalling responses its effects may also be more lasting. For example, in the aforementioned indolent glioma model TF-dependent changes in the tissue microenvironment, including angiogenesis and inflammation resulted in genetic and epigenetic evolution of tumor cells beyond the expression of procoagulant phenotype. The exact mechanisms, generality and the impact of the procoagulant milieu on the cancer cell genome and epigenome remain to be more thoroughly investigated [113].

Summary

Among many scenarios leading to development of human cancers cycles of microenvironmental and genetic changes are increasingly noticeable. Indeed, driver mutations are mostly acquired

and enriched for, through interactions of mutant (stem) cells with their surroundings. There are reasons to believe that the coagulation system is, at least in some cases, an important part of these perturbations. Haemostatic mechanisms are aberrantly activated by cancer cells harboring oncogenic mutations, and in a manner dependent on molecular subtypes of the underlying malignancy.

At the same time coagulation system is a part of the vascular milieu that may facilitate, often indirectly, the initiation of malignant process by pre-existing cancer cells or awakening of dormant tumors. It is also possible, as discussed earlier, that the coagulation pathway may contribute to a chain of events that change the genetic and epigenetic hardwiring of cancer cells, possibly resulting in oncogenic mutations. Thus, TF and coagulation effectors may play different roles not only in different cancers but also at different stages in cancer progression and in different biological settings.

These considerations raise several questions. Should clinical studies involving anticoagulants in cancer include stratification according to molecular subtype of the disease, and in view of the respective coagulomes? Is there a role for conventional, new [114], or ‘next generation (targeted)’ anticoagulation in the prevention and management of human cancers (which ones), possibly beyond thromboprophylaxis? Are coagulant events relevant occurring at older age relevant to age-related cancer incidence? If so does this involve awakening of dormant cells? Do coagulation perturbations act on such cells systemically (through emission of exosomes)?

Generalizations are tempting, but a rigorous scrutiny and careful analysis of the specific disease contexts is where some of the answers may lay.

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Figure Legends

Figure 1. Coagulome in glioblastoma multiforme is influenced by molecular subtypes.

Coagulation-related genes are expressed in brain tumor tissues as revealed by searching the available databases. While some of these changes represent quantitative increase in coagulant effectors, such as TF, in other cases coagulation related genes are expressed ectopically, as is the case for FVII (see text, adapted from Magnus et al 2013; see text).

Figure 2. A model linking differential pathways of genetic cancer progression with variability of the coagulant phenotype.

We propose that as in the case of GBM the source of deeper molecular diversity in human cancers stems from the variability of cells of origin and their transforming genomic events. The resulting formation of molecular subtypes of disease, often with similar morphology, may translate into correspondingly different interfaces with the host vascular system, and diversity in coagulation profiles. The procoagulant milieu of certain human cancers could impact genetic and phenotypic properties of cancer cells (see text).

Figure 3. Exit of cancer cells from dormancy – the possible interplay between cancer cell genome and coagulant microenvironment.

Indolent or dormant phenotype of cells lacking tumor initiating capacity may be altered in the presence of ‘wound healing microenvironment’, including angiogenesis, inflammation and procoagulant activity. Cancer cells exposed chronically to these factors may acquire permanent changes in their phenotype, epigenome and genome. In turn, oncogenic genomic events alter interactions of cancer cells with the coagulation system (see text).

Coagulomes in molecular subtypes of human glioblastoma

Figure 1. Magnus et al

Interrelationship between genetic tumor progression and cancer coagulome

Figure 2. Magnus et al

Exit of cancer cells from dormancy – a hypothesis

reciprocal interplay between cancer cell genome and coagulant microenvironment

Figure 3. Magnus et al