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TRANSIZIONE EPITELIO-MESENCHIMALE (EMT) E TRANSIZIONE MESENCHIMALE-EPITELIALE (MET) COME MARKER PROGNOSTICI NEI CARCINOMI E NEI SARCOMI

EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT) AND MESENCHYMAL-TO-EPITHELIAL TRANSITION (MET) AS PROGNOSTIC MARKERS IN CARCINOMAS AND SARCOMAS

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Abstract

Metastasis is the hallmark of cancer malignancy and is correlated with poor prognosis in both animals and humans. In this thesis, the key steps of metastasis are described, focusing on the evolution of the “Seed and Soil” Theory first introduced by Steven Paget more than a century ago. The role of Epithelial to Mesenchymal Transition (EMT) has emerged in a series of physiologic and pathologic event, including embryogenesis, fibrosis and cancer. EMT is inextricably related to many aspects of tumor progression, such as tumor growth, tumor microenvironment, premetastatic niches and immune evasion. Based on this, new EMT-related cellular prognostic markers have been proposed. The thesis then focuses on the actual knowledge regarding Mesenchymal to Epithelial Transition (MET), the reverse process of EMT, especially in sarcomas, pointing out its promising role as positive prognostic marker. In the end, this work shed light on the promising future therapeutic strategies involving the repression of EMT in carcinomas and stimulation of MET in sarcomas. A promising future therapy might be exploited by viral oncolysis that represent an efficient interplay between Human and Veterinary medicine proving and supporting in the most profitable and promising way the concept of “One Health-One Medicine”.

Riassunto

La metastasi è il segno distintivo della malignità neoplastica ed è correlata con una prognosi clinica sfavorevole sia negli animali che nell'uomo. In questo lavoro di tesi vengono descritte le fasi chiave delle metastasi, concentrandosi sull'evoluzione della “Seed and Soil” Theory introdotta per la prima volta da Steven Paget più di un secolo fa. Il ruolo della transizione

Epitelio-Mesenchimale (EMT) è emerso in una serie di eventi fisiologici, come nell'embriogenesi, e patologici, tra cui la fibrosi e le neoplasie maligne. L'EMT è indissolubilmente legato a molti aspetti della progressione neoplastica, come la crescita della cellula neoplastica, il microambiente tumorale (TME), le nicchie premetastatiche e l'evasione della cellula neoplastica dal controllo del sistema immunitario. Sulla base di questo, sono stati proposti nuovi marcatori cellulari prognostici legati ai EMT. Il lavoro di tesi si concentra poi sulle conoscenze attuali riguardanti la transizione Mesenchimale-Epiteliale (MET), il processo inverso della EMT, soprattutto nei sarcomi, evidenziando il suo promettente ruolo di marker prognostico positivo. Alla fine, questo lavoro di tesi fa luce sulle promettenti strategie terapeutiche future che comportano la repressione dell'EMT nei carcinomi e la stimolazione della MET nei sarcomi. Una terapia futura promettente potrebbe essere l'uso di vettori virali per provocare l'oncolisi (oncolisi virale), che rappresenta un'efficiente interazione, di patologia e clinica comparata, tra l'oncologia umana e veterinaria, dimostrando e sostenendo nel modo più proficuo e promettente il concetto di "One Health-One Medicine".

Introduction

Cancer in dogs is one of the biggest clinical concerns, both in terms of mortality[1] and overall incidence[2] and is becoming more and more a model of study of several human tumors too. During the course of the decades, human and veterinary medicine have been interconnected and fruitful results have come from this bond. This concept is described as "One Health-One Medicine", and has developed through the years promoting the collaboration between physicians and veterinarians[3]. This is proven by the numerous comparative studies and animal models for human diseases.

Comparative studies concerning cancer in dogs and humans include many different tumors, such as melanoma[4], osteosarcoma[5] and prostatic adenocarcinoma[6].

Metastasis

The metastatic process can be briefly resumed as the process that allows tumor cells to spread away from the primary site and colonize new sites. It is considered one of the hallmarks of cancer malignancy, and the worst stage[7]. The metastatic process is a multistep cascade of events, that require a correct tumor cells seeding in order to obtain a well-established secondary tumor. The first studies about metastasis were published in the end of XIX century, laying down the basis for all the different theories, that followed decades after decades, aiming to explain this pathological event. In 1889, Steven Paget, a British surgeon, published a study describing the "Seed and Soil" theory, with which he proposed that metastatic cells would not randomly spread in organs, rather with a precise interaction with specific host organs. Taking the metastatic cells as "seed" and the host organs as "soil", he concluded that only when these interactions were possible, i.e. the microenvironment of the host organ being compatible with the metastatic cells, metastasis could take place[8] One prior theory about metastasis was proposed, in the middle of XIX Century, by Rudolf Virchow who described metastasis as the result of cancer cells emboli arrest in the organs vasculature[9]. Interestingly, in 1922, another theory was formulated by James Ewing, explaining the whole metastatic process as a result of anatomic and vascular features of the involved organs. Ewing described organs as passive receivers of potentially metastatic cells. According to his theory, it was vasculature, number of potentially

metastatic cells, and morphology of tissues that conditioned the metastatic event. The more an organ received tumor derived cells through its vessels, the higher the probability to be prone for metastasis formation. The reason behind seemed to be linked with the increased number of those cells that would have been trapped in the organ itself, increasing the likelihood of metastasis formation. This explained the relationship between primary tumor and metastasis in adjacent organs (or other lobes of the same parenchymal organ), but did not explain why in some highly vascularized organs (e.g. heart, kidneys, spleen) metastases were not often described in most tumors. Moreover, some organs with a relatively low percentage of total circulatory volume such as adrenals, bones or brain, had showed to be frequent targets of metastases for specific cancers, neither necessarily close to them, nor vascularised from the same vessels[10]. Furthermore, in the 1952 Irwing Zeidman and JoAnne Buss showed that cells from different tumors interacted differently to the same capillary bed of a given organ[11].

About 30 years later, in 1960, evidences from David L. Kinsey supported the idea that Ewing's model of metastasis did not fully explain the process[12]. Afterwards, in 1979 a better comprehension of the process came from Paul H. Sugarbaker, who stated that while local metastasis could be conditioned by mechanical factors (lymph vessels, anatomic issues), distant metastasis must be site specific, for which a better explanation had to be investigated[13]. These studies were fundamental for Hart and Fidler investigations during the following years. Interestingly, they supported Paget's "Seed and Soil" theory showing how B16 melanoma cells could reach all organs with vasculature, but mostly targeted specific ones[14].

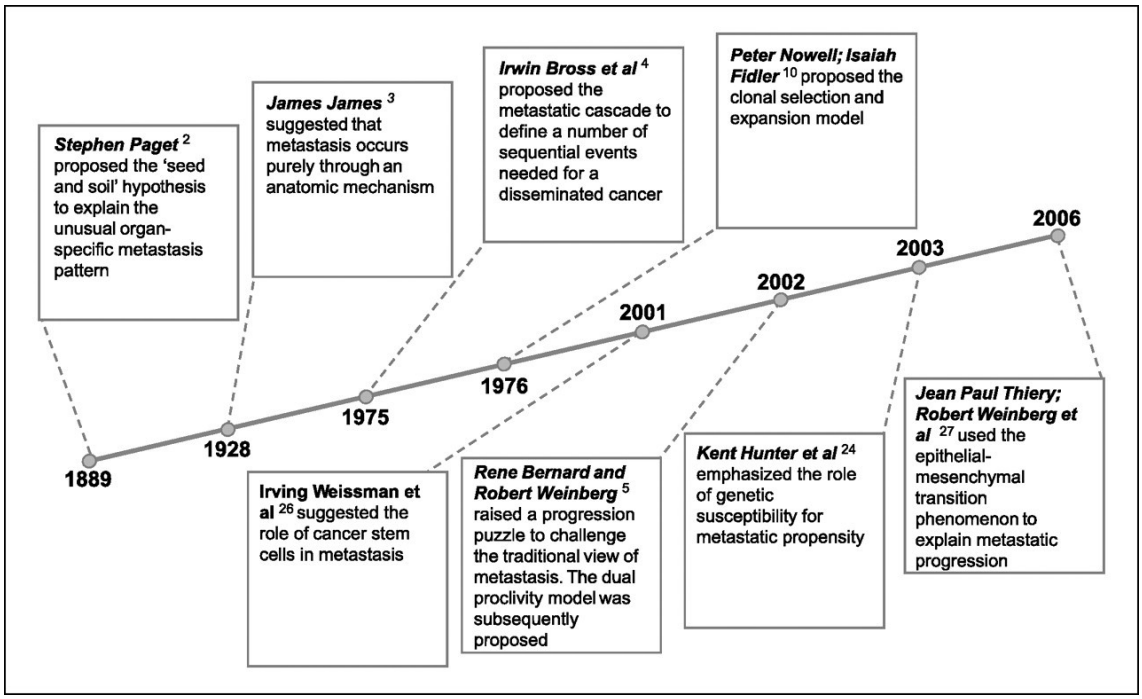

Figure 1: Developments of research concerning cancer metastasis during the past decades, starting from the ''Seed and Soil'' Theory of Stephen Paget to the most recent findings over the Epithelial to Mesenchymal Transition (EMT) and Mesenchymal to Epithelial Transition (MET). Picture taken from Dong et al.[15].

Steps of Metastasis

The metastatic event is a complex and challenging multistep process.

The first steps of metastasis begin when malignant cells detach from the primary tumor site, losing their connections with the surrounding cells and extracellular matrix (ECM), acquiring motility and migratory features, finally interacting with ECM and reaching the vessel[16]. All these morpho-functional changes in cells are possible in epithelial tumors, because of a process called Epithelial to Mesenchymal Transition (EMT). This process is characterized by down-regulation of epithelial features and due to a prompt activation of the so called "master genes regulators", a mesenchymal phenotype is gradually developed[17]. Extensive studies focused on this event, illustrating

its role in several tumors, proposed to use it for prognostic, diagnostic and even therapeutic approaches[18–20].

However, only a small percentage of the circulating tumor cells survives this step and will exit the circulation through a process called extravasation; this last process depends on many factors comprising the flow and remodelling of endothelium. An elegant study by Follain et al. showed for the first time *in vivo* the effect of blood flow on arrest, adhesion and extravasation of circulating tumor cells (CTCs)[21]. Moreover, cell plasticity determines the interactions between CTCs and endothelium, allowing extravasation[22].

Indeed, CTCs need a favourable microenvironment and it is believed that the primary tumor transmit signals to prepare the so called "premetastatic niches" in secondary target-organs[23]. It is noteworthy that these niches can be established by three main components: tumor-mobilized bone marrow derived cells (BMDCs)[24], tumor derived components and local stromal microenvironment of the host organ[25].

Research is focusing more on cell microvesicles and exosomes, lipid bilayered enclosed structures that are involved in a series of events as a mean of communication, thanks to the transport of proteins or genetic material. Their role is showed in cell differentiation[26], autocrine or paracrine regulation of angiogenesis[27] and tumor[28]. Among the class of the tumor derived components, microvesicles and exosomes can both be listed and grouped as extracellular vesicles (EVs) and tumor derived secreted factors (TDSFs). They promote the formation of the premetastatic niches[29], are involved in immunosuppression[30,31], as well as angiogenesis stimulation[32], progress in tumor invasion[33] and metastasis[29].

Epithelial to mesenchymal transition (EMT)

EMT is a cellular mechanism involved in different processes in which epithelial polarized cells with cell to cell adhesions are modified by a series of regulatory master genes to obtain a mesenchymal phenotype[34]. EMT involves the suppression of E-cadherin and a switch to the expression of mesenchymal cadherins such as N-cadherin[35] or cadherin 11[36]. At the center of this process is the inhibition of E-cadherin, the major mediator of cell adhesion in Adherens Junctions. Adherens junctions are members of a family of cell contacts sharing a common association with the microfilament system[37]. The main functional difference between epithelial and mesenchymal adherens junctions is their inter-cellular stability: epithelial ones are stable in the range of hours to days, whereas mesenchymal ones are transient (minutes to hours)[38]. Claudins and occludin are integral membrane proteins localized at tight junctions, which are responsible for establishing and maintaining epithelial cell polarity[39], and it has been proven Snail, master regulator of EMT, can down-regulate the tight junction components independently of E-cadherin downregulation[40].

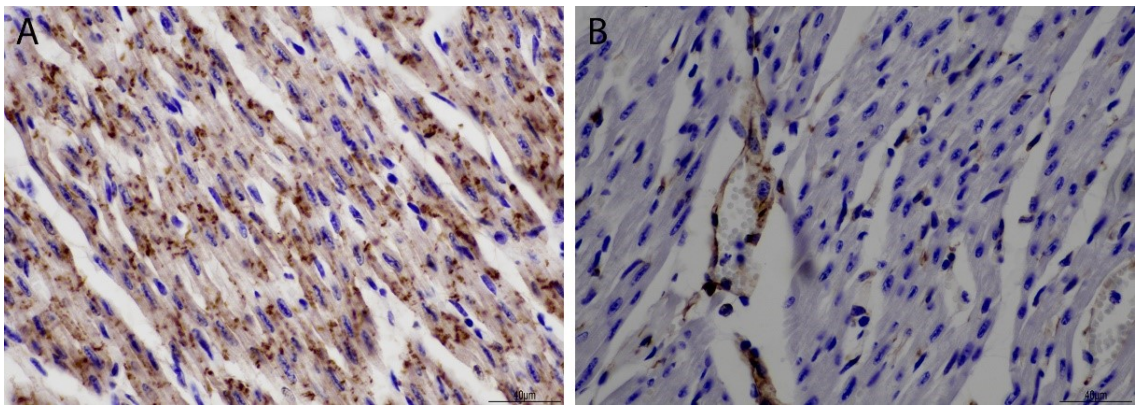

Figure 2: The panel (A,B) show the normal expression of typical mesenchymal markers. A: Cardiomiocytes from a dog expressing membranous N-cadherin signal at the Z-junctions (10x magnification). B: Endothelial cells and fibroblasts from a dog heart expressing cytoplasmic vimentin signal (20x magnification). Mesenchymal markers

expression has been detected using ABC-DAB immunohistochemical method. (Pathology Unit-Department of Veterinary Science, University of Parma).

With EMT, tight junctions are deconstructed and their proteins are relocalized and/or degraded. The dissolution of tight junctions during EMT is accompanied by decreased claudin and occludin expression, and the diffusion of zonula occludens 1 (ZO1) from cell–cell contacts[41]. During the destabilization of adherens junctions, epithelial cadherin (E-cadherin) is cleaved at the plasma membrane and subsequently degraded, thus impeding interaction with β-catenin[42]; interestingly, if not degraded, β-catenin can have a role in transcription through Wnt pathway[43]. EMT also disrupts desmosomes, as Snail2 (Slug) cause their dissociation[42,44]. During EMT junction proteins are not expressed because of transcriptional suppression , which, in fact, stabilizes the loss of epithelial junctions[45,46].

EMT can be both full or partial, and there can even be subsequent cycles of EMT and its reverse process, MET (mesenchymal to epithelial transition). First observed in 1982[47], research has widely described this event in many different moments of embryogenesis, fibrosis and cancer development, but many issues remain to be investigated to this day.

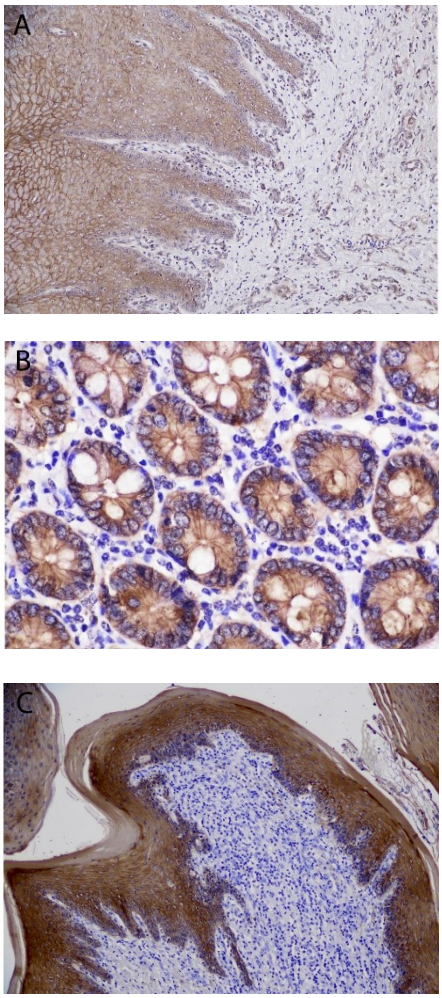

Figure 3: The panel (A, B, C) show the normal expression of typical epithelial markers. A: epithelial cells from a dog cutaneous epidermal layer expressing membranous E-cadherin signal. (4x magnification). B: epithelial cells from a dog large intestine tract expressing membranous β-catenin signal. (20x magnification). C: epithelial cells from a dog cutaneous epidermal layer expressing cytoplasmic cytokeratin signal (10x magnification). Epithelial markers expression has been detected using ABC-DAB immunohistochemical method (Pathology Unit, Department of Veterinary Science, University of Parma).

The regulation of EMT

Multiple genes, transcription factors, microRNAs, long-non-coding RNAs, epigenetic modifications and chromatin remodelling are involved in the regulation of EMT. EMT "Master Regulators" include Zeb, TWIST, SNAIL and others, each one of which has been extensively studied. Their role in EMT is to bind to DNA in promoter and enhancer sequences, working together with epigenetic regulators[48]. There are multiple reciprocal networks between transcription factors (TFs) and between TFs and miRNAs, regulating EMT, all following a complex temporal hierarchy, counting at least 59 EMT Master Regulators[49]. The role of E-cadherin is central in EMT; E-cadherin is a protein of the cadherins family, that mediate calcium

dependent cell-cell adhesion (*Ca* and *adherens* form the word Cadherin), functioning as key molecules in the morphogenesis of a variety of organs[50]. E-cadherin is typical of epithelial tissues, and behaves as a tumor suppressor gene and plays diverse roles in regulating cell polarity, differentiation, migration and stem cell-like properties[51,52]. It is regulated by the gene CDH-1[34], and one of the main mechanisms for loss of E-cadherin involves CDH-1 repression by EMT promoting TFs; the role of these TFs is therefore oncogenic, as they bind E-boxes in the promoter region of CDH-1, thereby repressing it[53].

Snail

Snail family members are zinc finger transcriptional repressors, including Snail1 (*Snail*) and Snail2 (*Slug*); their main role in EMT is the suppression of E-cadherin, also called uvomorulin, a protein typical of epithelial tissues[54]. The gene regulating Snail1 is SNAI1, the activity of which is stimulated for example by NF-kB[55], protein kinase Akt[56], and in some cases erythropoietin[57].

Snail1 and Snail2 are induced by a variety of pathways such as TGF-β[58], Notch in tumors associated hypoxia stress and in cardiac tissue development[59,60], Wnt pathways[61,62], reactive oxygen species[63] and hypoxia stress[64,65]. There are also repressors of Snail2, as in the case of mammary gland development, EMT and mammary gland cancer metastasis, where the short splice variant of transcription factor Singleminded-2 (SIM2s) and ELF5, an ETS (E twenty-six)-domain transcription factor family member, was shown to directly bind to the Snail2 promoter to inhibit Snail2 transcription[66,67]. Interestingly, both SIM2s and ELF5 are essential for mammary gland ductal development or alveologenesis during pregnancy,

and both are frequently lost during breast cancer development (*ibidem*). Mammary gland-specific knockout of either SIM2s or ELF5 hinders mammary gland development, but also induces EMT-like changes in those epithelial cells (*ibidem*). It has also been shown that ELF5 is linked with the Notch pathway for the mammary epithelium stem cell fate[68]. It is of note that not all Snail family members trigger EMT with the same potency[69], because zinc fingers and other domains change between different Snail TFs[70]. Snail family members not only repress CDH-1 gene; as shown by Guaita et al. they were found capable of repressing other epithelial markers, such as claudins 1, 3, 4, 7, occludins, cytokeratins and mucins[71].

Twist1

Twist-related protein 1 (TWIST1) is a basic helix-loop-helix transcription factor encoded by the TWIST1 gene[72], has a basic domain interacting with core E-box sequence 'CANNTG,' a helix–loop–helix (HLH) domain that mediates homodimerization or dimerization with E12/E47, and a highly conserved C-terminal domain, called "Twist box"[73]. Twist is implicated multiple epithelial cancers through its EMT promoting function, and it was shown to correlate with poor prognosis and invasiveness[74,75]. Its role is also described in embryogenesis, where it has been called "neural crest specifier" for its role in NC formation through EMT-promoting activity[76]. Interactions between Twist and other core epithelial-mesenchymal transition factors are controlled by GSK3-mediated phosphorylation[77]. An interesting study by Li et al. showed EMT and cancer stemness properties can be obtained with chronic treatment with TNF-α, a pro-inflammatory cytokine, which activates Twist1 in a NF-kB dependent fashion[78]. Twist represses E-cadherin not only binding CDH-1, but also inducing Snail1 or

Snail2, as Casas et al. showed in a study where knockdown of Snail2 resulted in no E-cadherin suppression by Twist1[79].

Zeb

Zeb family comprises ZEB1 and ZEB2, containing multiple independent domains to interact with other transcriptional regulators[80] and trigger an EMT by repression of epithelial markers and activation of mesenchymal ones[81,82]. ZEB1 and ZEB2 activate N-cadherin and Vimentin expression, markers of mesenchymal phenotype, and repress E-cadherin through the binding of E-boxes of CDH-1 promoter region and the recruitment of corepressors[83]. The repression of E-cadherin is obtained by ZEB1 recruiting a chromatin remodelling protein[84]. Phosphorylation of ZEB1 varies in different cell types[85], and both ZEB1 and ZEB2 repressing activity can be modulated by post-translational modifications such as SUMOylation by Pc2 or acetylation[86]. Nicotinamide adenine dinucleotide-dependent histone deacetylase (SIRT1) is recruited by ZEB1 to repress the E-cadherin promoter and also induces ZEB and Snail factors but not Twist[87]. Moreover, ZEB2 mRNA also functions as a competitive endogenous RNA (ceRNA) squelching other miRs targeting other transcripts, thus activating their expression[88], and can be controlled at the protein level, for instance by YB-1, a protein associated with increased invasiveness in breast carcinomas[89]. Even steroid hormones and growth had shown to upregulate ZEB in some cancers[90,91]. MiR200 family can regulate, through post transcriptional control, ZEB1 and ZEB2[92].

Other EMT Transcription Factors

A lot of other transcription factors has been described, including Goosecoid[96,98], LBX1[96–98], FOXC2[99–101], ETS-1[102–104], LEF-1[105–107]. Pioneer factors are proteins that bind compact chromatin to facilitate the binding of other transcription factors[108,109], and the most studied for its role in EMT, if FOXA2, that is also a transcriptional activator of E-cadherin[110]; FOXA1 seems to be a key mediator of hormonal response in both breast and prostate cancers in humans [111–113]. In some cancers, PRRX1 was found to induce EMT and worsen prognosis, whereas its silencing suppressed invasion, migration, cell proliferation and EMT itself[114–117].

All of these non-canonical EMT TFs have very specific direct roles in distinct tumors, but also have interaction with the canonical EMT TFs like Snail and ZEB, meaning they probably affect EMT in an indirect way too[118].

MicroRNAs

MicroRNAs (miRNAs) are non-coding RNA molecules, with a length of approximately 21–23 nucleotides, that regulate gene expression at the post-transcriptional level[119–121]. MiRs regulate invasiveness and metastasis by targeting the transcripts of a large number of genes involved in EMT/MET regulation, including those of EMT-ATFs, adding other interaction to the complex regulating network[122]. It was demonstrated, for example, that the loss of miR-200 correlates with a lack of E-cadherin expression in invasive breast cancer cell lines and in breast tumor specimens, supporting an *in vivo* role for the miR-200 family in EMT repression[92]. Overexpression of the individual miR-200 members or separate clusters represses EMT by directly targeting and downregulating ZEB1 and ZEB2, resulting in enhanced

E-cadherin expression and inhibition of murine mammary tumor cell migration and cancer cell motility[123,124].

Reactive Oxygen Species

ROS, continuously generated from mitochondrial respiratory chain, include superoxide radical (O2-), hydrogen peroxide (H2O2), hydroxyl radical (.OH), and singlet oxygen; they are continuously produced *in vivo* under aerobic conditions. Interestingly, ROS serve as a second messenger in the intracellular signal transduction pathway for a variety of cellular processes, including cell cycle progression, apoptosis, and aging and are involved in over 150 human disorders[125]. ROS activate numerous signalling pathways, including MMPs, integrins, EGF, EGFR, VEGF, TGF-β, HIF-1, HGF, NADPH oxidases, p53 and others[126–128], and the probable reason of this is that cells under oxidative stress are likely to have acquired adaptive mechanisms to counteract the potential toxic effects of elevated ROS to promote many cell survival pathways and factors[129]. ROS play a key role in TGF-β1-induced EMT primarily through activation of MAPK and subsequently through ERK-directed activation of Smad pathway[130] Antioxidants effectively inhibited TGF-β1-induced cellular ROS, p38 MAPK, ERK and EMT (*ibidem*). Interestingly, early redox mechanisms were found to turn-on the switch for hypoxia-dependent acquisition of EMT characteristics[131]. Another recent example of the role of ROS as second messenger for EMT is given by the study of Bayurova et al., showing that HIV-1 Reverse Transcriptase enhances tumor growth and metastasis formation via ROS-dependent upregulation of Twist[132].

Exosomes

A new metaphor for the "Seed and Soil" theory addresses extracellular vesicles as "fertilizers" of cancer cells (the "seed") in their respective host organ (the "soil")[133]. Exosomes are mediators of the crosstalk between metabolic organs, but also important factors for organ specificity of metastasis[134–136] and can induce EMT[137–139].

Microvesicles are small membrane-enclosed structures that are thought to be shed from a variety of cell types, and can be found in several body fluids[140,141]. They are morphologically distinct from exosomes and their dimension is more than twice the one of exosomes; other differences arise from biogenesis and release[142] The role of microvesicles is described in several processes including inflammation and coagulation[143], but is also described in tumors[144], where their role varies from Tumor Microenvironment (TME) regulation to Multi Drug Resistance, but also angiogenesis, metastasis and EMT[25,142]. Microvesicles, for example, can regulate MMPs activity favouring matrix degradation, a key step in the metastatic cascade that is often linked with EMT features[145,146]. Microvesicles can also be secreted and delivered to recipient cells inducing them to undergo EMT[147]. Exosomes and microvesicles are classified as Tumor-derived Secreted Factors (TDSFs), and their role in tumor signalling and metastasis is under research, hopefully leading to new strategies for cancer diagnosis, cancer prognosis and possibly cancer therapy in the future[148–152].

EMT in embryonic life

EMT is an important mechanism in different points of embryogenesis, as most of the tissues undergo different cycles of EMT and reverse program

Mesenchymal to Epithelial Transition (MET) [34]. Tight junctions, adherens junctions, desmosomes and gap junctions keep epithelial cells well bound to each other, allowing them to structure as polarized cells organised in layers. One of the first step of embryonic life is gastrulation, that is the formation of three embryonic germ layers. These are the ectoderm, mesoderm and endoderm, originating from the epiblast, the first epithelial germ layer. In gastrulation the ectoderm is positioned outside, the mesoderm in the middle and the inner layer becomes the endoderm. Thanks to an EMT process, called ingression, mesoderm and endoderm detach from the outer epiblast and are internalized[153]. Later, in the formation of a dorsal structure of the embryo called neural crest, EMT becomes once again of pivotal role, especially because this process is what distinguish vertebrates from all other animals; thanks to some similarities, in fact, it has also been addressed as a "second gastrulation" of vertebrates[154]. Other tissues during embryogenesis need EMT to develop, as in the case of kidneys: in order to obtain a functional kidney, multiple rounds of EMT and MET need to take place[155].
An interesting link between physiologic EMT during nephrogenesis and two frequent tumors in kidneys has been investigated by Balasubramaniam et al. in a study of NCX1, a sodium-calcium interchanger. Willms Tumor, a cancer typical of children, develops as a result of an arrest in development of renal mesenchymal cells[156], whereas Renal Cell Carcinoma (RCC) results from a pathological EMT like process of renal epithelial cells[157]. The study investigated the effects of a knockdown of NCX1, showing its relevance in the expression of E-cadherin, tightness of intercellular junctions, presence of mesenchymal markers. How NCX1 is down-regulated in RCC is nonetheless unclear to this day[158].

Another example of physiologic EMT during embryogenesis is in cardiac tissue development, in which some of its main signaling pathways such as Notch, Bmp2 and Wnt/β-catenin, drive a primary EMT[159–162]. The cardiac valve formation follows a different path, thanks to a very similar process called Endothelial to Mesenchymal Transition (EndoMT), in which endothelial cells detach from vessels and, to various extents, gain mesenchymal phenotype[163]. Moreover, Ubil et al showed the presence of the reverse process, called Mesenchymal to Endothelial Transition, during revascularization of myocardium by cardiac fibroblast after ischemic cardiac injury[164].

EMT in fibrosis

The role of EMT has been confirmed in cutaneous wound healing both *in vivo*, *in vitro* and *ex vivo*, as keratinocytes showed degradation of ECM, expression of the mesenchymal markers fibroblast-specific protein 1 (FSP1) and/or vimentin; moreover, injury-inducible mobilization of epithelial cells involving TNFα and bone morphogenetic protein (BMP)-2 produced a mesenchymal phenotype in migrating keratinocytes[165]. In an experimentally induced injury of murine lacrimal gland, inflammation induced by interleukin-1 (IL-1) injection triggered the generation and migration of cells with mesenchymal phenotype to the site of injury, but these cells subsequently reverted to an epithelial phenotype once repair was complete[166]. Fibrosis is a final stage of chronic inflammation in which resident fibroblasts acquire a smooth muscle cell-like phenotype, becoming myofibroblasts, and secrete excessive amounts of extracellular matrix (ECM)[167]. In physiologic remodelling process during healing, the main orchestrator is the contractile myofibroblast, which secretes large amounts

of ECM proteins and aids in the mechanical closure of the wound[168,169]. TGFβ1, a critical regulator of EMT signalling and physiologic wound healing, is also the major driver of fibrosis[170,171], partly thanks to its effect on myofibroblasts[172].

The two most studied organs for the pathogenesis of fibrosis are the kidney and the liver[173,174], but research is also focusing on its role in other organs, such as the heart[175–177] and the lung[178].

EMT in renal fibrosis

About 8% of US human population suffers from Chronic Kidney Disease (CKD)[179], and what's interesting is that, independently of the etiology, the final outcome is common; this includes renal fibrosis, associated capillary loop destruction, inflammation and damage of tubules and capillaries leading to atrophy and rarefaction of these structures[180]. A common final stage kidney fibrosis occurs in 30/40% of diabetic nephropathies[181], and the role of EMT in it has been shown but not fully explained. EMT induces local fibroblasts to become myofibroblasts, as showed by Iwano et al.[182], with several studies *in vitro* confirming this, but the effective role *in vivo* remains highly debated[183,184]. What is unclear is precisely the origin of these myofibroblasts[185], varying from bone marrow, pericytes, renal epithelium, vascular endothelium[186]. New studies suggest these different origins do not exclude each other and can be present at the same inflammation site[187]. Of recent interest is the role of EndMT in diabetic nephropathy[188]. One of the problems in demonstrating direct involvement of EMT in renal fibrosis is about the use of markers like alfa-smooth-muscle actin (α-SMA), vimentin,

desmin, fibroblast specific protein-1 (FSP-1) and β-catenin[189,190]. For what concerns dogs, a study by Aresu et al showed the role of EMT in kidneys, using immunofluorescence in the two most common canine glomerular renal diseases, membranous glomerulonephritis and membrano-proliferative glomerulonephritis. The markers used in this study were cytokeratin, vimentin, α-SMA and Proliferating Cell Nuclear Antigen (PCNA), with cytokeratin and vimentin being the most suitable ones for evidence for EMT in dog renal fibrosis[191].

EMT in hepatic fibrosis

Fibrosis is a natural consequence of damaged tissue repair, but often ends up being aberrant and uncontrolled, causing organ dysfunction[192], and is also one of the main events involved in hepatic cirrhosis[193]. The amount of collagen, elastin, and tenacin can in fact be 3-5-fold higher during hepatic fibrosis, thanks to the involvement of myofibroblasts or activated local fibroblasts[193,194]. Physiologically, chronic inflammation driven fibrosis is limited and eventually avoided by inactivation or apoptosis of myofibroblasts and the resolution of the scar. During chronic liver diseases, mechanisms driving or counteracting fibrosis are not balanced, leading to a persistent activation of hepatic myofibroblasts[195]. EMT leads to the loss of E-cadherin, Zonula Occludens-1 (ZO-1), replaces α-SMA, matrix metalloproteinase (MMP)-2, MMP-9, collagens, and vimentin[196]. The increased deposition of ECM in hepatic tissue thanks to EMT demonstrates its role in hepatic fibrosis[197]. In rats, the role of TGF-β1 has been shown to be of pivotal role in liver fibrogenesis[198], as it inhibits ECM degradation and promotes its deposition[199,200]. Another demonstration of the role of EMT in hepatic fibrosis is given by SMAD7: deletion of SMAD7 promotes it, whereas

overexpression of SMAD7 protects against it[201], also consistent with what has been described in different tumors[202–205]. A key difference between quiescent HSCs and myofibroblasts was demonstrated in cell culture, where the latter showed no negative feedback between SMAD7 and TGF-β1, indicating the lack of a central inhibition pattern for EMT[206]. A complex series of other pathways can be listed, such as SMAD4/TGFβ[207], and miR-199 and miR-200 enhancing profibrotic genes and being key regulators of EMT[208]. The role of EMT in hepatic fibrosis is being exploited for the development of new possible therapies, as in the case of MiR-146a, that seems to attenuate liver fibrosis by inhibiting it in hepatocytes, targeting both TGF-β1 and SMAD4[209]. An experimental study confirmed hypoxia cell colture condition too induces hepatic stromal cells to produce TGFβ, once again establishing an EMT process[210]. In dogs, one study showed staining area and intensity of α-SMA in hepatic stellate cells (HSCs) correlated with the intensity of hepatic fibrosis, giving a more contractile and profibrotic phenotype to these cells[211]. α-SMA is used in humans and rodents to confirm activation of HSCs and portal myofibroblasts in liver disease[212], but the reliability of this protein in dog hepatic fibrosis, appears not to be confirmed by other studies[213–215]. A possible future marker of severity of hepatic fibrosis in dogs is the aforementioned EMT-inducing transforming growth factor-β1 (TGF- β1)[216].

EMT in cancer metastasis

In the absence of E-cadherin expression , individual tumor cells can migrate with a mesenchymal movement i.e. a directional migration with proteolysis at the leading edge or an amoeboid movement, in the absence of a precise direction and polarity[217] In the presence of E-cadherin expression, instead,

tumor cells use collective migration pathway[217,218]. One hallmark of EMT is the shift from E-cadherin to N-cadherin expression, a “cadherin switch” that does not imply all E-cadherin is to be replaced; evidence shows that N-cadherin expression increases as cells undergo EMT, but it is not clear how that is regulated[219–221], although Twist and Snail have been found to induce it in some cases[222,223].

Integrins are the major class of receptors involved in homotypic and heterotypic adhesive events[224], and provide a link between the outside environment and cellular responses related to motility. These functions have shown in immune cell trafficking, homeostasis, and migration of cancer cells, and have been subject to study for therapeutic innovation protocols [225–228]. In malignant transformation in the epithelium, cells lose their dependence on integrin-mediated interactions with the extracellular matrix and resulting signaling events, while adherens junctions are lost, mainly because of promoter methylation or transcriptional repression of CDH-1[45,229,230].

Other structures of adhesion are hemidesmosomes, multiprotein complexes present in stratified epithelia, that are altered during EMT[231]. Integrins are also able to improve anchorage-independent survival of circulating tumor cells (CTCs)[232]. Integrin α6β4, present in hemidesmosomes, interacts with the keratin intermediate filament instead of actin filaments, and it is the only integrin to do so. In tumor cells, the lack of polarity is displayed by actin protrusions, which will disassemble the hemidesmosomes and mediate cell migration and invasion[233]. After the EMT-associated loss of hemidesmosomes, α6β4-integrin becomes

phosphorylated and relocates to an F-actin–rich protrusion, where integrin interacts with actin filaments[231,234].

While evidence of EMT in metastatic cancer cells is widespread, it has been complicated to demonstrate unanimously the presence of it *in vivo*; in 2008, Trimboli et al. showed for the first time *in vivo* the existence of EMT in breast cancer, using Rosa26LoxP reporter mouse to genetically mark tumor epithelial and stromal cells independently and determine their fate during tumor progression. EMT resulted to be associated only with *myc*initiated breast tumors[235] This means that the occurrence of EMT to different degrees depends on the initiating oncogenes (*ibidem*). Many studies showed quite different results, sometimes contradictory, and the exact role of EMT during metastasis formation is under debate. Clusters of CTCs have been found in the bloodstream of cancer patients in several studies, certifying the presence of a collective migration *in vivo*[236,237]. Plakoglobin, an adherens junction protein, was found crucial for cluster formation, while its knockdown resulted in reduced metastatic spread[238]. Lecharpentier et al. showed that the majority of isolated or clusters of CTCs in patients with advanced metastatic Non-Small Cell Lung Cancer (NSCLC) show a dual epithelial–mesenchymal phenotype. This confirms that EMT is a relevant process for invasion and metastasis in these patients[239]. In mouse, the role of Twist in lung cancer, a master regulator of EMT, was investigated by Yang et al., showing that interfering with its expression through siRNA3 led to a drastic decrease in the number of metastases but did not prevent them[74]. In a study by Lu et al., it was shown CTCs from human lobular breast cancer were predominantly epithelial, while those from HER2+ and triple negative subtypes were mostly mesenchymal; this provided evidence of EMT in human breast cancer specimens[240], consistent with other studies in

mice[241,242]. In another study it was shown that the inhibition of EMT by overexpressing miR-200 does not affect lung metastasis development, even though EMT plays a role (in the same cancer) in chemotherapy resistance[243]. In 2015, Zheng et al. published a study defining EMT as "dispensable" for pancreatic cancer metastasis, but the methods used only included the deletion of Snail and Twist1; cells were also stained for other EMT markers but without marking the tumor cells with a lineage-specific tracer[244]. As discussed by Aiello et al., further studies should demonstrate or contradict this assessment[245]. In another study by Aiello et al., it has been shown EMT markers are expressed in micrometastases, whereas epithelial markers become again expressed the more the metastasis grows; milli- and macro-metastases exhibited reduced staining with these markers relative to nano-metastases[246]. The same study also showed a link between myofibroblasts and the metastasis dimension, as the number of associated myofibroblasts significantly increased with lesion size; this has been shown by an increase in αSMA+ area at larger lesions (*ibidem*).

To show EMT role in metastasis other studies have been published; in Tran et al. study, it has been shown Snail expression is sufficient to drive breast cancer cells into the circulation, but it must be down-regulated once those cells reach the lung in order for them to successfully colonize the pulmonary parenchima[247].

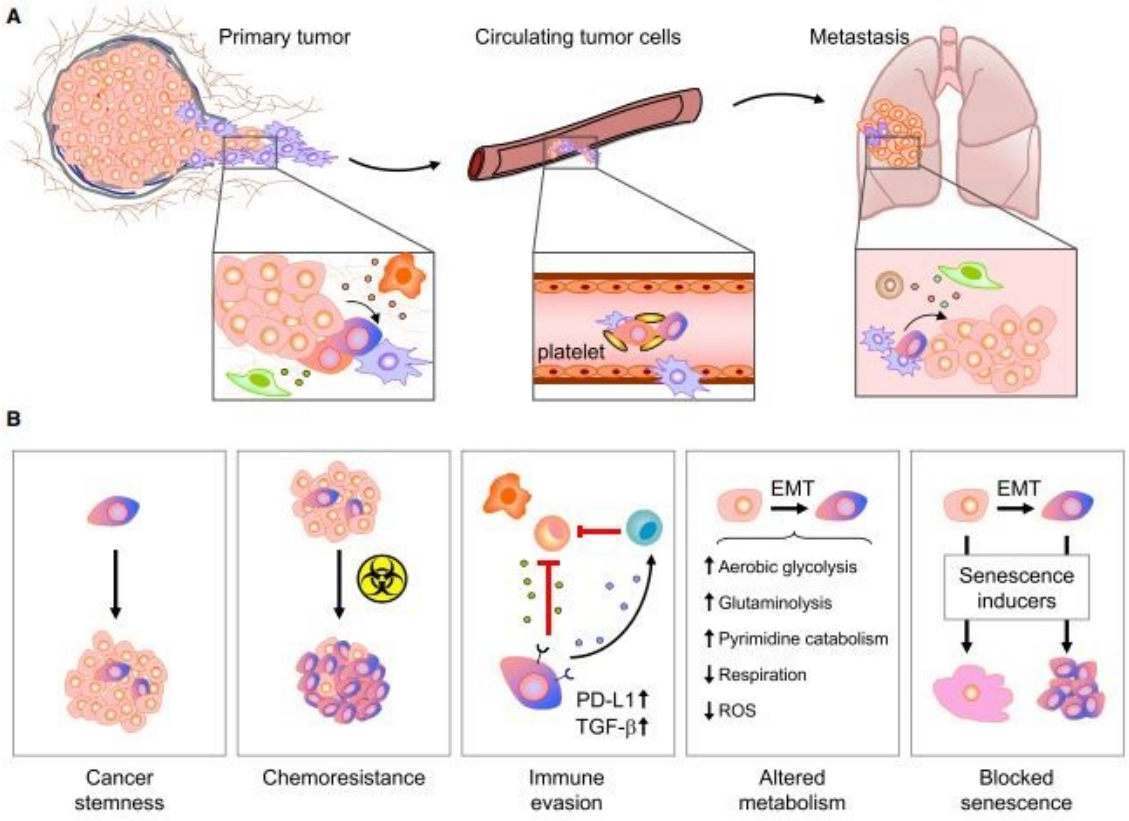

Figure 4: The main roles of EMT are briefly described in this picture by Lu and Kang[20]. A: the journey of cancer cells, from tumor invasion in adjacent tissues and intravasion, to the host organ, where secondary tumors can develop. EMT is involved in all of these three steps, as explained in B. B: a summary on some of the effects EMT can exert on cancer cells, including the block of senescence[248].

Circulating Tumor Cells (CTCs) and EMT

Circulating tumor cells (CTCs) represent an intermediate stage of metastasis. While rare (estimated to be as low as one to 10 cells per 10 mL of blood), they are uniquely accessible through simple non-invasive blood sampling[249]. Collective cells migration is defined as two or more cells migrating together, while retaining their cell-cell junctions, across a two-dimensional layer of ECM, or a three-dimensional interstitial tissue scaffold[250]. As already mentioned, CTCs can be represented by both individual cells or cluster of cells, the latter having a higher metastatic potential[238], but this does not mean they all are capable of producing

metastases. In order to adhere to the host organ cells, CTCs undergo a reverse process to regain epithelial phenotype, called Mesenchymal to Epithelial Transition (MET)[251], in which core transcription factors of EMT are targeted and repressed. One of the most studied examples of this process is the effect miR-200 family exert on ZEB2, or miR-34 with its double-negative feedback loop with SNAIL[252 253]. Interestingly, this allows the formation of micro-metastases, that will potentially grow into macro-metastases, although with a low percentage of success, as showed in some studies. In an experiment by Luzzi et al. after an intravenous melanoma cells injection, only 2.5% of the surviving cells formed micro-metastases. From these micro-metastases, just 1% grew up into macro-metastases[254]. Another study estimated that roughly only 0,1% of CTCs develop new secondary tumors[255], while Hedley and Chambers et al. Estimated roughly 0.02% of CTCs are capable of generating a proliferating metastatic lesion[256] In addition to cell-intrinsic features, the microenvironment and vasculature of the tumor can also contribute to CTCs generation. Evidence of EMT in CTCs deriving from carcinomas has been proven in different studies[240,257],others showed both epithelial and mesenchymal features demonstrating EMT is a *continuum* in some cancers[240,258,259]. A new model propose a dual phenotype for CTCs to better explain the data available; this model by Jolly et al. would explain both EMT-derived and MET-derived features of this “metastable phenotype” of CTCs, together with the observed collective migration of CTCs clusters[260]. CTCs within the bloodstream interact with the components of the blood, especially with platelets, as showed already in 1968 by Gasic et al., in a study where thrombocytopenic mice did not show any metastatic spread of tumors[261]. Platelets can protect CTCs from apoptosis through direct contact and

microvesicles[262], furthermore can protect them from immune NK cells[263] and potentially reduce shear stress in circulation[264]. The role of platelets in EMT has been shown, for example in human pancreatic cancer, where they induced an upregulation of Snail1 and a downregulation of E-cadherin[265,266], or by the fact that anti-platelets agents like aspirin hinders these processes in some cancers[267]. A key link between CTCs, EMT and platelets is given by TGF-β: CTCs express podoplanin, a platelet activator, that triggers platelet production of TGF-β, thereby inducing EMT in CTCs[268].

After surviving shear stress[269], CTCs need to survive immune response in the circulatory network. In various studies, PD-L1, PD-1 and CTLA-4, also called "immune checkpoint blockers" were related to EMT and immune evasion[270–274]. In some cancers, such as breast cancer, CTCs show a spindle-like morphology, and probably represent a small population of cells that underwent EMT; studies confirming this hypothesis involve the role of PD-L1. In particular, it was shown that there is bidirectional crosstalk between the expression of PD-L1 and EMT, both helping CTCs survive immune response[275]. Moreover, in Non-Small Cell Lung Cancer (NSCLC), coexpressed EMT and PD-1/PD-L1 pathway induced resistance to anti-PD-L1 agent Nivolumab[274]. EMT also can reduce CTL-mediated lysis on cancer cells, as studies confirm[276–278]. It is yet to be confirmed if immune check-point blockers other than PD-L1 are directly associated with a more mesenchymal phenotype.

Tumor Microenvironment (TME)

To better understand the variability of responses in experimental treatments directed against immune evasion related factors and EMT, one should consider the tumor microenvironment (TME) of the primary tumor.

TME consists of components of extracellular matrix, especially collagen, fibronectin, hyaluronan, laminin and tumor cells, tumor stromal cells (including stromal fibroblasts), endothelial cells and immune cells (microglia, macrophages and lymphocytes)[279–281]. Modifications of the TME are essential for immune evasion during primary tumor growth[282–285]; in the TME, different immunosuppressor cells can be found, comprising myeloid-derived suppressor cells (MDSC)[286,287], cancer-associated fibroblasts (CAFs)[288,289], tumor-associated macrophages[290,291] and Treg cells[292,293], producing immunosuppressive substances such as IL-10, tumor growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), PGE2, or PD-L1[294]. Dongre et al showed that tumors arising from carcinoma cell lines with a mesenchymal phenotype, or with higher level of Snail, exhibited more Treg lymphocytes and pro-tumoral macrophages compared to their more epithelial counterparts[295]. Tumor cells are able to produce TGF-β, an immune suppressor[296], which is an EMT driver and is more detectable in mesenchymal cells. TGF-β also inhibits immune response altering Fas ligand, IFN-γ, perforin and others[297], and in lung adenocarcinoma EMT drives pro-inflammatory pathways and alters many immune checkpoints, characterising a different TME[298]. A comprehensive review on EMT and tumor microenvironment was provided very recently by Romeo et al. [299].

Premetastatic niches and EMT

Cancer cells need a favourable environment in their host organ in order to metastasize[300]. Interestingly, primary tumors actively secrete factors to condition the nutrient, extracellular matrix and immune cell environment of a distant organ before the arrival of CTCs, thereby creating a supportive pre-metastatic niche, in which different characteristics and interactions

allow the formation of metastasis[301]. Pre-metastatic niches can contain pro-tumor immune cells like neutrophils[302] , monocytes[303], macrophages[304] and Bone Marrow Derived Cells (BMDCs)[305].Bone marrow-derived cells (BMDCs) are crucial for the generation of a suitable microenvironment for the primary tumor, and the development of metastasis[306]. Tumor-derived exosomes can even recruit BMDCs through up-regulation of pro-inflammatory molecules at pre-metastatic sites[307]. In their study, Hsu et al showed these cells can secrete extracellular vesicles containing miR-92a, promoting lung cancer metastasis specifically to the liver[308]. To summarize, the key components of the pre-metastatic niche include tumor-derived secreted factors (TDSFs), extracellular vesicles (EVs), bone marrow-derived cells (BMDCs), suppressive immune cells and host stromal cells[309]. Hypoxia can drive EMT[64,65,210] and promote pre-metastatic niches formation through HIFs, VEGFs[310]. Platelets have been found to be crucial for the promotion of metastasis in some cancers, by allowing survival of CTCs in circulation[265], by inducing EMT in CTCs[266] and favouring the establishment of pre-metastatic niches[311]. In a study on Lewis lung carcinoma spontaneous metastatic model, the knockout of platelet ADP receptor (P2Y12) led to decreased lung fibronectin, a major component of pre-metastatic niches, resulting in decreased pulmonary metastasis[312]. As P2Y12 is a target for common anti-platelet drugs, it may be developed into a new target for countering metastasis[313].

EMT in carcinomas

Many invasive and metastatic carcinomas have not undergone a complete transition to a mesenchymal phenotype or even lack signs of EMT, and

those invasive carcinomas do not invade adjacent connective tissue as individual mesenchymal-like cells, rather invade as multicellular aggregates or clusters[314,315]. It had shown minor subpopulation of cells that have undergone an EMT, constituting only 10% of the total, can have a marked effect on the ECM-degrading activity of the cancer cell population as a whole[316]. Many signalling pathways that are activated by genetic alterations common in carcinomas can cause an EMT, including SMADs, Snail, ZEB, β-catenin NF-kB and ras[317–321].

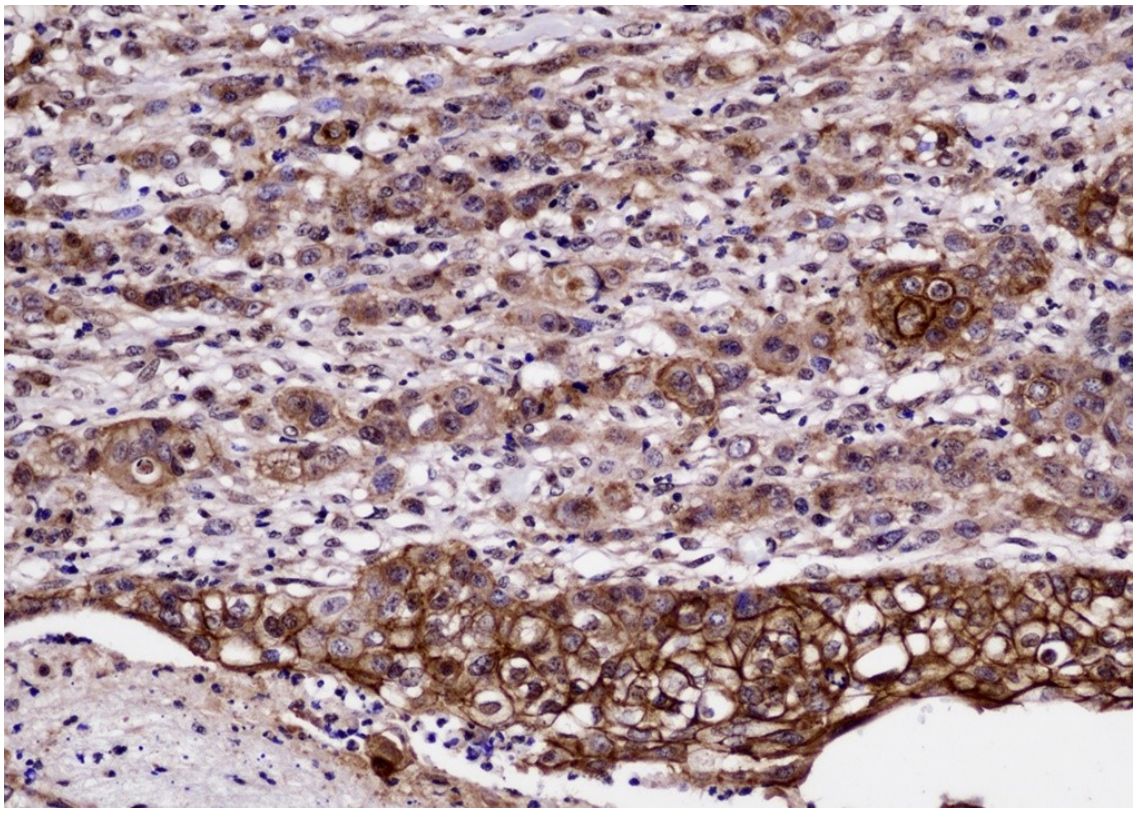

Figure 5: The picture shows an Epithelial to Mesenchymal Transition in a squamous cell carcinoma from a dog. Is noteworthy the gradual loss of E-cadherin expression from normal cells (picture bottom) towards invading tumor cells (picture middle and top) that are embedded in the underlying connective tissue (10x magnification). E-cadherin expression have been detected using ABC-DAB immunohistochemical method. (Pathology Unit-Department of Veterinary Science, University of Parma).

EMT in mammary gland carcinomas

Even though they all originate from the same anatomical site, these carcinomas have different phenotypes, and different biological subtypes, responding differently to treatments[322]. The two main classification used are immunohistochemistry and gene expression profiling. The latter divides breast carcinomas in luminal ER positive (luminal A and luminal B), HER2 enriched, and basal-like[323,324]. As immunohistochemical analysis of the same receptors does not overlap with gene expression profiling[325], other characteristics need to be added to this classification, such as Ki67, proliferative rates or cytokeratins expression[322]. Basal-like breast carcinomas are among the most aggressive and deadly cancer subtypes, as histologic studies confirm, displaying a high metastatic ability associated with mesenchymal features[326,327]. One molecular pathway responsible for the mesenchymal phenotype in this cancer is the expression of SNAI2, driven by KRAS, a RAS oncogenes family member[326]. Transcriptional profiling showed EMT regulators were expressed in this carcinoma, but in a heterogenous way across the tumor[328], and an hypothesis arose about the link between estrogen receptor (ER) silencing and EMT in human breast cancer cells. Recent findings indicate that probably the loss of ERα results in an EMT characterized by striking changes in the expression profile of specific matrix macromolecules, highlighting the potential role of matrix effectors in breast cancer endocrine resistance[329,330]. High grade carcinomas presented higher numbers of cells positive for vimentin, nuclear β-catenin, and CD44 expression as compared to low-grade carcinoma and benign lesions, suggesting that the process of de-differentiation of breast cancer cells could be related to the EMT[326]. The basal-like carcinomas, breast cancers showing triple negative expression of estrogen receptor,

progesterone receptor and HER2 receptor, have more mesenchymal features compared to the luminal (A and B) and HER2 enriched counterpart and are correlated with more invasiveness[330,331]. An interesting series of effects is exerted by ET-1, one of three isoforms of Endothelin in mammary tumors: through its receptors ET_AR (or ETA) and ET_BR (or ETB); it has been shown that ET-1 is highly expressed in mammary tumors in humans, and it has been shown it can modulate angiogenesis, invasiveness, mitogenesis, apoptosis, and metastatic potential via autocrine or paracrine action[332,333]. Chen et al showed that tumor-associated macrophages induce the ET axis in endothelial and breast cancer cells through IL-8 and TNF-α secretion[334]; the latter of the two is of key importance in the pathogenesis of breast cancer and of the presence of epithelial to mesenchymal transition in it[335]. It is tempting to speculate that the role of ET-1 can be linked to EMT, as it seems to do in other tumors like chondrosarcoma[336]. Canine mammary carcinomas are widely studied as a comparative model for humans[337]. Restucci et al. showed the correlation between ET-1 presence in canine mammary tumors (mostly G2 or G3 graded) and the malignancy of the neoplasm, also suggesting a positive feedback between hypoxia and ET-1 expression[338]. Breast cancer incidence in humans is related to various chemicals of the environment, including synthetic chemical bisphenol A (BPA)[339]. BPA is the main component used in the manufacturing of polycarbonate plastic, can be found in many common household products, and is present in air and drinking water[340,341]; an interesting study by Zhang et al. showed BPA stimulates the epithelial mesenchymal transition of estrogen negative breast cancer cells via FOXA1 signals[342]. As pet dogs fed with canned food showed high circulating BPA concentration in serum, it would be intriguing to know if this chemical product can induce EMT and

impact canine mammary carcinoma incidence[343]. EMT is widely involved in breast cancer metastasis, as several studies confirm[78,240,344], and research is now focusing on its main pathways, to elucidate their role in this carcinomas and to hypothesise future therapeutic approaches. The main ones are TGF-β[345], silencing of CDH-1 with controversial results[346,347], WNT/β-Catenin Pathway[348–350], Notch[351], TNF-α through NF-κB-mediated transcriptional upregulation of Snail1[78], and miRNAs[350,352,353], especially miR-300 targeting Twist to inhibit EMT[354].

EMT in prostatic carcinomas

Prostatic tumors are a major cause of death of human male population. The most common therapy with locally advanced and metastatic disease, androgen deprivation therapy, is most of the time subject to resistance[355]. The presence of EMT-like states is reported in prostatic tumors[356], and it plays a role in both resistance to treatment and metastasis[357]. In the prostate an axis between androgen and its receptors in the tissue is part of physiologic function and cancer development of the secretory epithelium[358]; these functions are possible through testosterone testicular synthesis, its transport to target tissues, and its reduction to 5α-dihydrotestosterone (DHT) androgens display their biological activity by binding and consequently activating the androgen receptor (AR)[359]. In prostate cancers, androgen signalling is deregulated, allowing these hormones to suppress the expression of E-cadherin, activate the expression of mesenchymal markers[360], and activate Snail[361]. Even though these results have been acknowledged, conflicting results have been published in recent years about the exact link between androgens and EMT. In some studies, it was androgen deprivation that seemed to induce EMT[362,363], and in

prostatic tissues ablation of androgens induced a more mesenchymal phenotype compatible with an EMT-like state[364]. Apart from the aforementioned the activation of Snail, androgens can also activate ZEB1 transcription, although in physiologic conditions they do not directly regulate it[365,366], while androgen receptors (ARs) can modulate miR-200 mediated activation of TGF-β/ZEB2 signalling pathway[367]. Estrogens also play a role in prostate cancers, through the mediation of prostatic estrogen receptor alpha (ER-α) and -β (ER-β), whose expression patterns progressively differ during cancer progression [368]. ER-β for example impedes EMT thanks to its inhibitory action on HIF1-α and Snail[369], while ER-β2 and ER-β5 variants can stabilize HIF-1α and favour the expression of hypoxic genes in prostate cancer[370]. EMT in prostatic cancers is induced both by hypoxia and TGF-β, and it is probable that their presence in the TME is responsible for the loss of ER-β protection[371]. Epidermal growth factor (EGF) and EGF Receptor (EGFR) are aberrantly expressed in both androgen independent and metastatic prostate cancers, with high EMT related features, and are strongly associated with aggressive phenotype, poor clinical prognosis, high Gleason score, reduced survival rate[372]. Moreover, EGF can induce Twist1 expression and prostate cancer cell invasion through a ROS/STAT3/HIF-1α signalling cascade[373], and increase the expression of fibronectin and N-cadherin, causes E-cadherin concurrent decrease[374]. Dogs are the only species where spontaneous prostatic carcinomas occur, comparable to those of humans, although with a much lower incidence[375,376]. Evidence of EMT in canine prostatic cancers is available, and comprises overexpression of vimentin[377], repression of E-cadherin expression[378], changes in β-catenin localization[379], loss of E-cadherin and β-catenin translocation in prostatic metastases[380].

EMT in squamous cell carcinoma

Squamous cell carcinomas are tumors arising from squamous cells, located in various anatomical sites, including oral cavity, skin, esophagus, vagina, lung, thyroid in humans. Interesting studies investigated the role of EMT in the invasive front of oral squamous cell carcinoma (OSCC) and tongue squamous cell carcinoma (TSCC). In oral cancers, morphological and functional characteristics of the invasive tumor front (ITF) underline the biological aggressiveness of oral cancer, showing cells with increased aggressive metastatic potential[381]. The ITF showed increased cell invasiveness, motility, and several features of EMT, including vimentin expression[382], loss of E-cadherin[383], loss of claudins[384] and loss of laminin 5[385]. In TSCC an interesting link between EMT and tumor "budding", has been studied, demonstrating high-intensity tumor budding is associated with reduced E-cadherin expression and enhanced Vimentin expression[386]. Tumor buddings show EMT features in esophageal adenocarcinoma, endometrial carcinoma, colorectal carcinomas and have shown to be prognostic markers in colorectal and rectal carcinomas[387–390]. Inflammation pathways, mediators and cytokines like COX-2/PGE2, IL-6, ROS, RNS, miRNAs, NF-kB, are often involved in a series of cancer, as tumors initiate inflammation[391,392]. The role of COX-2/PGE2 was investigated in rectal cancers showing how COX-2 expression was related to higher tumor stages. Interestingly, its expression was higher in metastatic lesions than in primary tumor lesions, and it was related to lower E-cadherin expression, indicating it probably induced an EMT-like phenotype[393]. The link between EMT and COX-2 can lead to future therapeutic approaches, as showed by the fact that COX-2 role is extensively studied in several cancers, including breast carcinomas and OSCC[383,394,395]. Coherent results have been achieved in

veterinary medicine in dogs; in 2017, Nagamine et al. showed EMT presence at the invasive front of OSCC and cutaneous squamous cell carcinoma, evidencing loss of β-catenin, desmoglein, E-cadherin and presence of EMT markers Vimentin and N-cadherin[396].

Particulate matter (PM) and EMT

Interesting data suggest that ambient particulate matter with an aerodynamic diameter of 2,5µm ($PM_{2,5}$) induces inflammation and apoptosis, largely sharing collective key messengers with putative EMT molecular processes; TGF-β/SMAD2/3 is one of the pathways involved in this event, leading to possible carcinogenesis or lung fibrosis, but several others might be involved, including epigenetic regulations involving miRNAs, lncRNAs, and DNA methylation acting as possible transcriptional or posttranscriptional regulators[397,398]. $PM_{2,5}$-derived EMT has also been shown *in vivo* in 2018 by Chi et al., in a research focusing on the effect of particulate matter on bronchial epithelial cells[399].

EMT as a prognostic marker

The stage of a cancer is determined by its extent and its spread at the time of diagnosis, which is essential for guiding cancer surveillance and control, possible therapies and prognosis[400]. One of the points of studying EMT in different stages of cancer and metastasis is to find out whether it is possible to use it as a prognostic marker, and evidences in some cancers suggest that the presence of EMT features can pre-emptively indicate prognosis. In order to create EMT-related prognostic markers, studies focused on EMT regulation (establishing correlations between its master regulators and tumor progression), on the expression of biomarkers[401], and on the

presence of particular microRNAs, both oncomiRs[402] and tumor-suppressing miRs[403]. In human breast tumors, the loss of E-cadherin expression has been successfully related to poor prognosis because of high-risk clinic-pathological characteristics, including increased tumor size, higher grade[404,405], and coherent results have been published in canine mammary tumors[406,407]. Another example is microRNA-9, that drives EMT through E-cadherin expression and cancer metastasis[408], and is up-regulated in breast carcinoma[409]. MiR-9 can be used as a prognostic marker for high tumor stage, high histologic grade and CSC promotion[410], invasive and EMT/CSC promotion[411], poor disease-free survival and distant metastasis-free survival[412]. Another study by Martin et al. showed how the expression of EMT master regulators Snail1, Slug, Twist can be directly associated to higher mortality and metastasis of the aforementioned cancer[413]. Similar results regarding EMT regulators expression have been published for hepatocellular and ovarian carcinoma in humans[414–417].

In bladder, cancer can be muscle invasive bladder cancer (MIBC) or non-muscle invasive bladder cancer (NMIBC), the first having worse prognosis and a 5 years-survival rate of <50%[418]. In a study focusing on E-cadherin, Vimentin and Twist expressions in bladder cancer, only vimentin appears as an independent predictor for cancer progression and survival[419]. A research by Cao et al. conducted a Gene set variation analysis (GSVA) establishing a correlation between EMT and the transition from NMIBC and MIBC, and eventually developed an EMT signature that can be used as a negative prognostic marker[420]. Another well studied EMT gene signature has been developed for hepatocellular carcinoma[421]; in a cohort of 128 hepatocellular carcinoma patients, the research team examined the prognostic value of four candidate genes: CDH1, inhibitor of DNA binding 2

(ID2), matrix metalloproteinase 9 (MMP9), and transcription factor 3 (TCF3). This four gene-signature was correlated with significantly shorter overall survival, furthermore tumor stage and this four gene-signature were independent prognostic factors (*ibidem*).

Even though successful results have been published, these markers are still not widely used for prognosis in clinical routine. One of the main problems is that in different locations of a same tumor the expression of EMT marker can differ, because of tumor heterogeneity. Moreover, these studies do not provide clear cut-offs for prognosis, that are present in other prognostic methods instead, like mitotic index, Ki67, Her2 and others[422–424]. One possible future application of these wide oncogenomic data set will be the creation of personalized medicine programs, allowing clinicians to obtain a cancer specific and patient specific prognosis[425].

Mesenchymal-to-Epithelial Transition

Mesenchymal to Epithelial transition (MET) is the reverse process of EMT, in which mesenchymal cells acquire an epithelial phenotype, and has been observed in physiologic conditions and in cancer[426].

In embryogenesis, many examples are described; in somitogenesis, Snail genes define a class of cyclic genes that coordinates segmentation, allowing somite epithelialization[427]. MET is required for the formation of Langerhans islets in pancreatic development[428]. In heart embryogenesis, cardiac mesodermal cells get their mesenchymal phenotype through EMT at gastrulation[429], but then cardiac progenitors quickly become organized into a two-layered epithelium via MET. A secondary EMT occurs, and mesenchymal cells arising from this delamination give rise to the

endothelial cell lining of the heart through another MET, forming an endocardial tube surrounded by the myocardial epithelium. These tubes will lead the formation of the four compartments of the primordial heart. Another round of EMT, in this case more precisely endothelial to mesenchymal transition (EndMT) allows the formation of the endocardial cushion, the cells that later assemble into the atrioventricular valvulo-septal complex[430]. Nephrogenesis requires multiple rounds of EMT too. In mammalians, kidney arises from the metanephric mesenchyme and the ureteric bud. Reciprocal inductive interactions transform the ureteric bud into the renal collecting system, while the metanephric mesenchyme condenses and subsequently undergoes MET to give rise to the nephrons[431]. Failure of cells to undergo MET can lead to development of the paediatric kidney malignancy, Wilms' tumor[432].

The role of EMT in cancer metastasis was apparently contradicted by findings revealing that distant metastases derived from primary tumors were largely composed by epithelial phenotype, closely resembling the primary tumor cells' one. In some cases, metastatic lesions of carcinomas showed even higher E-cadherin levels than in the primary tumor[433–436]. To explain how this is possible one could argue that epithelial cancer cells are able to escape the primary tumor and reach the host organ for metastasis, but this is in contrast to the strong evidence of a positive correlation between loss of epithelial phenotype and metastatic potential[437]. To further investigate this, Yates et al. co-cultured human prostate carcinoma cells with hepatocytes, showing it led to increased expression of E-cadherin, demonstrating that phenotypic plasticity can occur late in prostate cancer progression at the site of ectopic seeding[438]. A showed mechanism for the re-expression of E-cadherin in ectopic tissues, was loss of demethylation of

CDH-1 promoter, probably induced by the tissue microenvironment of the host organ[439]. These data and other studies provide proof of principle that carcinoma cells may undergo MET, regaining E-cadherin, in response to the host organ microenvironment to establish connections with the resident, nonneoplastic epithelial cells[440,441].

MET in sarcomas

EMT is widely studied mesenchymal reversion involved in the pathogenesis of several carcinomas; is it possible that, in sarcomas, a similar reversion occurs from a mesenchymal to an epithelial phenotype? Sarcomas in humans are rare malignant tumors that account for approximately 1% of malignancies, and about 80% of these originate from soft tissue[442]. Evidence of MET in sarcomas has been published in several studies, such as synovial sarcomas[443], chondrosarcomas[444], epithelioid sarcomas[445] and leiomyosarcomas[446]. MET in sarcoma is characterised by an increased expression of classical epithelial markers, even tumor cells still predominantly express classical mesenchymal markers[447]. Epithelial markers in sarcoma show a higher expression, and they can be used as prognostic markers[448–452].

MET can be induced by several signalling pathways and cytokines, including c-MET[453], platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) through Fox-2 regulation[454], transforming growth factor beta-1 (TGF-β1), Insulin-related growth factor 1 receptor (IGF1R) and regulatory kinases such as phosphoinositide 3-kinase (PI3K), AKT and mammalian target of rapamycin (mTOR)[348,440,443,455]. MicroRNAs are known to regulate EMT[122] and have been discovered to regulate MET in

recent years[456–459]. MicroRNA cluster 302–367 was found to accelerate MET and induce somatic cell reprogramming[460]. One example is miR-147, found to primarily act by increasing the expression of E-cadherin and decreasing that of ZEB1, EMT inducer, which it targets directly. This results in the inhibition of cell motility and invasion in mouse cancer models[459]; ZEB1 is also targeted by miR150, in a similar pathway [458]. MiR-9 inhibits NF-kB/SNAI1 pathway in melanoma, thereby increasing E-cadherin expression, and inducing MET[461]. Similar results were published for miR-23b and miR-29c in endometrial carcinosarcoma[462,463]. These data provide knowledge for the creation of new prognostic markers, especially in tumors such as leiomyosarcoma or synovial sarcoma[464], in which the low incidence in humans does not help research and statistical analysis. Canine sarcomas, especially osteosarcoma (OSA) are under focus for comparative studies with humans, because they have a higher incidence, representing 9 to 15% of all cutaneous or subcutaneous tumors, and 10–15% of all malignant tumors in dogs. It appears that 20% of these tumors originate in the bone and the other 80% is represented by soft tissue sarcomas (STS)[452,453]. Note that not all mesenchymal tumors are classified as STS in dogs, with the main exceptions being hemangiosarcoma, synovial cell sarcoma and oral fibrosarcoma[466].

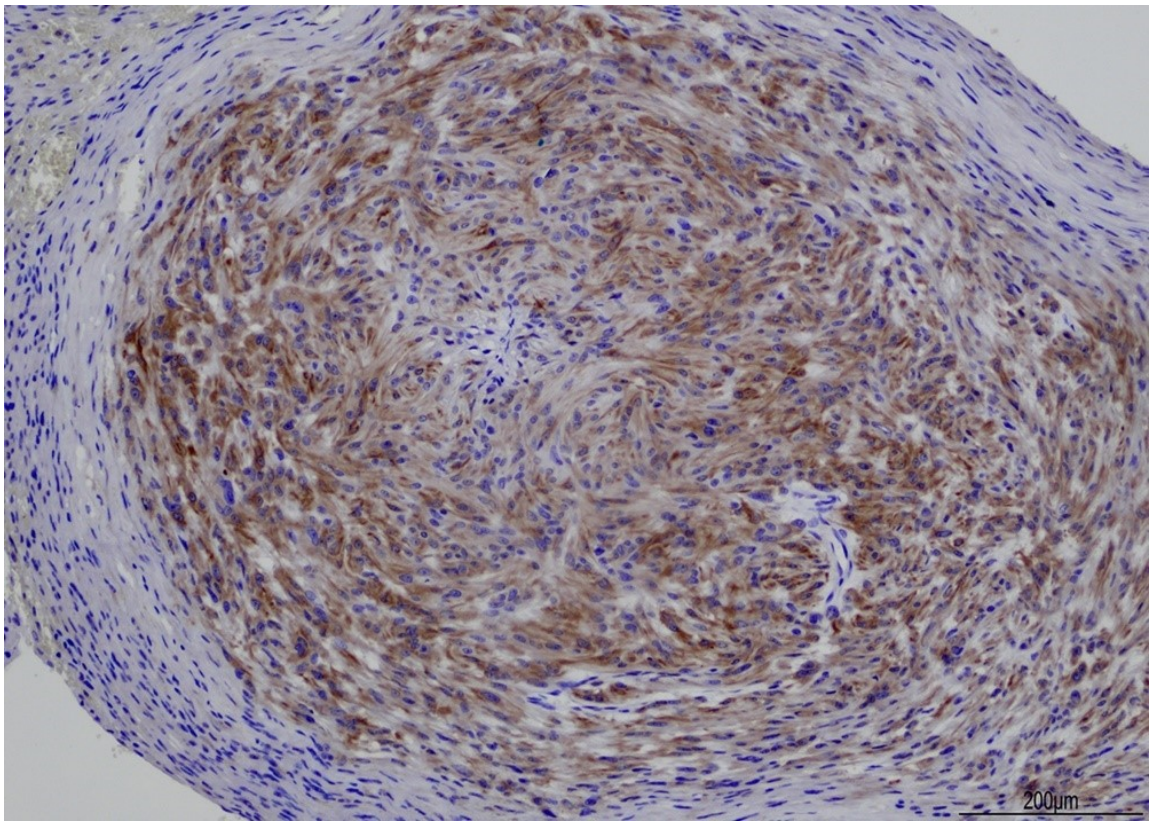

Figure 6: The picture shows a Mesenchymal to Epithelial Transition in a Perivascular Wall Tumor from a dog. Is noteworthy the diffuse increased Cytokeratin cytoplasmic expression within neoplastic mesenchymal cells (10x magnification). Cytokeratin expression have been detected using ABC-DAB immunohistochemical method. (Pathology Unit-Department of Veterinary Science, University of Parma).

Therapeutic approaches for EMT and MET

Immune response is one of the key targets studied in order to obtain tumor regression. T cells circulate in the organs and tissues, and their T cell receptors (TCRs) are activated by different peptide-MHC complexes. The capability of T cells is to bind pathogen and cancer associated signals that alert them; there are certain tumor-specific T cells, activated by the presence of tumor-associated antigens, directly or thanks to by Antigen Presenting Cells (APCs)[467]. Regulatory T cells can suppress immune response, favouring cancer progression[468]. Research has focused on the transfer of naturally occurring or gene-engineered T cells, called adoptive

immunotherapy[469] and on re-activating these T cells through the action of immune checkpoint blockers[470]. The most interesting results come from studies of three agents: anti-Programmed cell Death protein 1 (anti-PD-1), anti-Programmed cell Death protein Ligand 1 (anti-PD-L1) and anti-Cytotoxic T-Lymphocyte Antigen 4 (anti-CTLA-4), in various cancers[272,273,293,471,472]. A large number of patients still show acquired or intrinsic resistance. The latter is possible because genomic and epigenomic instability of transformed cells allows certain resistant phenotypes to be naturally selected[473]. Acquired resistance, instead, occurs when single tumor cells are able to survive or escape immunity; one perfect example is provided by the exploitation of immune homeostasis mediators by cancer cells, such as PD-1 in response to Interferon-γ. (IFN-γ)[474]. A study by Mak et al showed the positive correlation between EMT signature and the high expression of several immune checkpoints including PD-1, PD-L1, PD-L2, B7-H3, OX40, OX40L, CD137, TIM3, LAG3, and CTLA4[475]. EMT is also responsible for drug resistance to anti-cancer chemotherapies, as many studies prove[476,477]. For instance, in preoperative chemotherapy-treated patients with esophageal cancer, both increased SNAIL1 and decreased E-cadherin expression were predictive of poor chemotherapy response and inferior overall survival[478]. Can EMT be targeted to favour immune system-related tumor regression in carcinomas? MicroRNA-200 family is proven to be potent repressor of EMT[92], and studies showed that upregulation of some of its members can increase sensitivity to chemotherapy in both chemoresistant prostate carcinoma and pancreatic cancer cells[479–481].

An interesting new approach in cancer therapy research is the use of nanocarriers, usually made of noble materials; one of the advantages of these nanostructures is that they overcome most of the obstacles of

traditional drugs, first of all the lack of specificity for cancer cells[482]. Nanocarriers do not cause cytotoxicity[483], and also have intrinsic properties, so that the use of unmodified nanoparticles exert different effects too[484]. Arvizo et al. showed that administration of unmodified gold nanoparticles (AuNPs) induced a reversion of EMT in ovarian cancer models, inducing a higher expression of E-cadherin, lower expression of Vimentin and Snail[485]. Another study of a similar cancer model showed AuNPs also induced higher sensitivity to cisplatin[486]. Coherent studies have been published also for pancreatic cancer[487], for melanoma (where AuNPs also reduced metastasis)[488] and others[489,490]. Some studies also focus on the delivery of small molecules like short interfering RNAs or miRNAs, such as MiR-200 family, to counter metastasis and tumor growth[491,492]. In the future, one possible application of this knowledge would be directly targeting cancer cells undergoing EMT to block the pathogenesis of cancer cell proliferation, stemness, metastasis and chemoresistance.

Cytotoxic T Lymphocyte (CTLs) mainly use the perforin/granzyme pathway to destroy target cells, including cancer cells[493]. Interestingly, it has been shown that cells with experimentally-induced high expression of Brachyury, an EMT inducer, had decreased susceptibility to lymphocyte-mediated killing compared to control cells[494]. Another link between EMT and immune escape was hypothesised by Akalay et al. in a study where MCF-7 human mammary carcinoma cells underwent EMT and exhibited reduced susceptibility to CTL-mediated lysis. This was possible through stable expression of SNAIL or after prolonged exposure to tumor necrosis factor alpha (TNF-α)[276]. Interestingly curcumin, a phytochemical derived from *Curcuma longa*, showed to repress EMT in the same cancer cells[495].

Nonetheless, no therapeutic strategy, to this date, specifically target EMT to obtain an increase in CTL activity.

In human Non-Small Cell Lung Cancer (NSCLC), therapy resistance is acquired in many patients treated with epidermal growth factor receptor tyrosine kinase inhibitors, and this is positively correlated with EMT markers overexpression[496]. The use of moscatilin, bufalin, CX-4945 and the inhibition of TGF-β are new different strategies that suppress EMT in this tissue, that could lead to new combination therapies[497–499]. Another hypothesised target in NSCLC therapy is Notch3, as it inhibits apoptosis of cancer cells, through cooperation with EGFR[500]. It was shown, in different cancers, that anti-Notch agents induce increased sensitivity to chemotherapy or significantly reduce metastasis[501–503].

Vimentin is highly expressed in carcinoma cells that underwent EMT, and new drugs targeting it might lead to improvements in cancer therapy. Withaferin-A (WFA) is a steroidal lactone derived from *Withania somnifera*, a medicinal plant commonly used in India, and has shown to have anti-cancer properties, including the repression of tumor growth and tumor-associated angiogenesis[504,505]. Focusing on the exact mechanisms of WFA action, it has been discovered that it acts through the degradation of vimentin[506]. A recent study also show how knockdown of vimentin in cancer cells renders them less sensitive to WFA[507]. The latter results were obtained in sarcoma cells, and are promising for the future development of anti-vimentin therapies in Soft Tissue Sarcomas[507].

Another substance, paeoniflorin, derived from the roots of peonies, affects the expression level of E-cadherin and Vimentin at the cell level, reversing EMT. This results were obtained in colorectal cancer cells, and will

potentially lead to new combination therapies for colorectal cancer in humans[508].

Viral oncolysis and EMT, MET

Viruses can exert different effects on host cells, both naturally and after genetic engineering; this concept is exploited for oncolytic virotherapy, where this potentiality is turned against malignancies[509]. Viruses can also increase cancer susceptibility to anti-tumor therapies, significantly improving its efficacy[510]. Thus, a new approach to cancer has developed in this sense, using oncolytic viruses (OVs) that selectively replicate in tumor cells and lyse tumor tissues, while sparing the non-neoplastic host cells and simultaneously restoring antitumor immunity[511]. One of the first studies that exploited this concept was published by Mastrangelo et al. over 20 years ago, in which they induced anti-tumor response against melanoma cells through intralesional vaccinia virus injection[512]. The latter was an oncolytic vaccinia virus expressing granulocyte macrophage colony stimulating factor (*GMCSF*) that led to inflammation of the tumor site and infiltration with different immune cell types[512].

Bovine Herspesvirus-4 (BoHV-4) can infect several cells in different animal species, including cancer cells, without Cytopathic Effect (CPE); moreover, it has the capability to accommodate large amounts of foreign genetic material[513,514]. This makes it an ideal candidate for the creation of recombinants capable of gene delivery and possibly cancer oncolytic therapy[513]. Many oncolytic viruses, such as measles virus (MV), vesicular stomatitis virus, reovirus, and adenovirus have shown promising results for the treatment of Multiple Myeloma in humans[515]. The disadvantage of these naturally occurring human viruses is that their efficacy is limited by

the antiviral immune response of the patients[516]. To overcome this, BoHV-4 seems to be an ideal candidate, as no antiviral immunity for this bovine virus is present in humans[517]. In their recent work, in fact, Marchica et al. showed BoHV-4 selectively exert oncolytic effect on Multiple Myeloma cells[517]. This provides a perfect example on the application of animal-specific viruses in oncolytic therapy in human medicine.

Other wide improvements have been achieved in this field, exploiting a variety of oncolytic viruses in different models, including *Adenovirus*[518], Coxsackie virus[519], *Poliovirus*[520] and different *Morbillivirus*[521]. Canine Distemper Virus (CDV), a virus belonging to the genus *Morbillivirus*, is able to infect and induce apoptosis in lymphoid cells[522]. In a recent study by Armando et al. the role of CDV as an oncolytic virus able to infected a histiocytic sarcoma cell line (DH82) was investigated[523]. Canine Histiocytic Sarcoma (HS), a neoplasia of hematopoietic origin, is an interesting translational model for histiocytic sarcomas in humans, due to its higher prevalence in dogs, but similar prognosis and poor response to classical therapies[524]. The aim of this study *in vitro* was to demonstrate whether CDV virus could induce MET in canine HS cells leading to decreased cellular motility. The main findings reported increased epithelial markers such as E-cadherin and Cytokeratin 8 together with a decreased cell motility and invasive features in the infected cancer cells. This confirmed that CDV persistently infected canine HS cells underwent MET phenomenon leading to a decreased cell motility *in vitro*[523]. Given this evidence, future strategies might exploit the benefits of MET for OV therapies in sarcomas.

EMT seems to increase response to an oncolytic herpesviral therapy in human and murine models, suggesting that some oncolytic viruses

specifically target cells undergoing EMT[525]. This knowledge is nonetheless far from establishing a clear clinical application of oncolytic therapy in cancer cells undergoing EMT. In lung cancer, for instance, oncolytic adenovirus armed with the apoptosis inducer TRAIL showed to target Cancer Stem-like Cells (CSCs)[526], but CSCs with an EMT-related phenotype were significantly more resistant to therapy, compared to controls[527]. New strategies to obtain more efficient oncolytic therapies are enhancing OVs infiltration and diffusion, find the most effective method of administration and finding a balance between anti-tumor immunity and anti-viral immunity in the TME[528]. To some extent, OVs are able to re-program TME, leading to a switch from immunosuppressive to immunocompetent[529]. Given the important role EMT has in the immune regulation of TME, new research investigating Epithelial to Mesenchymal Transition interaction with OV therapy may develop in the future. One strategy might be represented by the suppression of EMT in carcinomas, to counter its consequences for tumor malignancy. Another one might be altering EMT regulation of the TME to potentiate the effect of OV therapy.

Discussion and conclusions

EMT and MET have been found to be fundamental for several physiologic and pathologic events in humans and animals, including embryogenesis, fibrosis and neoplasia. Their role in cancer has been shown for tumor progression, invasion, and metastasis, yet many aspects need to be further investigated. Many events in tumors remain unclear, as they lack demonstrated explanations, or show an inextricable regulation network[530]. Therefore, it is difficult to formulate clear pathogenetic models for EMT-related tumor malignancy. New perspectives arise from regulation

pathways involving MicroRNAs, several “master regulators” of EMT and Tumor-Derived-Secreted Factors (TDSFs). Among TDSFs, microvesicles and exosomes are found to interact with potential host organs for metastasis, even before the primary tumor has released cancer cells in circulation. Because of this , they may be used for diagnostic and therapeutic approach to cancers[141,148,531–533].

Promising results arise from studies linking EMT cellular markers and gene expression to carcinoma progression, allowing researchers to ideate new prognostic procedures for several cancers, such as hepatocellular carcinoma in humans[421]. The ultimate aim of these findings is to favour the development of new therapeutic strategies exploiting EMT in carcinomas and MET in sarcomas. Recent findings show that different EMT-repressing substances or inhibitory pathways are correlated with better prognosis and tumor regression, varying from microRNAs to nanoparticles, but also phytochemicals[354,446,482,492,506,508]. Several evidences describe the role of EMT in the regulation of primary tumor and CTCs immune evasion, but also in the creation of an immunosuppressive TME[294]. As new anti-tumor therapeutic strategies, such as immune checkpoint blockers, involve the blockade of immunosuppressor pathways, EMT has emerged as a mechanism for chemotherapy resistance[270,534]. Starting from this, some findings suggest that the repression of EMT during cancer treatment can result in better prognosis and anti-tumor effects[123,480,495]. Further aspects remain to be investigated to ideate new clinical trials for combination therapies involving EMT regulation. Another promising strategy for anti-tumor therapy is the use of Oncolytic Viruses that specifically infect and lyse tumor cells[528]. Even though evidences confirm EMT has a role in the

response to these therapies[525,528], clinical trials specifically involving EMT-suppressing OVs are yet to be discovered.

Unlike EMT, MET has only recently been under focus of research, hence such a vast knowledge concerning its regulation and involvement in cancer is not currently available for sarcomas[535], both in animal and human models. One of the reasons behind this is the lower incidence of sarcomas in humans. Despite this, the knowledge concerning its role in embryogenesis and sarcoma is growing, even in anti-tumor therapy. Very recently, in fact, a new study concerning oncolytic CDV infection in dogs has been recently published. In the study, this virus showed to revert MET in histiocytic sarcoma, leading to decreased cellular motility[523]. This promising result in dogs may serve as a pioneer model for future investigations, both in veterinary and human medicine and oncology, further demonstrating the actuality and potentiality of collaboration between all the fields of medicine, as summarised by the concept of "One Health-One Medicine"[3]

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