Lavori MICROVESCICOLE

1. Scaricabili dalla rete gratis

- Menck K et al. , **Tumor-derived microvesicles mediate human breast cancer invasion through differentially glycosylated EMMPRIN**. J Mol Cell Biol. 2015 Apr;7(2):143-53.

Tumor cells secrete not only a variety of soluble factors, but also extracellular vesicles that are known to support the establishment of a favorable tumor niche by influencing the surrounding stroma cells. Here we show that tumor-derived microvesicles (T-MV) also directly influence the tumor cells by enhancing their invasion in a both autologous and heterologous manner. Neither the respective vesicle-free supernatant nor MV from benign mammary cells mediate invasion. Uptake of T-MV is essential for the pro-invasive effect. We further identify the highly glycosylated form of the extracellular matrix metalloproteinase inducer (EMMPRIN) as a marker for proinvasive MV. EMMPRIN is also present at high levels on MV from metastatic breast cancer patients in vivo. Anti-EMMPRIN strategies, such as MV deglycosylation, gene knockdown, and specific blocking peptides, inhibit MV-induced invasion. Interestingly, the effect of EMMPRIN-bearing MV is not mediated by matrix metalloproteinases but by activation of the p38/MAPK signaling pathway in the tumor cells. In conclusion, T-MV stimulate cancer cell invasion via a direct feedback mechanism dependent on highly glycosylated EMMPRIN.

- Hong BS et al. **Colorectal cancer cell-derived microvesicles are enriched in cell cycle-related mRNAs that promote proliferation of endothelial cells.** BMC Genomics. 2009 Nov 25;10:556. doi: 10.1186/1471-2164-10-556.

BACKGROUND: Various cancer cells, including those of colorectal cancer (CRC), release microvesicles (exosomes) into surrounding tissues and peripheral circulation. These microvesicles can mediate communication between cells and affect various tumor-related processes in their target cells. RESULTS: We present potential roles of CRC cell-derived microvesicles in tumor progression via a global comparative microvesicular and cellular transcriptomic analysis of human SW480 CRC cells. We first identified 11,327 microvesicular mRNAs involved in tumorigenesis-related processes that reflect the physiology of donor CRC cells. We then found 241 mRNAs enriched in the microvesicles above donor cell levels, of which 27 were involved in cell cycle-related processes. Network analysis revealed that most of the cell cycle-related microvesicle-enriched mRNAs were associated with M-phase activities. The integration of two mRNA datasets showed that these M-phase-related mRNAs were differentially regulated across CRC patients, suggesting their potential roles in tumor progression. Finally, we experimentally verified the network-driven hypothesis by showing a significant increase in proliferation of endothelial cells treated with the microvesicles. CONCLUSION: Our study demonstrates that CRC cell-derived microvesicles are enriched in cell cycle-related mRNAs that promote proliferation of endothelial cells, suggesting that microvesicles of cancer cells can be involved in tumor growth and metastasis by facilitating angiogenesis-related processes. This information will help elucidate the pathophysiological functions of tumor-derived microvesicles, and aid in the development of cancer diagnostics, including colorectal cancer.

- Minciacchi VR et al. **Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes.** Semin Cell Dev Biol. 2015 Apr;40:41-51.

Since their first description, extracellular vesicles (EVs) have been the topic of avid study in a variety of physiologic contexts and are now thought to play an important role in cancer. The state of knowledge on biogenesis, molecular content and horizontal communication of diverse types of cancer EVs has expanded considerably in recent years. As a consequence, a plethora of information about EV composition and molecular function has emerged, along with the notion that cancer cells rely on these particles to invade tissues and propagate oncogenic signals at distance. The number of in vivo studies, designed to achieve a deeper understanding of the extent to which EV biology can be applied to

clinically relevant settings, is rapidly growing. This review summarizes recent studies on cancer-derived EV functions, with an overview about biogenesis and molecular cargo of exosomes, microvesicles and large oncosomes. We also discuss current challenges and emerging technologies that might improve EV detection in various biological systems. Further studies on the functional role of EVs in specific steps of cancer formation and progression will expand our understanding of the diversity of paracrine signaling mechanisms in malignant growth.

- Zhang L et al. **Transfer of microRNAs by extracellular membrane microvesicles: a nascent crosstalk model in tumor pathogenesis, especially tumor cell-microenvironment interactions.** J Hematol Oncol. 2015 Feb 22;8:14.

Anticancer treatments aiming at killing malignant cells have been applied for decades but have been unsuccessful at curing the disease. The modern concept of tumor microenvironment, especially angiogenesis, suggests that the tumor is not only composed of malignant cells, but also consists of other groups of cells that work together. Recently, genetic message transfer has been revealed between tumor cells and their microenvironment. The latest cell-derived vector, extracellular membrane microvesicles (EMVs), has been found to provide membrane protection and allowed to deliver genetic information beyond the cells. Additionally, EMV-associated microRNAs are involved in a variety of cellular pathways for tumor initiation and progression. Previous published reviews have focused on miRNA that included EMVs as a sensitive marker for tumor monitoring in clinical applications that are based on the alteration of their expression levels in conjunction with disease occurrence and progression. From the aspect of cellular crosstalk, this article will review the role of EMV-mediated microRNA transfer in tumor pathogenesis, including tumor treatment obstacles, history and features, and current research in inflammatory/immune pathologies, as well as in solid tumors and hematological malignancies. This nascent crosstalk model will provide a novel insight into complementing the classic mechanisms of intercellular communication and contribute to the potential therapeutic strategy via small RNA molecule-carrying EMVs for multimodality treatment Cancer Metastasis Rev. 2013 Dec;32(3-4):623-42. doi: 10.1007/s10555-013-9441-9.

- Azmi AS et al. **Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review**. Cancer Metastasis Rev. 2013 Dec;32(3-4):623-42.

Trafficking of biological material across membranes is an evolutionary conserved mechanism and is part of any normal cell homeostasis. Such transport is composed of active, passive, export through microparticles, and vesicular transport (exosomes) that collectively maintain proper compartmentalization of important micro- and macromolecules. In pathological states, such as cancer, aberrant activity of the export machinery results in expulsion of a number of key proteins and microRNAs resulting in their misexpression. Exosome-mediated expulsion of intracellular drugs could be another barrier in the proper action of most of the commonly used therapeutics, targeted agents, and their intracellular metabolites. Over the last decade, a number of studies have revealed that exosomes cross-talk and/or influence major tumor-related pathways, such as hypoxia-driven epithelial-to-mesenchymal transition, cancer stemness, angiogenesis, and metastasis involving many cell types within the tumor microenvironment. Emerging evidence suggests that exosome-secreted proteins can also propel fibroblast growth, resulting in desmoplastic reaction, a major barrier in effective cancer drug delivery. This comprehensive review highlights the advancements in the understanding of the biology of exosomes secretions and the consequence on cancer drug resistance. We propose that the successful combination of cancer treatments to tackle exosome-mediated drug resistance requires an interdisciplinary understanding of these cellular exclusion mechanisms, and how secreted biomolecules are involved in cellular cross-talk within the tumor of cancer.

- Clancy JW et al. **Regulated delivery of molecular cargo to invasive tumour-derived microvesicles.** Nat Commun. 2015 Apr 21;6:6919.

Cells release multiple, distinct forms of extracellular vesicles including structures known as microvesicles, which are known to alter the extracellular environment. Despite growing understanding of microvesicle biogenesis, function and contents, mechanisms regulating cargo delivery and enrichment remain largely unknown. Here we demonstrate that in amoeboid-like invasive tumour cell lines, the v-SNARE, VAMP3, regulates delivery of microvesicle cargo such as the membrane-type 1 matrix metalloprotease (MT1-MMP) to shedding microvesicles. MT1-MMP delivery to nascent microvesicles depends on the association of VAMP3 with the tetraspanin CD9 and facilitates the maintenance of amoeboid cell invasion. VAMP3-shRNA expression depletes shed vesicles of MT1-MMP and decreases cell invasiveness when embedded in cross-linked collagen matrices. Finally, we describe functionally similar microvesicles isolated from bodily fluids of ovarian cancer patients. Together these studies demonstrate the importance of microvesicle cargo sorting in matrix degradation and disease progression.

2. Disponibili in .pdf

- Martins VR et al. **Tumor-cell-derived microvesicles as carriers of molecular information in cancer**. Curr Opin Oncol. 2013 Jan;25(1):66-75.

PURPOSE OF REVIEW: Exosomes and microvesicles are secreted particles of 30-200 nm in diameter, delimited by a lipid bilayer and containing a wide range of membrane-bound or free proteins and nucleic acids (in particular mRNA and miRNA). Here, we review the properties of tumor-cell-derived microvesicles as carriers of molecular information in relation to cancer progression and promotion of metastasis. RECENT FINDINGS: Microvesicles from tumor cells operate as signaling platforms that diffuse in the extracellular space to target cells in the microenvironment, modulating the interactions of tumor cells with stromal, inflammatory, dendritic, immune or vascular cells and priming the formation of the metastatic niche. SUMMARY: Because of their stability, exosomes and microvesicles can be retrieved in bodily fluids as biomarkers for cancer detection and monitoring. They offer a range of molecular targets for controlling cell-cell interactions during invasion and metastasis.

- Yanez-Mo M. et al. **Biological properties of extracellular vesicles and their physiological functions**. J Extracell Vesicles. 2015 May 14;4:27066. doi: 10.3402/jev.v4.27066. eCollection 2015.

In the past decade, extracellular vesicles (EVs) have been recognized as potent vehicles of intercellular communication, both in prokaryotes and eukaryotes. This is due to their capacity to transfer proteins, lipids and nucleic acids, thereby influencing various physiological and pathological functions of both recipient and parent cells. While intensive investigation has targeted the role of EVs in different pathological processes, for example, in cancer and autoimmune diseases, the EV-mediated maintenance of homeostasis and the regulation of physiological functions have remained less explored. Here, we provide a comprehensive overview of the current understanding of the physiological roles of EVs, which has been written by crowd-sourcing, drawing on the unique EV expertise of academia-based scientists, clinicians and industry based in 27 European countries, the United States and Australia. This review is intended to be of relevance to both researchers already working on EV biology and to newcomers who will encounter this universal cell biological system. Therefore, here we address the molecular contents and functions of EVs in various tissues and body fluids from cell systems to organs. We also review the physiological mechanisms of EVs in bacteria, lower eukaryotes and plants to highlight the functional uniformity of this emerging communication system.

- Lowry MC et al. **The Role of Exosomes in Breast Cancer.** Clin Chem. 2015 Dec;61(12):1457-65.

BACKGROUND: Although it has been long realized that eukaryotic cells release complex vesicular structures into their environment, only in recent years has it been established that these entities are not merely junk

or debris, but that they are tailor-made specialized minimaps of their cell of origin and of both physiological and pathological relevance. These exosomes and microvesicles (ectosomes), collectively termed extracellular vesicles (EVs), are often defined and subgrouped first and foremost according to size and proposed origin (exosomes approximately 30-120 nm, endosomal origin; microvesicles 120-1000 nm, from the cell membrane). There is growing interest in elucidating the relevance and roles of EVs in cancer. CONTENT: Much of the pioneering work on EVs in cancer has focused on breast cancer, possibly because breast cancer is a leading cause of cancer-related deaths worldwide. This review provides an in-depth summary of such studies, supporting key roles for exosomes and other EVs in breast cancer cell invasion and metastasis, stem cell stimulation, apoptosis, immune system modulation, and anti-cancer drug resistance. Exosomes as diagnostic, prognostic, and/or predictive biomarkers and their potential use in the development of therapeutics are discussed. SUMMARY: Although not fully elucidated, the involvement of exosomes in breast cancer development, progression, and resistance is becoming increasingly apparent from preclinical and clinical studies, with mounting interest in the potential exploitation of these vesicles for breast cancer biomarkers, as drug delivery systems, and in the development of future novel breast cancer therapies.

- Gai C et al. **Extracellular vesicle-mediated modulation of angiogenesis.** Histol Histopathol. 2016 Apr;31(4):379-91.

Angiogenesis is a tightly regulated process where a number of different players are involved. Recently, a role for membrane vesicles actively released from cells has been proposed. Virtually all cell types may release non-apoptotic membrane vesicles in the nano-size range containing critical components of the cell of origin. The two main categories of these vesicles include exosomes and microvesicles that differ for biogenesis but, sharing several features and mechanisms of action, have been collectively named extracellular vesicles (EV). EV are able to transfer from one cell to another bioactive lipids, proteins and nucleic acids that may induce changes in the phenotype and functions of the recipient cells. This new mechanism of cell to cell communication has been involved in modulation of the angiogenic process. Tumor cells, inflammatory cells and stem/progenitor cells were shown to release EV with angiogenic properties suggesting that they may act on vascular remodeling in different physiological and pathological conditions. In this review we discuss the evidence for the role and the mechanisms of action of EV in vascular homeostasis and in the angiogenic processes occurring in tumors, inflammation and tissue regeneration.