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Exosomes: Extracellular Vesicles Transporting Macromolecules

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Extracellular vesicles (EVs), firstly identified in 1983 in the conditioned culture medium collected during the maturation of reticulocytes into erythrocytes [1,2], are released by the cells into the extracellular milieu. EVs are present in all human body fluids; their number and content are often modulated in pathological samples, thus making interesting their evaluation as possible disease biomarkers [3]. On the basis of their size (50-5000 nm) and origin (multivesicular bodies or plasma membrane), three main classes have been described within the family of EVs (Table 1), i.e., exosomes, microvesicles and apoptotic bodies [4]. EVs can be isolated from few milliliters of body fluids (mainly blood) through sequential centrifugations, filtration and sucrose gradients. Notably, they host macromolecules such as proteins, lipids and nucleic acids, and can release these molecules into recipient cells, thus becoming a vehicle for cellular communications [5,6].

The best-characterized EVs are the cup-shaped exosomes, so called in 1987 to define small vesicles surrounded by a double-layer membrane and containing organelle-free cytosol [7]. Microscopic analysis of exosomes by immunocytochemistry procedures provides the first useful information about their content; more sophisticated and miniaturized "omics" protocols can be applied to detect specific protein or RNA (especially miRNA) signatures in EVs.

Exosomes derived from cancer cells are able to transfer some modulators of tumor formation, progression and spread, such as oncogenes/oncoproteins, pro-angiogenic and anti-apoptotic factors, immunomodulators and macromolecules promoting epithelial-to-mesenchymal transition (EMT) (Figure 1). In this respect, the characterization of cancer-derived circulating exosomes (and, in general, EVs) could be useful for early cancer diagnosis and for monitoring prognosis and follow up, avoiding invasive procedures in the favor of the so-called "liquid biopsy" [8-10].

As an example of protein biomarkers, proteomic/peptidomic approaches applied to serum protein profiling of patients with different solid tumors allowed the identification of a correlation between high levels of the protein SPINK1 (serine peptidase inhibitors Kazal type) and poor prognosis [11]. Also the investigation of the exosomal protein HMGB1 (high mobility group box 1) revealed that, when expressed at increased levels in serum from cancer patients, it is a general marker of bad outcome [12]. An active search for miRNAs packaged within EVs is done, exploiting modern technologies such as microarray profiling, PCR arrays and next generation sequencing; in fact, specific miRNA "signatures" have been found in serum from cancer patients [13,14]. However, to validate circulating EVs and their cargo as disease markers, multicenter surveys are required and standard procedures of isolation/characterization have to be developed.

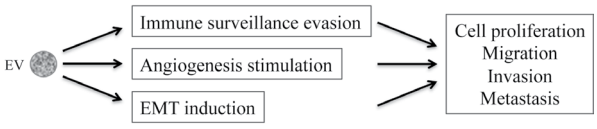

Figure 1: Effects of extracellular vesicles (EVs) secreted by cancer cells. In recipient cells, EVs stimulate angiogenesis, affect the immune system and promotes epithelial-to-mesenchymal transition (EMT). These changes, in turn, favor cancer cell proliferation, migration and invasion, leading to metastasis formation.

EV type	Origin	Shape	Size (nm)	Density (g/cm^3)
Exosomes	Multivesicular bodies	Cup-shaped	50-150	1.13-1.19
Microvesicles	Plasma membrane	Heterogeneous	50-2000	?
Apoptotic bodies	Plasma membrane	Heterogeneous	50-5000	1.16-1.28

Table 1: Distinctive features of the different EVs.

EVs/exosomes field is very "hot", not only because these extracellular structures mediate cell-to-cell communication but also because they can be considered as circulating biomarkers, in particular of cancer, where they promote proliferation, migration, invasion and metastasis [15,16]. Given the growing interest towards cell free circulating EVs, the *Journal of Extracellular Vesicles* (Co-Action Publishing) becomes the reference Journal for the scientific community; updated libraries of macromolecules included in exosomes can be found at http://microvesicles.org and http://evpedia.info. As a cautionary note, it has to be taken into account that validation of circulating biomarkers, as well as setting of reproducible sensitive/specific protocols focusing on the pre-analytical, analytical and post-analytical quality requirements for identifying and validate reliable cancer markers, are required to make "liquid biopsy" a fundamental clinical tool [17].

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