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Editorial

Fundamentals in Extracellular Vesicles Biology

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EDITORIAL

Extracellular vesicles (EVs), including microvesicles and exosomes, are small membrane vesicles derived from the cellular membrane or from multivesicular bodies and are secreted into the extracellular space by many cell types.

Microvesicles, that differ from nanovesicles because of their size and their mechanism of generation, are released by shedding or budding from the plasma membrane. They are typically bigger than 0.2 μm and are also termed microparticles or ectosomes. On the contrary nanovesicles, that comprise exosomes, show a diameter between 30 - 100 nm, are characterized by an endocytic origin and are formed by the reverse budding of the peripheral membrane of multivesicular bodies or late endosomes [1].

The therapeutic potential of extracellular vesicles is enormous. The aim of this Editorial is to feature their role in regulating cell communication and in addition their potential therapeutic applications.

EVs convey a collection of bioactive molecules: membrane-derived receptors, proteins, nucleic acids, lipids, carbohydrates, and genetic material including mRNA and microRNAs [2]. The state of activation, infection and/or transformation and the lineage of the parent cells as well as their microenvironment define the composition of the EV cargo. Viceversa, the phenotype of recipient cells is also affected by the content of "donor" EVs. From this point of view, the combination of several mediators delivered at the same time by EVs is considered a more potent way of intercellular signalling than the common transfer of single molecules.

The involvement of EVs in the development of numerous diseases as infectious, neurodegenerative, cardiovascular diseases and cancer has been addressed in multiple studies [3-5].

Regarding viral infection, the expression of viral proteins can alter the production and secretion of exosomes, leading to microenvironment modification. Exosomes produced by Human Papillomavirus (HPV)-positive cells can potentiate the virus-induced tumorigenesis. Their exosome cargo is composed, among the others, by E6 and E7 oncogenes as well as HPV-deregulated microRNAs that finally affect different target cells [6].

Many studies also addressed the role of EVs, expecially exosomes, in cellular comunication during tumorigenesis. It has been reported that exosomes are able to establish a sophisticated network of communication between tumor and normal cells and this feature is peculiar of each step of cancer progression ranging from tumor growth to spreading and metastasis. Nevertheless, scarce evidences are available on *in vivo* data as well as on human samples. This underlies the need of new approaches to elucidate the interplay between EVs and the other players in the tumor microenvironment.

Based on the EVs occupancy of different body fluids and their molecular content, EVs are potentially strong biomarkers for disease.

Moreover, EVs are being investigated as vehicles for delivering therapeutic purposes [7]. Several ongoing clinical trials involving EVs are under evaluation in cancer, autoimmune, metabolic and degenerative disesases. This approach has some advantages compared to nano- or liposome-based therapies. For example, EVs and exosomes elude recognition and phagocytosis by macrophages and, by consequence, stay longer in the bloodstream; however, a number of limitations also hamper the translation of EVs into clinical use. One of the major issue hindering EVs and exosomes into clinical applications is the lack of highly purified, GMP-grade, EVs/exosomes preparation. Indeed, exosomes are in low number and a consensus on protocols to isolate/purify them is still missing [8]. To optimize EVs therapeutic use, EVs dosage, number of particles to be used, protein content and protein-to-vesicle ratio is still matter of debate [9]. Another critical point to fix for granting an efficient delivery is to combine an optimal load of bioactive components into EVs without altering their structural architecture. Indeed, it has been demonstated that, based on the nature of the donor cells, the loading of different types of bioactive cargoes could render EVs immunogenic, making them susceptible to immune recognition and degradation. Future studies should address these critical issues in order to develop and standardize appropriate procedures to modify exosome contents in a loading process.

EVs can act locally by binding neighbouring cells or the extracellular matrix, or distantly through passively movement into the bloodstream or other body fluids. Certain blood-borne extracellular vesicles are quickly caught by marginal zone phagocytes in the spleen, by Kupffer cells in the liver and by DCs and macrophages in the lungs. Unfortunately, the fast clearance of extracellular vesicles by phagocytic leukocytes could be an issue for their therapeutic use.

This brief overview would like to provide researchers from both inside and outside of the EV community with an outlook of the current status of the EV research field and the future challenges.

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