The field of extracellular vesicle (EV) biology has undergone a rapid and extensive expansion in the last few years. What began as a story of cellular "garbage cans" has in the course of 30 years or so developed into a saga of a nanoparticle-driven universal communication system that appears to be operating in all multicellular as well as unicellular organisms (1,2). It is clear that this communication system is preserved by the evolution and is necessary for the survival of the species.

The number of publications featuring EVs and their participation in biological interactions between cells in health and disease has increased exponentially in the last 10 years, reflecting an enormous interest in the molecular and genetic reprogramming that EVs mediate. The collection of articles presented in this volume serves as an example of the width and breath of research in the EV field that reaches into diverse aspects of physiological and pathological changes induced by EVs in tissues, organs and organisms. The broad coverage of the impact EVs exert in health and disease is intentional, and it serves to emphasize functional versatility of EVs as well as their potential to serve as future biomarkers for many different human diseases.

The remarkable progress in nano-biology has enabled us to recognize, identify and begin to evaluate EVs not only in the supernatants of various human cell lines but also in human body fluids (3). This has led to a better, although still fragmentary, understanding of the complexity of this communication system. As the articles included in the present volume indicate, EVs appear to be involved in the development, maturation and homeostasis of all major signaling pathways and to actively participate in many disease states. An interesting caviat of EV interactions with recipient cells is their dual capability to activate or inhibit responses. The EV cargos contain both stimulatory and inhibitory messages that are delivered as an array or a "bundle" to recipient cells. This implies that the recipient cell has a choice to accept or reject the message, depending on the environmental cues it receives. Interactions of EVs with their cellular targets are thus contextual and environmentally regulated.

As much as the EV functions engage the interest of the scientific community, a number of unanswered questions exist. One commonly voiced criticism is that EVs "are involved in everything," defying the concept of regulated biological processes that are expected to be cell-, tissue- or organ-specific. While it is not known whether or how the EV release by parent cells is regulated, their excessive production by stressed or diseased cells suggests that in case of pathologic situations, EVs are especially needed. The fact that EV mediate autocrine signaling provides additional evidence for the important role of EVs as guardians of the parent cell wellbeing. EV-mediated long-range paracrine-type communication depends on their ability to safely deliver precisely-designed messages from the parent to recipient cells. These messages, in the form of nucleic acids, are safe and protected inside the EV lumen, a distinct advantage for effective communication. Specificity of the EV network might rest on the unique identity of the parent and recipient cells. The address imprinted into EVs by the parent cell might be recognized only by a designated recipient cell. Cross-talk is maintained by the biological mechanisms normally used by a recipient cell that may include endocytosis, phagocytosis or receptor/ligand-type signaling. Thus, messages delivered by EVs are not haphazard but are directed to where they are needed most. While this view of the EV communication network is not yet backed by experimental evidence and might be entirely ficticious, it makes biological sense. A communication network has to operate efficiently and precisely, otherwise it becomes useless. EVs have a potential to meet the required specifications for representing such a network.

EVs are a heterogeneous population of vesicles with different sizes and different cellular origins. The current lack of the nomenclature for various EV subsets reflects this heterogeneity (4). It may be that different EV subsets have distinct phenotypic and functional characteristics and that a division of labor in distributing the messages exists. Technologies for separation and characterization of different EV subsets are rapidly emerging, and it is likely that it will be possible to differentiate among these subsets in the near future. There is great interest in the identification of the cargo EV subsets, such as, e.g., exosomes, carry. This interest is fueled by the likely possibility that EVs will prove to be useful in the near future as non-invasive biomarkers of various pathological conditions. There is also interest in the use of *in vitro* engineered EVs for therapy based on their potential to deliver drugs to disease sites.

The attributes of EVs discussed in this book provide for an interesting overview of the multiple roles EV subsets assume in several different human diseases. The book consists of a series of short and focused chapters grouped by a common theme and covering EV-mediated contributions to cancer, hematopoiesis, inflammatory conditions, tissue repair, infections or immune therapies. This selected series of short and focused presentations is an easy read. At the same time, it provides a comprehensive appraisal of the recent progress in the EV biology.

References

1. Boyiadzis M, WhitesideTL. Information transfer by exosomes: anew frontier in hematological malignancies. Blood Rev 2015;29:281-290.
2. Antonyak MA, Cerione RA. Microvesicles as mediators of intercellular communication in cancer. Methods Mol Biol 2014;1165:147-173.
3. Li P, Kaslan M, Lee SH, et al. Progress in exosome isolation techniques. Theranostics 2017;7:789-804.
4. Lotvall J, Hill AF, Hochberg F, et al. Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular vesicles. J Extracell Vesicles 2014;3:26913.

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