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PERSPECTIVE

Extracellular vesicles and homeostasis—An emerging field in bioscience research

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Abstract

To keep abreast of developments in the biological sciences and in parallel fields such as medical education, *FASEB BioAdvances* (*FBA*) has created a special collections category, *FBA* special collections (*FBA* SC), that target, among other topics, emerging disciplines in the biomedical sciences. This *FBA* SC is focused on the emerging field of extracellular vesicles (EVs) and homeostasis. Leading investigators in the biology of EVs around the globe have contributed to this collection of articles that cover the gamut of research activities from biogenesis and secretion to physiological function.

The biology of extracellular vesicles (EVs) is a developing field of biological research that has broad and fundamental implications for our understanding of signaling and communication within broad swaths of the biological kingdom, including plant and animal cells.[1,2] A novel EV hypothesis states that many eukaryotic cells secrete small membrane-bound vesicles (called exosomes and microvesicles) that package informational content and directional queues that are part of a larger communication system in multicellular organisms. Vesicle cargo may include signaling molecules, enzymatic machinery necessary for metabolic function, or derelict biomolecules ready for disposal. It is proposed that EV-mediated communication within tissues can be either monodirectional or bidirectional that functions as a novel -crine system—(i.e., EV-crine). EV-based cellular conversations can be monologues, for the benefit of the producing cell or, perhaps less prevalent, dialogues, where the receiving cell signals to the producing cell in a feedback manner. EV-crine signaling could be a component of well characterized macromolecular signaling systems operating in multicellular organisms—for example, EV angiocrine, EV paracrine, and EV endocrine systems. The EV-crine hypothesis is outlined in Figure 1.

We have witnessed extraordinary developments in our understanding of membrane trafficking and signaling over the last half century bookmarked by the Noble Prize to Christian deDuve, George Palade, and Albert Claude at one end for their discovery of cellular organelles and the recent prize to Randy Scheckman, James Rothman, and Thomas Sudhof, at the other, for their pioneering work establishing the molecular basis of vesicle transport. The field of EV biology builds on this remarkable progress. Several discovery papers have

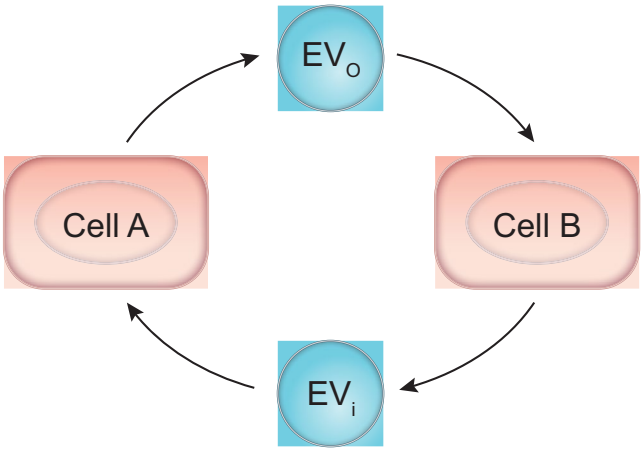

FIGURE 1 The EV-crine hypothesis consists of donor cells that assemble and secrete outward bound extracellular vesicles (EV_o) that make their way via extracellular and body fluids to designated cellular or tissue targets. Upon reaching their targets, with potentially high specificity, signaling events, exchange of cellular components, or degradation activities proceed. The acceptor cell/tissue may respond (monologue) without feedback or it may participate in a feedback cycle (dialogue) by secreting EV_i (inward bound EVs) or other factors that target the donor population by selectively suppressing the assembly/secretion of Ev_o. The balance of these two biological vectors (monologues and dialogues) creates a dynamic homeostatic state

been key—the discovery of a novel intracellular protein sorting and secretion pathway (the exosome secretion pathway) almost four decades ago[3] and the discovery that EVs secreted by antigen presenting cells are signaling entities capable of carrying informational molecules from one cell to another.[4] Additional breakthroughs include research from two groups who independently showed that EV s can carry nucleic acids including mRNA and miRNA that mediate cell to cell signaling.[5,6] Buoyed by these latter findings, interest in EV research community surged and the wheels of discovery unleashed. Over the past two decades, thousands of papers have been published, scholarly societies have been formed, international meetings have been organized, and these efforts collectively have seeded the broad acceptance of the EV concept among the international research community.

Although the concept of EV-mediated information transfer is broadly accepted, many challenges face this nascent field of research in establishing a mechanistic understanding of vesicle assembly, secretion, and targeting. The assembly and secretion of EVs represents a unique challenge to the membrane trafficking community. The multivesicular body (MVB), historically associated with the lysosomal degradation pathway has taken on an entirely new role as an EV packaging organelle.[7] Several mechanisms and molecular machineries operate at the MVB and the plasma membrane (PM) to segregate cargo (proteins, lipids, genetic material) and generate vesicles [1] often leading to a heterogeneous population of vesicles in terms of size and composition. It is likely that the formation of physiologically relevant vesicles is cargo driven (either inside MVBs or at the PM). In the context of a homeostatic system, the secretion of EVs, either by fusion of MVBs with the plasma membrane or by contemporaneous assembly and disembarkation of EVs from the plasma membrane, represent highly controlled and choreographed signaling and trafficking events.

Lastly, the targeting of secreted EVs to their cognate targets within biological systems and the mode of incorporation of information into recipient cells represent a second major challenge, understanding of which is not only important to comprehend fully the physiological and pathophysiological importance of EV communication but the exploitation of EV targeting to diagnostics and therapeutics and in the plant world, to agriculture. Is there a single EV with the requisite cargo and targeting information to be physiologically relevant? Or is the delivery system dependent on the aggregate effect of multiple EVs perhaps tethered or clustered together as suggested by a recent report.[8] Delineating EV biology by establishing first principles at both the cellular and systems level will expand our understanding of physiology, both animal and plant, writ large.

In this special collection entitled "Extracellular Vesicles and Homeostasis," we selected contributions from investigators whose work reveals and highlights the leading edge of EV research at both the cellular and systems level. At the cellular level, we explore the biogenesis of both exosomes and microvesicles and the role of the autophagic pathway in vesicle assembly. The key role that animal models will play in understanding the physiological role of EVs is highlighted. We include an analysis of specialized cellular structures such as flagella and the targeting of EVs across biological barriers such as the blood—brain barrier. From the systems side, we have chosen investigators whose work bears on fundamental questions of the role of EVs in metabolism and disease as well as the role of EVs in aging and development. The role of EVs in the plant world of research, an ever-growing component of the EV biology, is also highlighted. It is not possible to cover all aspects of this broad and widely developing field which touches virtually all aspect of eukaryotic cells and their exchange with their microenvironments in multicellular organisms but the collection will serve as a 'tip of the iceberg' glimpse of some of the most exciting developments in EV biology.

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