Quick guide

Ectosomes

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What are ectosomes? Ectosomes are vesicles of various size (0.1–1 μm in diameter) that bud directly from the plasma membrane and are shed to the extracellular space. At variance with living cells, ectosomes have on their surface the phospholipid phosphatidylserine. These vesicles were long considered to be artefacts, and then they were confused with exosomes — the vesicles discharged upon exocytosis of multivesicular bodies — and with cytoplasmic particles generated during apoptosis. Now, ectosomes attract great interest: of the hundreds of papers published so far on ectosomes, over 50% have appeared in just the last two years.

How did ectosomes get this name? Ectosomes are also known by other names, for example, microparticles, microvesicles, and shedding vesicles. These names may be misleading, however, whereas the term ectosome is clear: it emphasizes that these vesicles are discharged outside, and not inside the cell, and that they are similar to, but distinct from, exosomes.

Are ectosomes all the same? No, they are highly heterogeneous, both in size and in composition. Ectosomes are made up of components (proteins, mRNAs, and miRNAs) that are typical of their cell of origin and are therefore distinct from those of other cell types. They can vary depending on the cellular state (e.g. resting, stimulated) and depending on the agent employed for stimulation. This variance arises because the membrane and the content of ectosomes are not identical to the plasma membrane and the cytosol of the cell of origin.

How are ectosomes generated? Generation of ectosomes is a complex but efficient process. Specific domains are assembled in the plane of the plasma membrane; proteins destined to appear in the ectosomes are sorted to these domains, and proteins destined to remain in the cell are excluded. Concomitantly, specific cytosolic proteins and nucleic acids (mRNAs and miRNAs) accumulate in contact with the plasma membrane domains. The mechanisms of this accumulation might resemble those of retrovirus budding, as they are dependent on anchoring proteins protruding from the plasma membrane into the cytosol. Budding of the plasma membrane domains with their associated protein/RNA packages requires the local disassembly of the cytoskeleton, possibly by activation of caspase 2. Finally, ectosome discharge occurs by an actomyosin-based abscission process. The mechanisms of its regulation (perhaps involving the ESCRT machinery and/or the small GTPase ARF6) are just beginning to emerge.

Is ectosome release a regulated process? Ectosomes are discharged even by resting cells, but the rate of release is increased considerably upon appropriate stimulation. Impressive responses, mimicking eruptive gun shooting from warships of the early 19th century, have been reported from macrophages and microglia. Weaker responses do occur from many, possibly all other, cell types. The local signal that triggers the response is the increase of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) inducing the disassembly of the cytoskeleton and membrane abscission. The p38 MAPK, acid sphingomyelinase and the Rho–ROCK axis also appear to be involved. $[Ca^{2+}]_i$ increase and MAPK activation can be induced by a variety of agents, for example, ATP-mediated activation of the P2X7 receptor in macrophages and TNFα signalling in endothelia.

How do ectosomes work? This depends on their site of discharge and on the properties of their membrane.

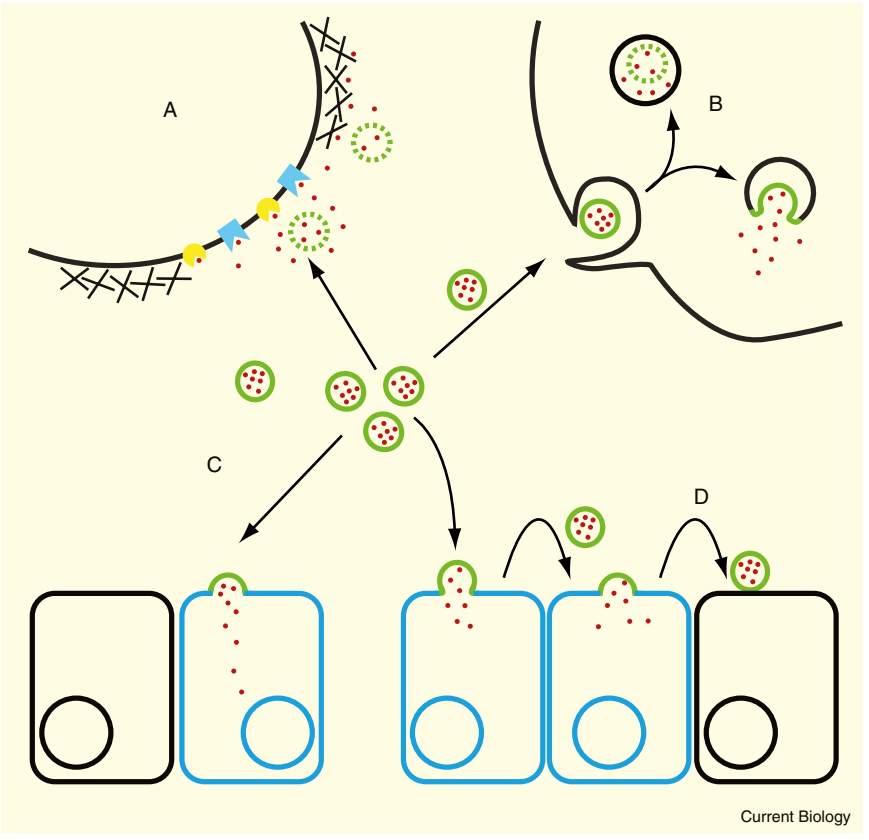

Figure 1. Life cycle of ectosomes.
Generation of ectosomes requires the segregation of membrane domains with associated packages of proteins and RNAs. After their release, ectosomes can (A) diffuse into the extracellular space where they can release their content (released molecules interact with receptors/enzymes in the surrounding cells and digest the extracellular matrix), (B) be endocytosed by cells, ending up in lysosomes or releasing their content to the cytoplasm, or (C) fuse with a target cell, with the ensuing incorporation of their membrane and release of the segregated proteins/RNAs to the cytosol. These processes can lead to changes to the target cell phenotype, with generation and budding of new vesicles that establish a horizontal transfer of their proteins/RNAs to adjacent cells (D). This transfer can play a critical role in important functions, such as proliferation.

Ectosomes from platelets, endothelia and leukocytes are discharged directly into the blood where they can release their content rapidly or persist in the circulation for quite some time. Ectosomes discharged to the tissue intercellular space can also release their content there, remain trapped locally or diffuse some distance. Effects are triggered when ectosomes (or their released molecules) reach their targets, often in cell types distinct from the cells of origin. Released molecules activate key cell-surface molecules, such as receptors and enzymes. Intact ectosomes can either fuse with target cells (with the ensuing incorporation of their membrane in the plasma membrane and release of the segregated package to the cytosol) or be taken up by endocytosis. The fate of the latter is variable: fusion with lysosomes; release of contents in the cytosol; or discharge to the extracellular space by transcytosis (Figure 1).

What is the role of ectosomes in cell biology, physiology and pathology?

Ectosomes are specific, multi-purpose carriers that expand the borders of cells away from the plasma membrane, establishing communication networks by which specific properties and information can be shared among cells. By delivering their molecules at distance without dilution or degradation they reproduce effects otherwise induced by direct cell–cell contact, playing major roles in the integrated functioning of tissues and organs. Digestion of the intercellular matrix by metalloproteinases activated by ectosomes can induce profound changes to the cell environment. Fusion of ectosomes at the surface of target cells delivers exogenous antigens, enzymes and other proteins to discrete sites of the plasma membrane. Concomitantly, release of the segregated protein/RNA packages to target cells can alter gene expression. This might explain, among other events, the functional and phenotypic changes taking place in stem cells without transdifferentiation, sustained by genetic information transferred from tissue cells via ectosomes. Conversely, transfer of genetic information from stem cells to target cells may redirect altered functions, inducing repair of damaged tissues without replacement of parenchymal cells. The heterogeneity of ectosomes can play different, even opposing roles. Ectosomes containing cytokines, in particular interleukin 1β, are pro-inflammatory; others, however, are anti-inflammatory. Monocyte and endothelial ectosomes are often rich in tissue factor, a potent activator of the coagulation cascade, and can therefore trigger coagulation, thrombosis and also angiogenesis. Platelet ectosomes, however, contain low levels of tissue factor, and therefore work differently. Ectosomes derived from leukocytes and platelets have profound effects on innate immunity and also on the induction of adaptive immunity, reprogramming macrophages and dendritic cells toward immunosuppression.

What about ectosomes and disease?

Great interest has been raised by the increased levels of endothelial ectosomes in the blood of patients affected by acute coronary syndromes, atherosclerosis and stroke, a finding now considered for the development of new diagnostic tests. Ectosomes of specific origin are also being studied as a target of new therapies for rheumatoid arthritis and multiple sclerosis, where ectosomes are believed to promote inflammation and cell death, and for cancer, in which ectosomes play a role in invasion and metastasis. The mechanisms of the effects on cancer are multiple. In addition to the above-mentioned roles in digestion of the intercellular matrix and immunosuppression, ectosomes can induce the horizontal transfer among tumor cells of critical molecules such as proteins (e.g. P-glycoprotein (which confers multidrug resistance to the cells), glutaminase, and fibronectin), mRNAs and miRNAs. This transfer is considered to be greatly important for cancer progression.

Where can I learn more?

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Primer

The optimism bias

Tali Sharot

The ability to anticipate is a hallmark of cognition. Inferences about what will occur in the future are critical to decision making, enabling us to prepare our actions so as to avoid harm and gain reward. Given the importance of these future projections, one might expect the brain to possess accurate, unbiased foresight. Humans, however, exhibit a pervasive and surprising bias: when it comes to predicting what will happen to us tomorrow, next week, or fifty years from now, we overestimate the likelihood of positive events, and underestimate the likelihood of negative events. For example, we underrate our chances of getting divorced, being in a car accident, or suffering from cancer. We also expect to live longer than objective measures would warrant, overestimate our success in the job market, and believe that our children will be especially talented. This phenomenon is known as the optimism bias, and it is one of the most consistent, prevalent, and robust biases documented in psychology and behavioral economics.

The optimism bias is defined as the difference between a person's expectation and the outcome that follows. If expectations are better than reality, the bias is optimistic; if reality is better than expected, the bias is pessimistic. The extent of the optimism bias is thus measured empirically by recording an individual's expectations before an event unfolds and contrasting those with the outcomes that transpire. This methodology reveals, for instance, that students expect to receive higher starting salaries and more job offers than they end up getting. People tend to underestimate how long a project will take to complete and how much it will cost. Most of us predict deriving greater pleasure from a vacation than we subsequently do, and we anticipate encountering more positive events in an upcoming month (such as receiving a gift or enjoying a movie) than we end up experiencing (Figure 1A). Across many different