

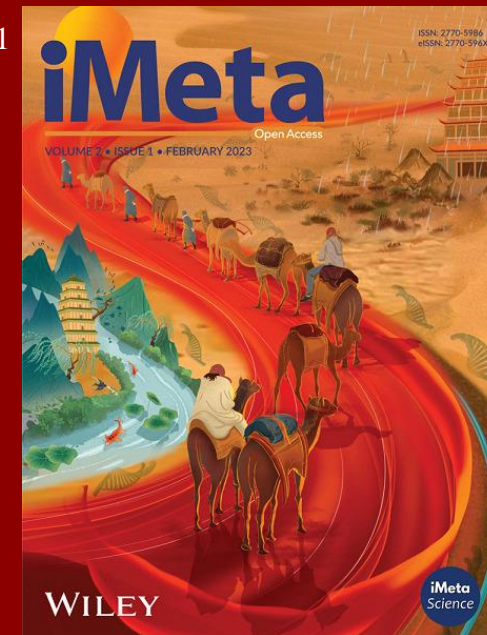
# Interactions between extracellular vesicles and microbiome in human diseases: new therapeutic opportunities

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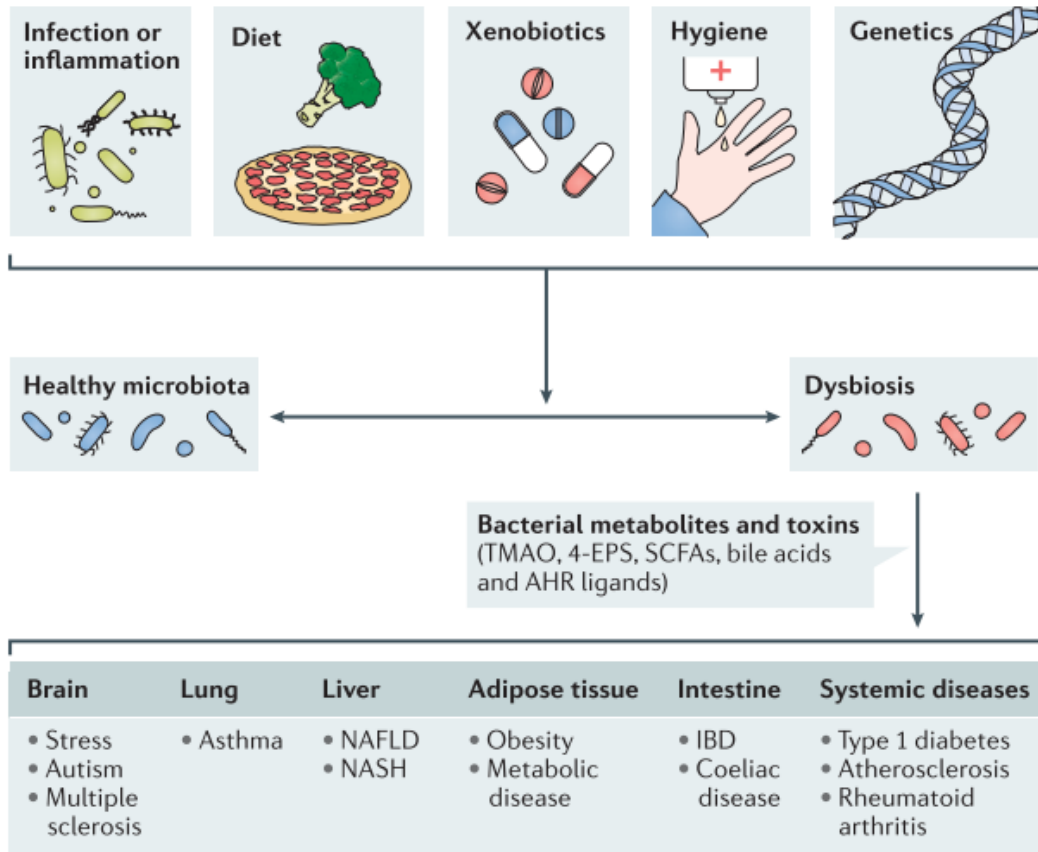


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<https://doi.org/10.1002/imt2.86>



# Introduction



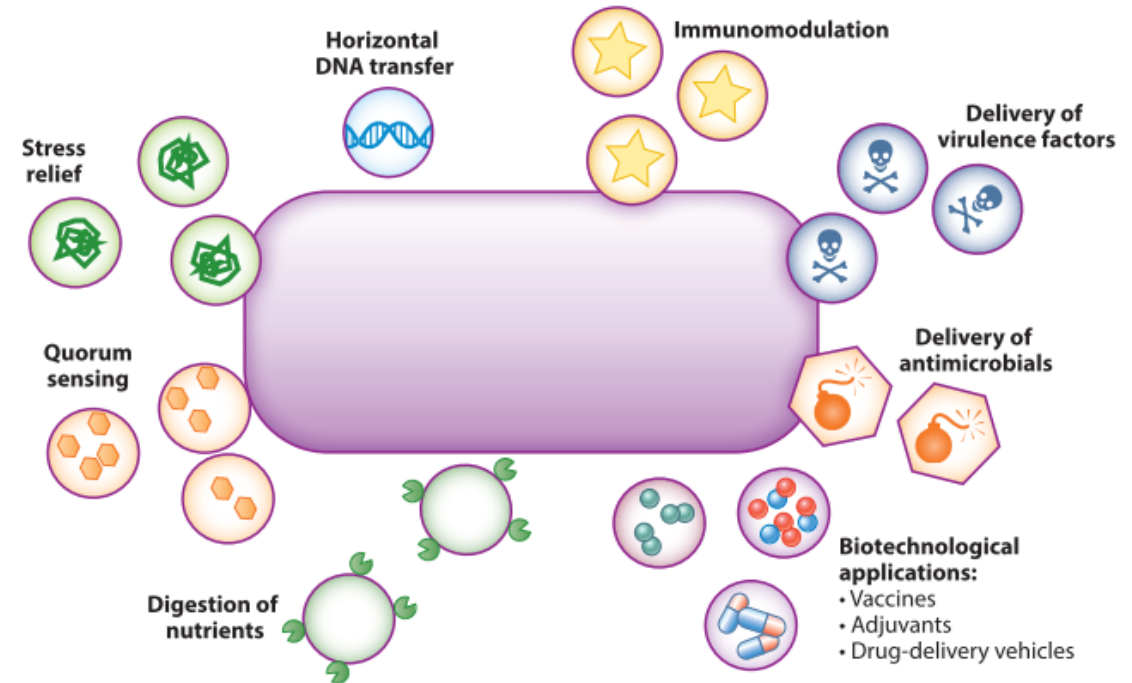
(Nat Rev Immunol. 2017 Apr;17(4):219-232)

- The human body is a symbiotic ecosystem that contains a diverse range of commensal and symbiotic microorganisms, collectively termed microbiota .
- More than 100 trillion microbial cells are estimated to inhabit almost every niche of the human body, especially the skin, oral cavity, respiratory, gastrointestinal, and urogenital tracts
- The composition and quantity of the microbiota community are evolutionarily maintained in homeostasis and perform specific genetic and metabolic functions in human health.
- dysbiosis of the microbiome may result in the onset of various diseases, including inflammatory bowel, autoimmune, metabolic, and psychological/neurological diseases.



# Introduction

- Extracellular vesicles (EVs) are nano-sized, heterogeneous membrane-bound structures that are secreted by nearly all types of cells,
- EVs serve as key intermediaries of intercellular communications by transporting biologically active molecular cargos from parent cells, including lipids, proteins, nucleic acids, and small molecules.
- EVs are responsible for the complex, dynamic, and bidirectional relationship between microbiota and host cells, exerting an essential role in microbiota-host communications and contributing to the regulation of various pathophysiological processes such as inflammation, angiogenesis, nutrient metabolism, and adaptive and innate immunity responses.

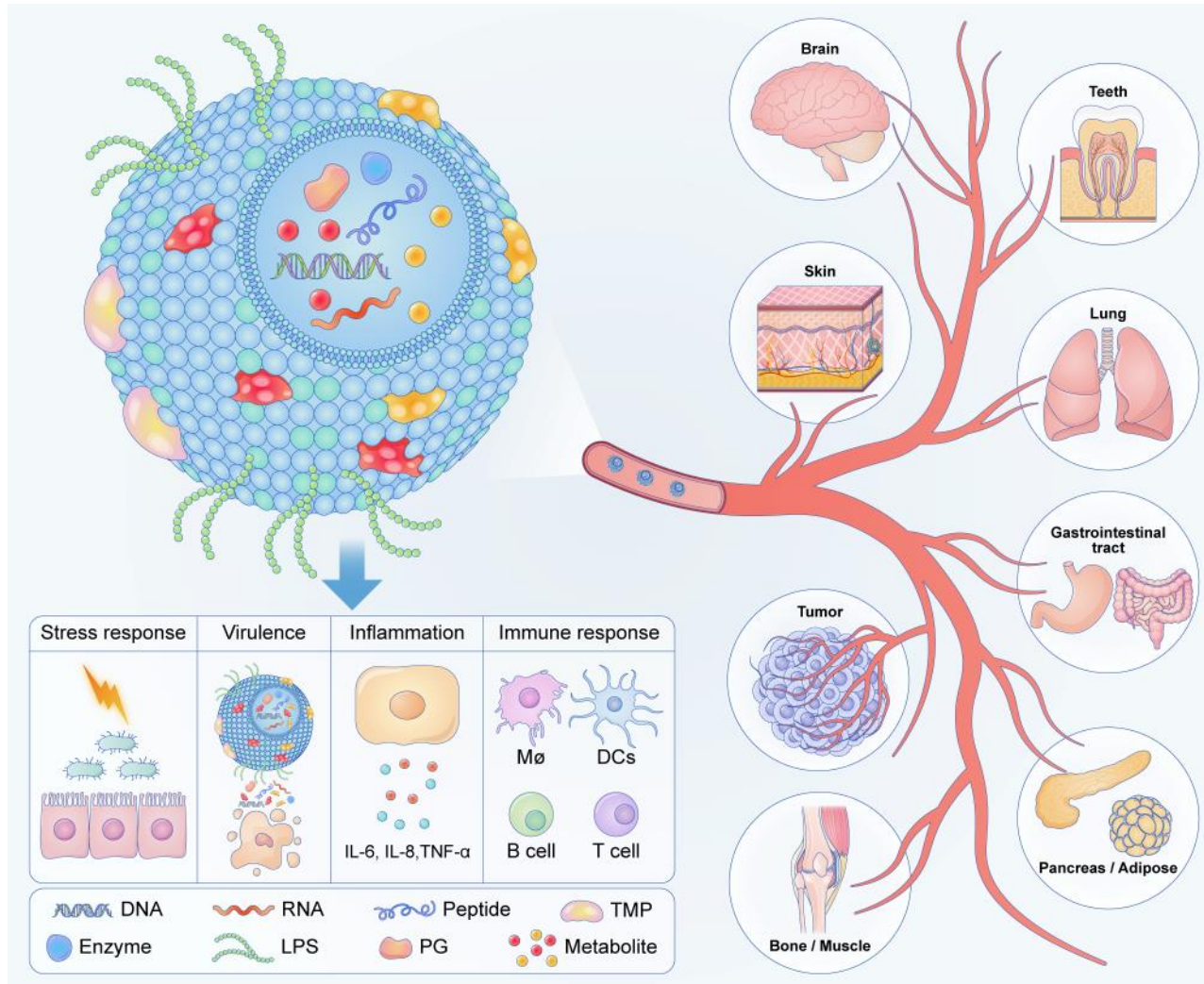


(Annu Rev Microbiol. 2021 Oct 8;75:609-630)



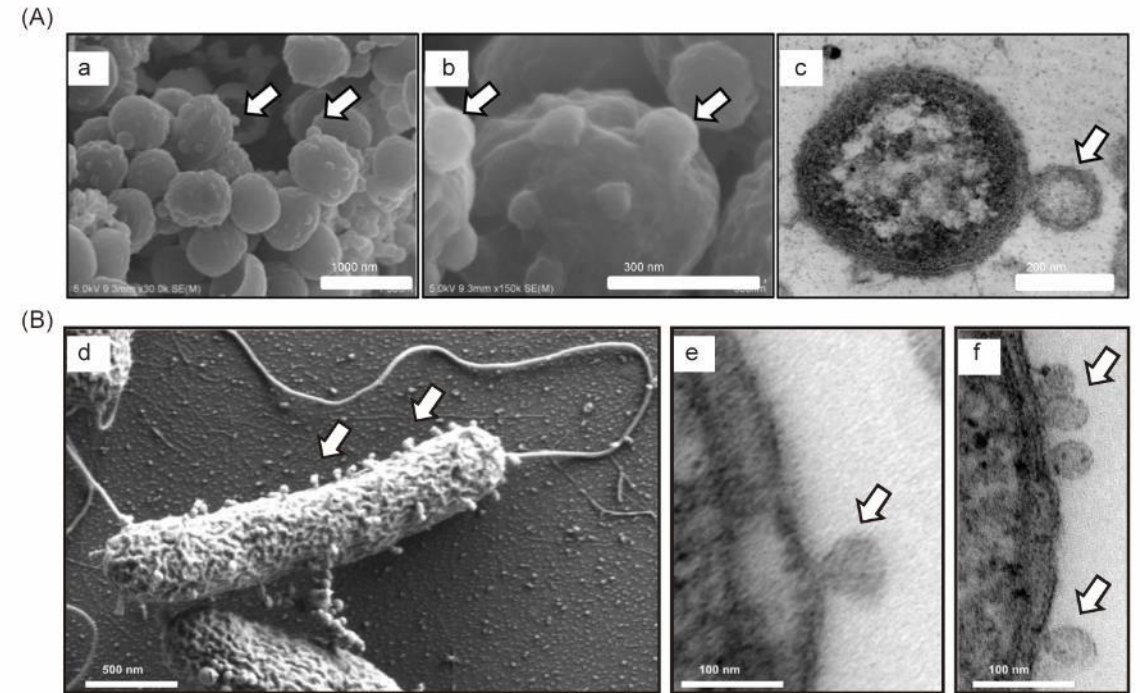
# Contents

- BEVs origin, classification, and biogenesis
- BEVs composition
- BEVs biological functions
- BEVs in pathogenesis
- BEVs clinical applications  
diagnostics, vaccines, and novel therapeutics



# Origin, Classification, and Biogenesis of BEVs

- In 1967, BEVs were observed to bulge out and pinch off from part of the cell wall of *Vibrio cholerae*, which are relevant to toxin excretion.
- In the early 1980s, EVs were found to be secreted from maturing sheep reticulocytes and function as a mechanism for iron transfer
- In 2007, abundant functional RNA were found to present in EVs, suggesting a crucial role for EVs in cell-to-cell communication by RNA delivery



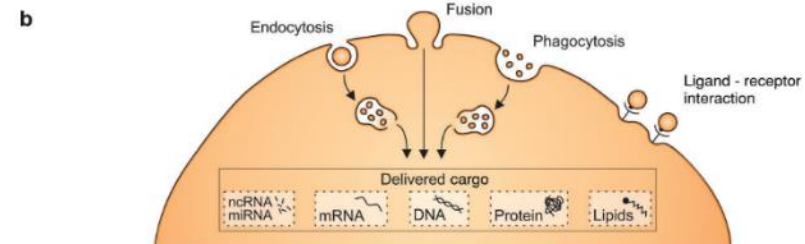
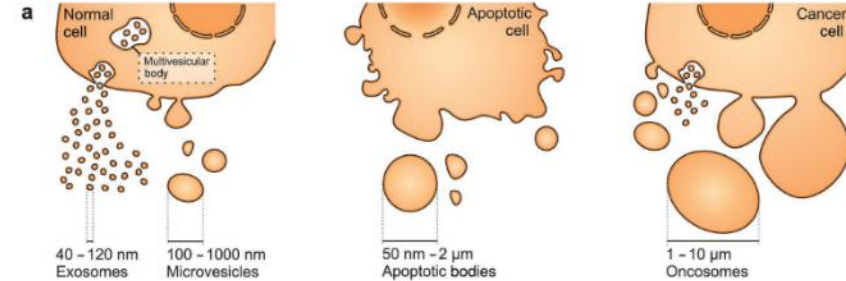
EV production has been identified in nearly all cell types. EV production is a highly regulated process transporting diverse bioactive molecules into recipient cells either in their microenvironment or in distant tissues.



# Origin, Classification, and Biogenesis of BEVs

## Eukaryotic EVs :

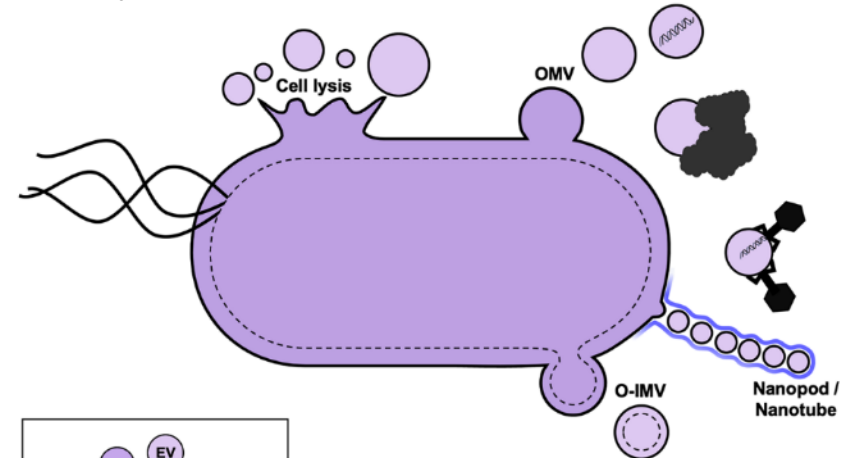
- exosomes (30-150 nm),
- ectosomes or microvesicles (100-1000 nm),
- apoptotic bodies (1000–10,000 nm)



(Bioscience. 2015 Aug 1;65(8):783-797)

## Bacterial EVs:

- OMVs (outer membrane vesicles, G-)
- MVs (membrane vesicles, G+)
- other types: outer-inner membrane vesicles (OIMVs), nanotubes...



(FEMS Microbiol Rev. 2019 May 1;43(3):273-303)



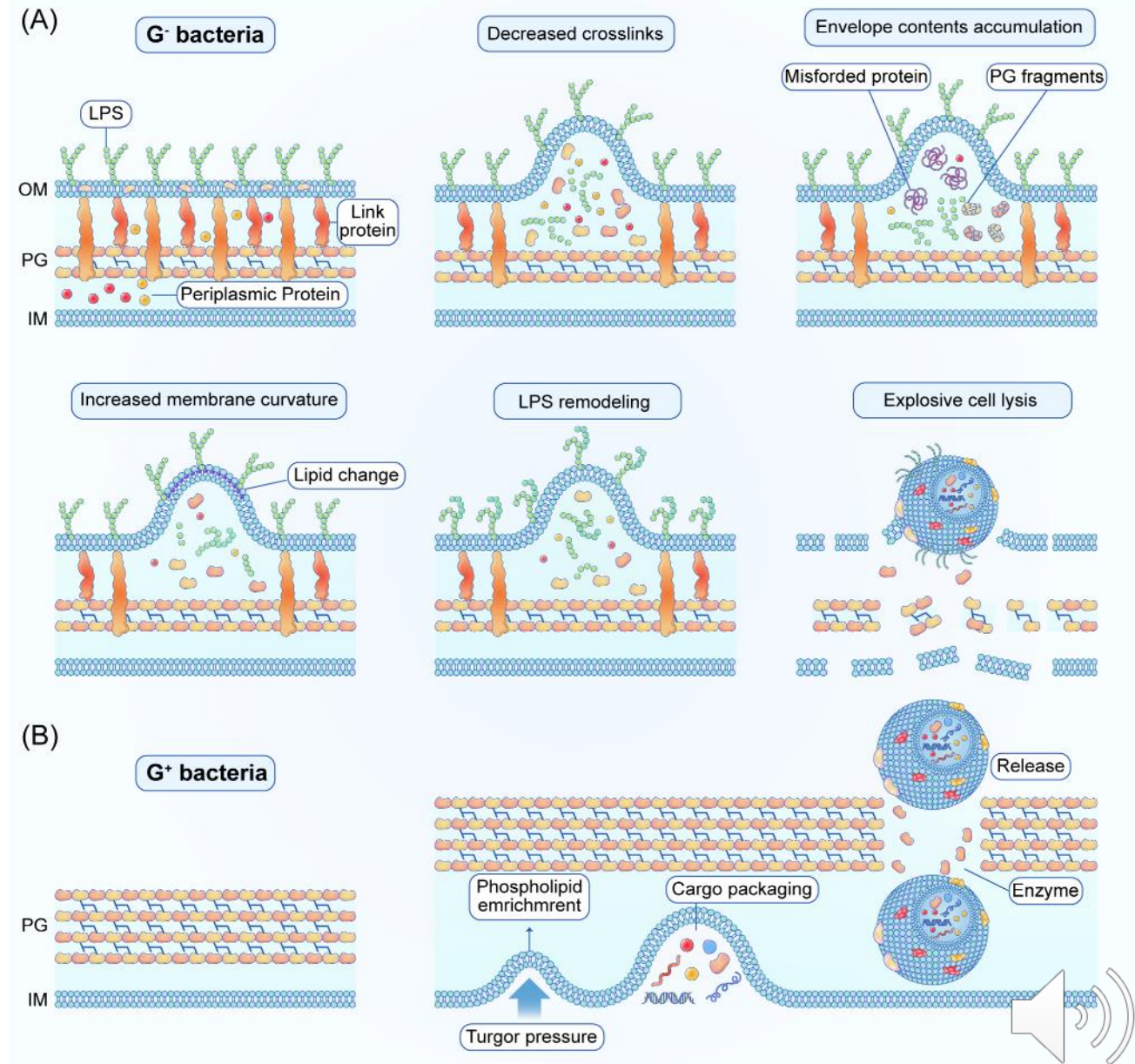
# Origin, Classification, and Biogenesis of BEVs

## OMVs formation:

- decreased interaction between the outer membrane and the PG layer.
- local turgor pressure overload.
- increased outer membrane curvature.
- LPS remodeling.
- explosive cell lysis.

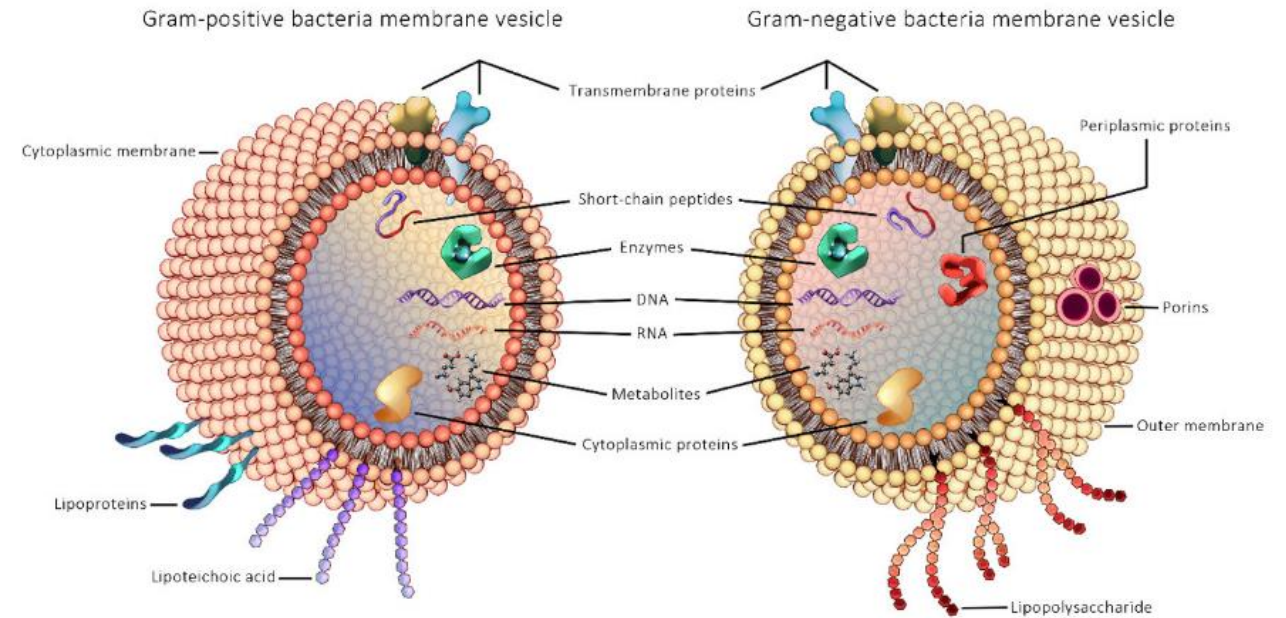
## MVs formation:

- accumulation of phospholipids in membrane.
- turgor pressure .
- cell wall modification / degradation
- release by protein channels or structural cables.



# Cargo Packaging into BEVs

- BEVs incorporate different biological components, including **proteins, lipids, nucleic acids, and small molecules.**
- The quantity and variety of cargo selectively packaged into BEVs are influenced by their **producer bacteria** and environmental factors, such as **growth phases, nutrient availability, pH, and temperature**



(Cancers (Basel). 2021 Oct 29;13(21):5450)



# BEVs Biological Functions

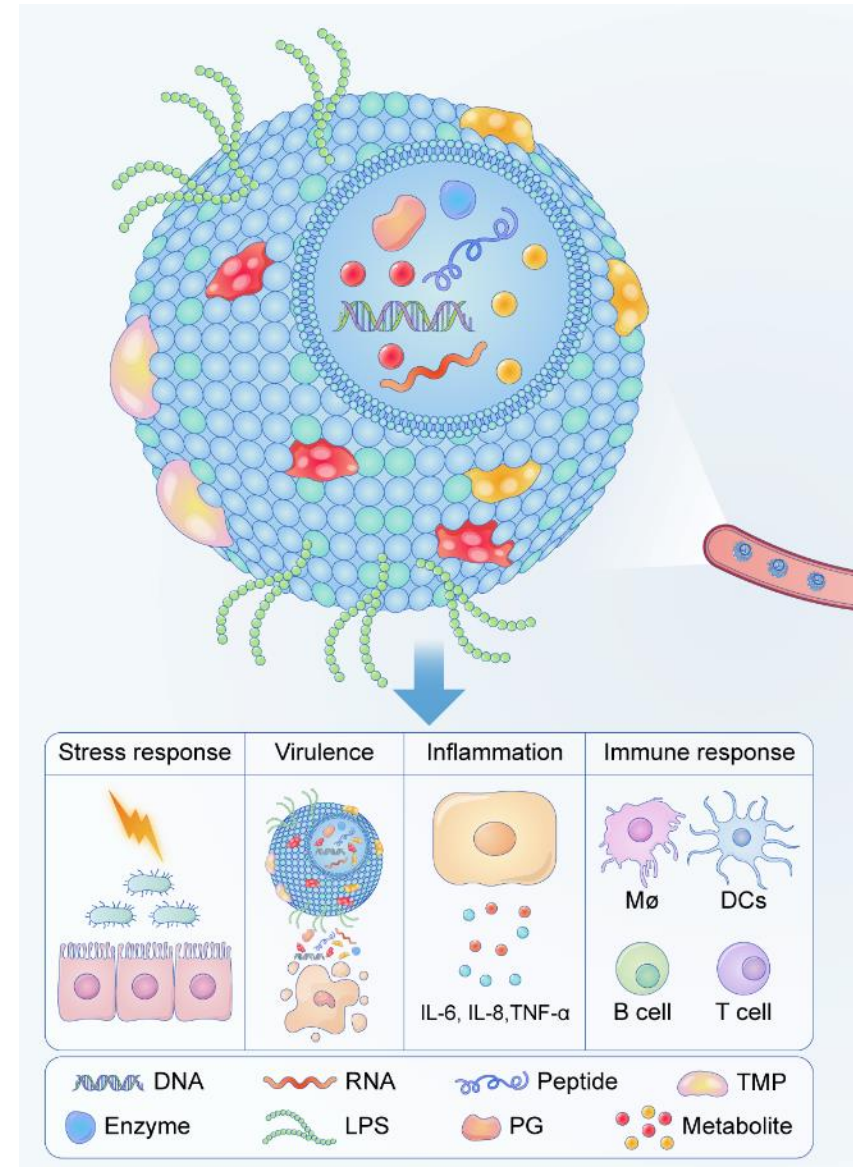
## ➤ **Defensive stress response**

Biofilms formation,  
neutralizing environmental attacks,  
antimicrobial resistance

## ➤ **Delivery of virulence factors**

## ➤ **Pro- and anti-inflammatory responses**

## ➤ **Immunomodulation**

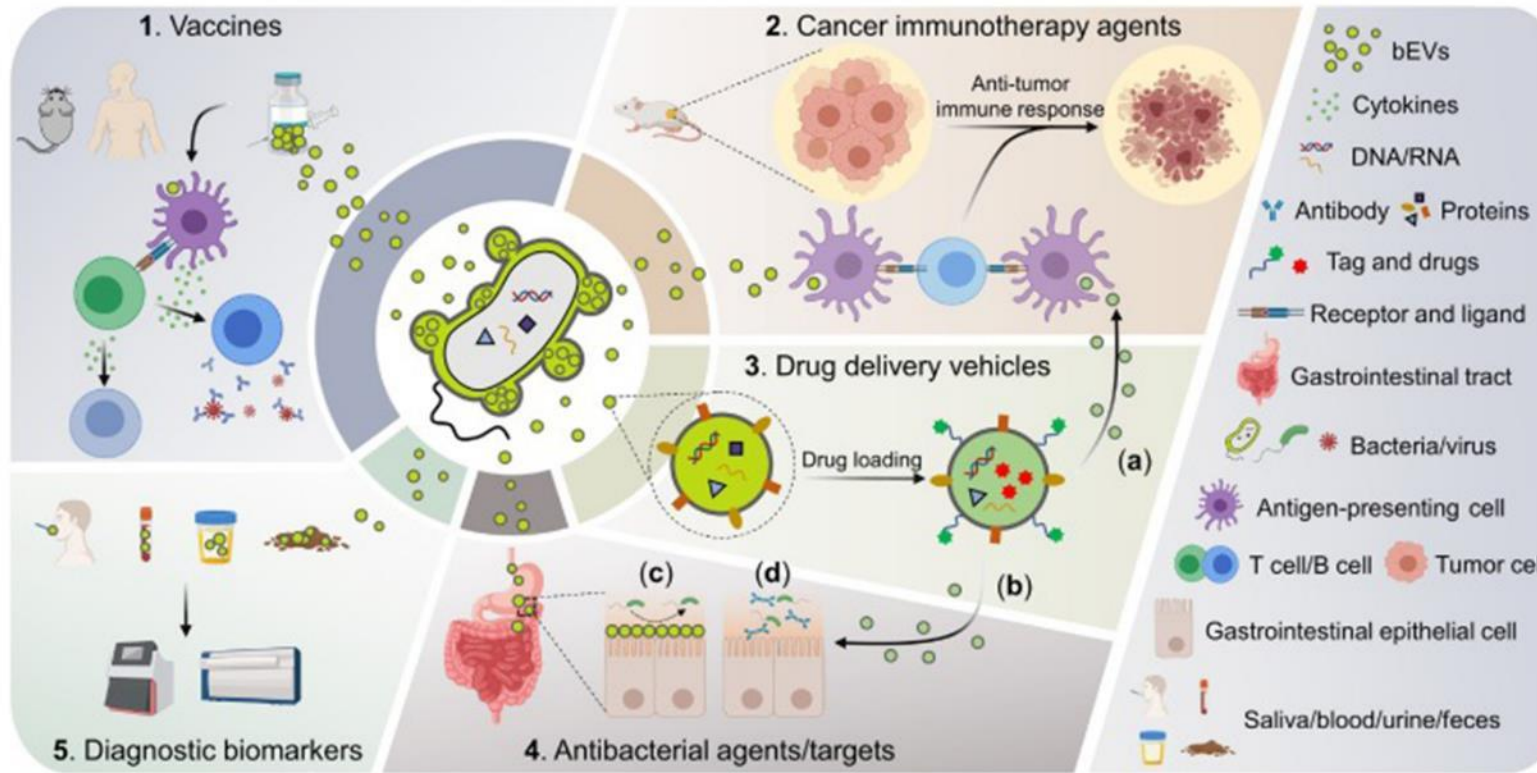


# BEVs in Pathogenesis

- Gastrointestinal Disease
- Respiratory Disease
- Dermatological Disease
- Neurological Disease
- Periodontal Disease
- Metabolic Disease
- Musculoskeletal Diseases
- Cancer
- .....



# BEVs in Clinical Applications



(Trends Biotechnol. 2022 Oct;40(10):1173-1194)

BEVs advantages in clinical applications:

- cost-effectiveness in production;
- stability to transport and storage;
- convenience for modification;
- immunomodulatory properties.



# BEVs in Clinical Applications

## BEVs in diagnostic analytics:

- BEVs released by microbiota can rapidly travel throughout the body.
- BEVs packaged with diverse parental genomic and metabolic information indicate their origin and reflect the composition and metabolic status of the microbiota.
- Meta-omics technologies (metagenomics and metabolomics) combined with bioinformatics analytic technologies provide detailed BEVs landscape.
- BEV-based diagnostic models integrated with other diagnostic modalities can provide improved diagnostic performance.



# BEVs in Clinical Applications

**BEVs in vaccine design:** BEVs are non-replicating entities, with a size of 20–250 nm, and contain key antigenic components to stimulate immune response.

## ➤ **Native BEVs-based vaccines**

BEVs vaccines have immunostimulatory efficiency comparable to that of the whole inactivated cell vaccine.

BEV vaccine against *Neisseria meningitidis* has been licensed for clinical use in 1987. BEVs are promising candidate vaccines against pathogenic infections.

## ➤ **BEVs as vaccine adjuvants**

BEVs contain multiple PAMPs (such as LPS and lipoproteins), promoting APCs maturation and antigen-specific immune response activation

## ➤ **Bioengineered BEVs-based vaccines**

Genetic engineering techniques improve BEVs immunogenicity, safety, and production, while removing BEVs toxins and deleterious compounds.



# BEVs in Clinical Applications

## **BEVs in therapeutics development:**

- **Native or natural BEVs-based therapeutics.**

intrinsic bioactive properties, including anti-inflammation, immunomodulation, pro-survival.

- **BEVs serve as drug delivery vehicles.**

loading capacity, specific targeting, and temperature stability

- **BEV-based anti-cancer therapies.**

specific targeting, , drug loading, protection against degradation, and fewer adverse side effects



# Summary

## SUMMARY POINTS:

- BEVs are key intermediators of microbiota-host communications by transporting their versatile bioactive cargoes, including proteins, nucleic acids, lipids, and metabolites.
- BEVs are proposed to exert both positive and negative roles in diverse physiological and pathological processes.
- BEVs secreted by pathogenic bacteria are strongly associated with the onset and progression of various human pathologies.
- BEV-based platforms show promising clinical potential, including applications in diagnostic analytics, vaccine design, and novel therapeutic development.



# iMeta: Interactions between extracellular vesicles and microbiome in human diseases: new therapeutic opportunities

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