BACTERIAL PATHOGENESIS

LEGIONELLA PNEUMOPHILA

ENCOUNTER

NATURAL ENVIRONMENT

- FRESHWATER ENVIRONMENT (RIVERS AND LAKES)
- GROW BEST IN WARM WATER IN PRESENCE OF AMOEBAE AND CILIATED PROTOZOA
- FOUND GLOBALLY (USA, CANADA, NEW ZEALAND, AUSTRALIA, JAPAN, SINGAPORE, AND IN EUROPE).
- CAN ALSO SURVIVE FOR SEVERAL DAYS ON WARM MOIST SOIL.

ARTIFICIAL ENVIRONMENT

SHOWERS ,TAPS, AIR CONDITIONING SYSTEM ,

PLUMBING SYSTEMS, DECORATIVE FOUNTAINS

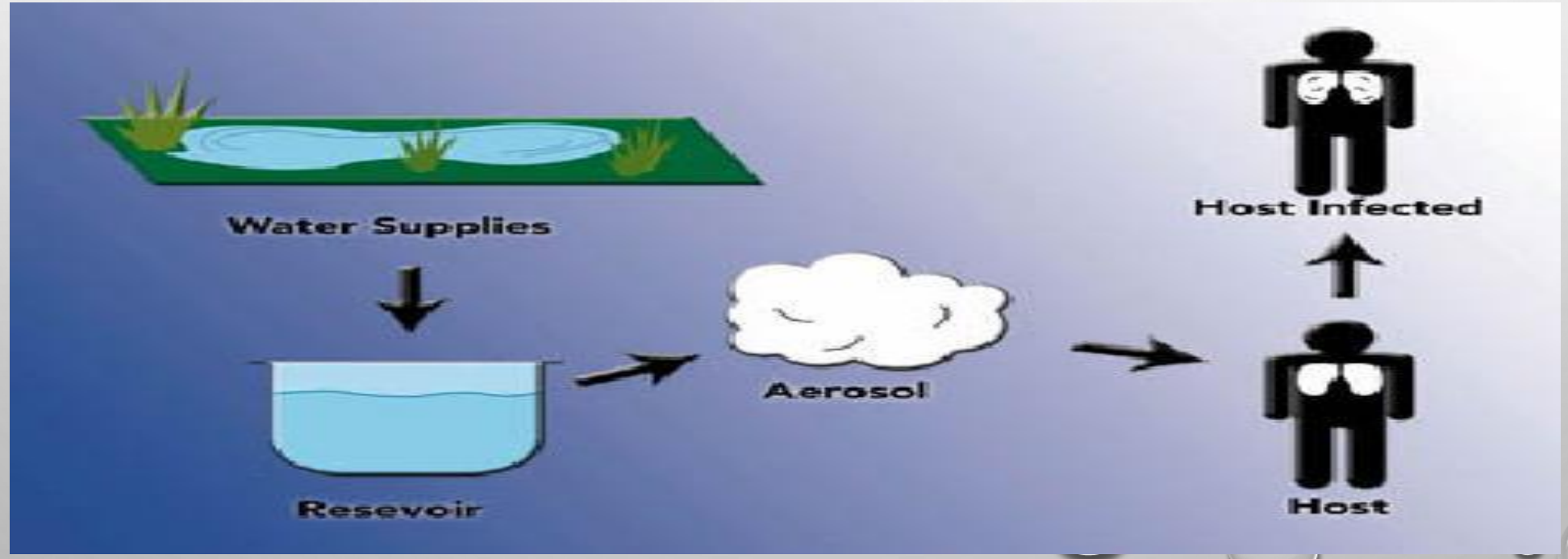
NORMALLY FOUND IN HOT WATER TANKS

RESIDE

- THE OPTIMAL GROWING TEMPERATURE FOR L. PNEUMOPHILA IS 35C, BUT THEY CAN GROW AT TEMPERATURES BETWEEN 20C AND 50C
- HOT TUBS AND POOLS CAN PROVIDE OPTIMAL CONDITIONS FOR THIS BACTERIA TO PROLIFERATE.
- THE PRIMARY CAUSES OF BACTERIAL OUTBREAKS IN HOT TUBS ARE UNCONTROLLED WATER TEMPERATURES, INSUFFICIENT LEVELS OF DISINFECTANTS, AND LACK OF CLEANING LEADING TO THE FORMATION OF BIOFILMS
- HOT TUBS ARE SIGNIFICANT SOURCE OF AEROSOLS

MEANS OF TRANSMISSION

- INHALATION OF LEGIONELLAE IN AEROSOLIZED DROPLETS
- AEROSOLIZED DROPLETS MUST BE OF A RESPIRABLE SIZE (1–5 MM).
- NO PERSON-TO-PERSON TRANSMISSION OF LEGIONNAIRES' DISEASE HAS BEEN DOCUMENTED.



BACTERIAL CONTACT

- AEROSOLS AND DROPLETS WITH L. PNEUMOPHILA ARE SPREAD FROM SOME COMMON ARTIFICIAL WATER SYSTEMS, INCLUDING FAUCETS, BUILDING AIR-CONDITIONING UNITS, HOT TUBS NOT DRAINED AFTER USE, WATER FOUNTAINS, WATER TANKS AND HEATERS, AND MORE
- LESS COMMONLY, PEOPLE CAN BE INFECTED BY HAVING CONTAMINATED DRINKING WATER ENTER THEIR RESPIRATORY TRACT, EITHER THROUGH ACCIDENTAL INHALATION OR DUE TO SWALLOWING DIFFICULTIES.

CHARACTERISTICS SUITABLE FOR SURVIVAL

- COPES WITH STRESSFUL CONDITIONS BY ENTERING A TEMPORARY **NONCULTIVABLE STATE,** WHERE CELL DIVISION IS DECREASED, BUT METABOLIC ACTIVITY IS MAINTAINED
- CAN ALSO FORM **BIOFILMS** TO PROVIDE PROTECTION WHEN OUTSIDE A PROTOZOAN HOST
- **TYPE II SECRETION SYSTEM**- PRODUCES EFFECTORS THAT ALLOW L. PNEUMOPHILA TO OBTAIN NUTRIENTS AND SURVIVE STRESSFUL CONDITIONS SUCH AS OXIDATIVE STRESS OR THE PRESENCE OF BACTERICIDAL/BACTERIOSTATIC MOLECULES FROM OTHER MICROBES
- **LPG0730 AND LPG0122** - GENES THAT ARE NECESSARY FOR SURVIVAL AND REPLICATION IN BOTH AMOEBA AND HOST MACROPHAGE CELLS. ENCODE PARTS OF AN ATP BINDING CASSETTE (ABC) TRANSPORT COMPLEX.

BACTERIAL ENTRY INTO HOST

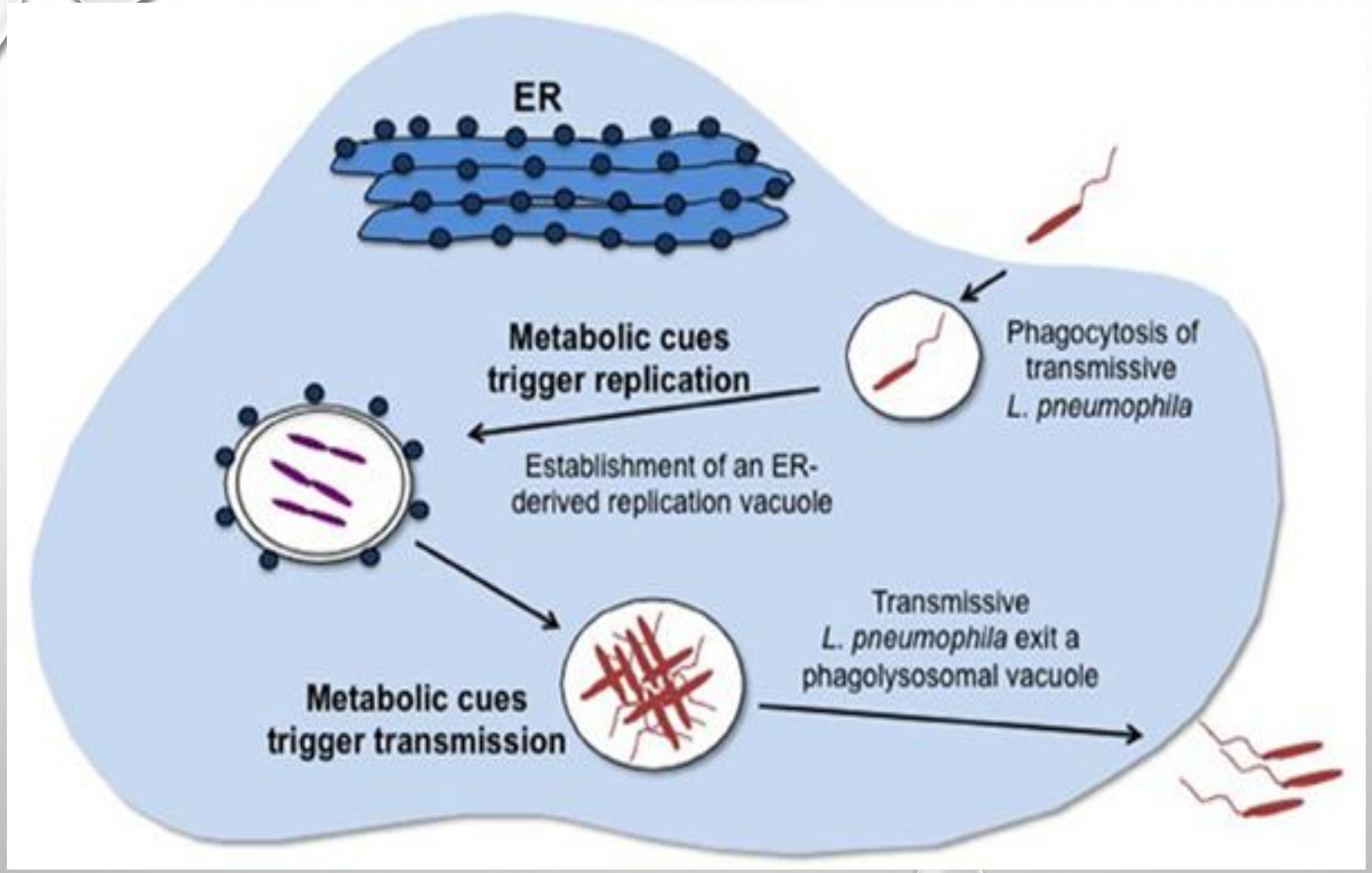
- LEGIONELLA ORGANISMS ARE CLEARED OUT OF THE UPPER RESPIRATORY TRACT THROUGH MUCOCILIARY ACTION.
- CHRONIC DISEASES HAVE A WEAKENED IMMUNE SYSTEM AND COMPROMISED MUCOCILIARY CLEARANCE AND THEREFORE, HAVE A HIGHER RISK OF LEGIONELLA INFECTION.

ADHERENCE

- **ENHC-** PERIPLASMIC PROTEIN, CARRIES THE RESPONSIBILITY TO MAINTAIN CELL WALL INTEGRITY
- **HSP60**- THIS PROTEIN IS ABLE TO MEDIATE PHAGOCYTOSIS OF BY MODULATING THE FUNCTION OF MACROPHAGES, PLAYING AN IMPORTANT ROLE IN BACTERIAL ENTRY
- **LCL, LADC**- CONTRIBUTE TO ADHERENCE, AND INVASION OF HOST CELLS
- **MOMP**- THE FIXING OF C3 TO THE BACTERIAL SURFACE BY THE ALTERNATIVE PATHWAY OF THE COMPLEMENT SYSTEM IS MEDIATED BY MOMP(
- **TYPE IV PILI**- ATTACHMENT AND ENTRY OF THE BACTERIA INTO HOST CELLS
- **LPNE**- ITS ENCODING GENE, THE IPNE GENE, WAS FOUND TO BE REQUIRED FOR FULL ENTRY OF THE BACTERIA INTO MACROPHAGE
- **RTXA**- SEEMS TO PLAY A ROLE IN BACTERIAL ATTACHMENT AND ENTRY HOWEVER ITS MECHANISMS ARE STILL YET TO BE KNOWN

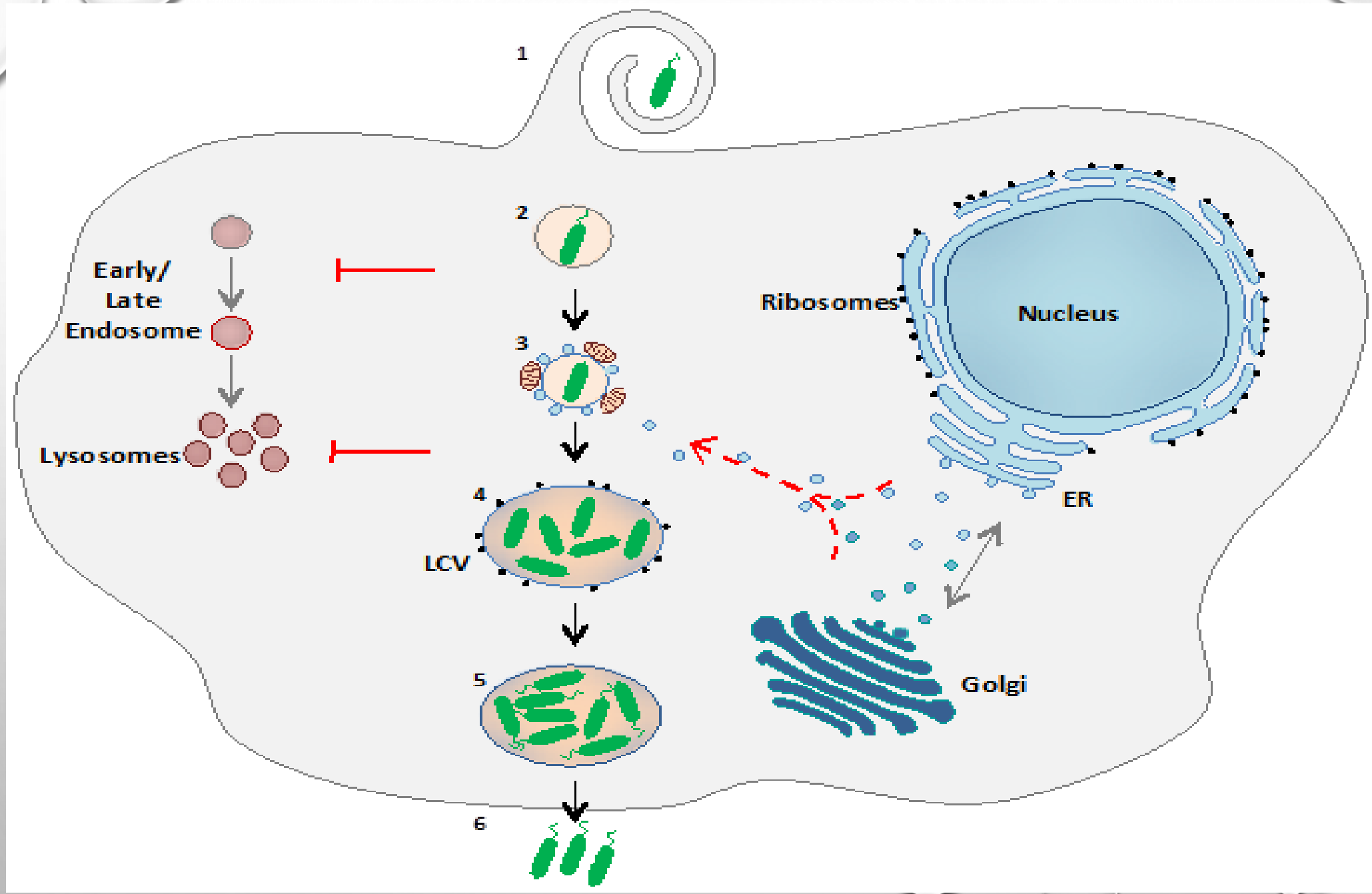
MULTIPLICATION AND SPREAD

- THE ORGANISM IS AN INTRACELLULAR PATHOGEN FOR ITS REPLICATION PHASE
- L. PNEUMOPHILA INVADES AND REPLICATES IN MACROPHAGES.
- THE INTERNALIZATION OF THE BACTERIA CAN BE ENHANCED BY THE PRESENCE OF ANTIBODY AND COMPLEMENT, BUT IS NOT ABSOLUTELY REQUIRED.
- INTERNALIZATION OF THE BACTERIA APPEARS TO OCCUR THROUGH PHAGOCYTOSIS HOWEVER L. PNEUMOPHILA IS ALSO CAPABLE OF INFECTING NON-PHAGOCYTIC CELLS THROUGH AN UNKNOWN MECHANISM.
- ONCE INTERNALIZED, THE BACTERIA SURROUND THEMSELVES IN A MEMBRANE-BOUND VACUOLE THAT DOES NOT FUSE WITH LYSOSOMES THAT WOULD OTHERWISE DEGRADE THE BACTERIA. IN THIS PROTECTED COMPARTMENT, THE BACTERIA MULTIPLY.


ER
Phagocytosis of transmissive *L. pneumophila*
Metabolic cues trigger replication
Establishment of an ER-derived replication vacuole
Transmissive *L. pneumophila* exit a phagolysosomal vacuole
Metabolic cues trigger transmission

MULTIPLICATION AND SPREAD

- AFTER UPTAKE OF THE BACTERIA BY THE EUKARYOTIC HOST CELL (AMOEBA OR ALVEOLAR MACROPHAGE THE *LEGIONELLA*-CONTAINING VACUOLE (LCV) ESCAPES DEGRADATION BY THE ENDOCYTIC PATHWAY BY AVOIDING FUSION WITH ENDOSOMES AND LATER DELIVERY TO LYSOSOMES .
- THE LCV INTERACTS WITH MITOCHONDRIA AND INTERFERES WITH THE EARLY SECRETORY PATHWAY BY RECRUITING ER-DERIVED VESICLES TRAFFICKING TO THE GOLGI , BECOMING A ROUGH ER-LIKE REPLICATIVE VACUOLE SURROUNDED WITH RIBOSOMES .
- IN THIS REMODELLED PHAGOSOME BACTERIA UNDERGO SEVERAL ROUNDS OF REPLICATION, BECOME FLAGELLATED . AND ULTIMATELY ESCAPE THE HOST AND START A NEW INFECTION CYCLE IN NEIGHBOURING CELLS .


1
2
3
4
5
6
Early/
Late
Endosome
Lysosomes
LCV
Ribosomes
Nucleus
ER
Golgi

FORMATION OF THE LCV FOR REPLICATION

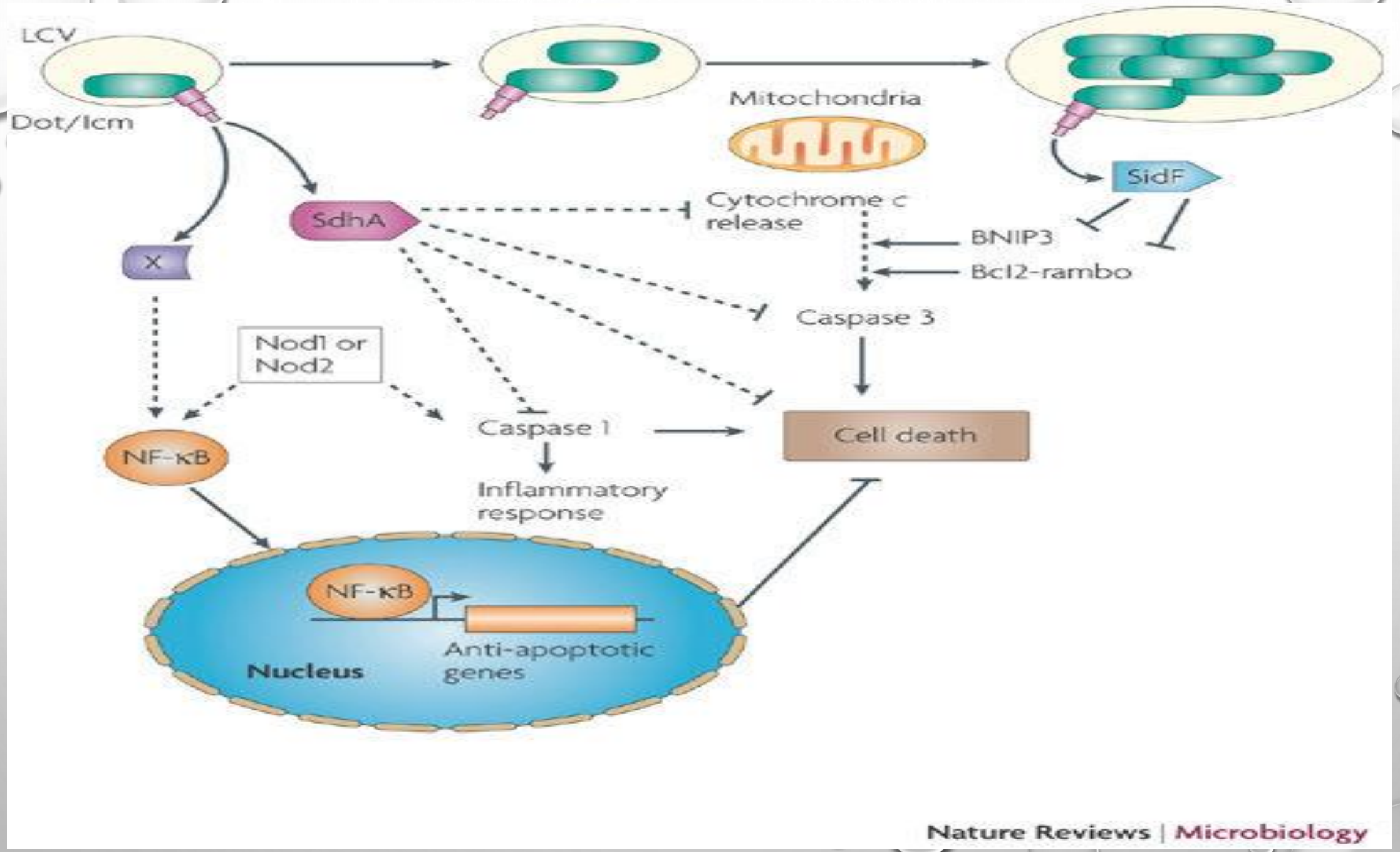
- *L. PNEUMOPHILA* EMPLOYS THE ICM/DOT TYPE IV SECRETION SYSTEM (T4SS) TO FORM THE REPLICATION-PERMISSIVE *LEGIONELLA*-CONTAINING VACUOLE (LCV), WHICH IS DECORATED WITH MULTIPLE COMPONENTS OF THE RETROGRADE TRAFFICKING MACHINERY AS WELL AS RETROGRADE CARGO RECEPTORS.
- THE *L. PNEUMOPHILA* EFFECTOR PROTEIN RIDL IS SECRETED BY THE T4SS AND INTERFERES WITH RETROGRADE TRAFFICKING.

SECONDARY INFECTION

- SOMETIMES LEGIONELLA BACTERIA CAN BE INTRODUCED VIA WOUNDS OR INFECTED SURGICAL EQUIPMENT. DURING LEGIONNAIRES DISEASE, AFTER PULMONARY INFECTION, BACTERIA WILL BE PRESENT IN THE BLOOD (BACTEREMIA).
- RARELY, MANIFESTATIONS OF LEGIONNAIRE'S DISEASE OUTSIDE OF THE LUNG OCCURS AND THESE ARE GENERALLY CONSIDERED SECONDARY TO AN INITIAL PULMONARY INFECTION.
- SOME EXAMPLES INCLUDE SPLENOMEGALY (ENLARGEMENT OF SPLEEN) AND SPLEEN RUPTURE, PERICARDITIS, WOUNDS, JOINT INFECTION (ARTHRITIS), AND CNS.

BACTERIAL DAMAGE

- INVADES AND REPLICATES WITHIN THE ALVEOLAR MACROPHAGES, MONOCYTES AND, POSSIBLY, ALVEOLAR EPITHELIAL CELLS
- INDUCES APOPTOSIS IN MACROPHAGES AND ALVEOLAR EPITHELIAL CELLS
- REGULATED BY THE DOT/ICM TYPE IV-LIKE SECRETION SYSTEM
- CELL FACTORS SUCH AS INTERLEUKIN-1 MAY BE RESPONSIBLE FOR SIGNS AND SYMPTOMS INCLUDING FEVER RESPONSE. THIS BACTERIAL FACTOR IS RELEASED FROM MONOCYTES .
- THE INFLUX OF INNATE IMMUNE CELLS TO THE SITE OF INFECTION COULD ACCOUNT FOR THE INCREASE IN BODY TEMPERATURE .
- OTHER SYSTEMIC FEATURES SUCH AS HEADACHE ARE LIKELY DUE TO THE IMMUNE RESPONSE TO L. PNEUMOPHILA. IN PARTICULAR, THE SECRETION OF TUMOR NECROSIS FACTOR MAY BE LINKED TO THIS SYMPTOM.


LCV
Dot/Icm
Mitochondria
SidF
SdhA
Cytochrome c release
BNIP3
Bcl2-rambo
X
Caspase 3
Nod1 or Nod2
Caspase 1
Cell death
NF-κB
Inflammatory response
NF-κB
Anti-apoptotic genes
Nucleus
Nature Reviews | Microbiology

INDIRECT HOST DAMAGE

HOST CELL'S DEFENCE MECHANISMS AGAINST THE BACTERIA.

- OXYGEN DEPENDANT KILLING DIRECTED BY NEUTROPHILS OF THE INNATE IMMUNE SYSTEM CAN DAMAGE THE LUNG EPITHELIAL AND ENDOTHELIAL CELLS. LEADS TO THE ACCUMULATION OF PROTEIN-RICH FLUID THAT FLOODS THE ALVEOLAR SPACE
- RESULT IN AN INFLAMMATORY RESPONSE AS NEUTROPHILS AND MONOCYTES ARE RECRUITED TO THE SITE OF INFECTION
- LEAKY CAPILLARIES ALLOW FOR THE INFLUX OF SERUM AND INCREASED DEPOSITION OF FIBRIN IN THE ALVEOLI.
- THE RESULTING PNEUMONIA DESTROYS THE AIR SPACES, COMPROMISING RESPIRATORY FUNCTIONS.