Brain sequelae caused by bacterial meningitis: Interactions between pneumococci and neurons

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Background

Bacterial meningitis: Inflammation of the meninges caused by a bacterial infection of the brain, bacteria reach the brain mainly through bloodstream. Streptococcus pneumoniae is the main etiological cause of bacterial meningitis worldwide. Although, bacterial meningitis does not have extremely high mortality (10–30%), but permanent brain damages are a major consequence among meningitis survivors, and neuronal damage is often the reason of such brain sequelae. Previous studies have suggested bacterial toxin, pneumolysin, causes neuronal cell death. Moreover, pilus-I plays important role in bacterial adherence to the cells. However, whether S. pneumoniae can physically interact with neurons and cause neuronal damage is still unknown.

Aim

➢ To study the capacity of pneumococci to directly interact with neurons.
➢ To study the molecular mechanism regulating the interaction of pneumococci with neurons.

Material & Methods

1. SH-SY5Y cells: Neuroblastoma cell line (Human)
2. Pneumococcal strain
   Laboratory strains: piliated type 4 TIGR4 wild type and non-piliated TIGR4:ungA-srtD. Clinical isolates: serotypes 11A (non-piliated) and 15A (piliated).

Results

1. Validation of neuronal differentiation: SH-SY5Y cells were successfully differentiated to mature neurons after 7 days treatment with Retinoic Acid.

2. S. pneumoniae can actively adhere and invade neurons, pilus-I plays important role both in bacterial adhesion and invasion. Pneumolysin is crucial for bacterial invasion.

3. S. pneumoniae co-localize with neuronal protein DBN1 on the plasma membrane through pilus-I and co-localize with MAP2 intracellularly.

4. S. pneumoniae causes increased level of neuronal cell death in the presence of pilus-I and pneumolysin.

➢ Take-home messages

Our study shows for the first time in literature that S. pneumoniae can directly interact with neurons and ultimately invade neurons; Cell death occurs not only through indirect interaction with neurons such as secreting pneumolysin, but also through direct interaction (adhesion and invasion) with neurons. Possibly, through the interaction with microtubule-associated proteins to induce disruption of cytoskeleton.

➢ S. pneumoniae actively adhere and invade to the neurons, the pneumococcal pilus-I showed to have an important role in this process.

➢ Pneumolysin does not play as adhesin, but crucial for bacterial invasion.

➢ MAP2 is important neuronal target for S. pneumoniae transport inside neurons.

Future Prospects

➢ Co-immune precipitation to identify bacterial target protein on the neuronal membrane.
➢ Blockade of MAP2-bacteria interaction to prevent bacterial interaction with neurons
➢ Investigate the mechanism of pore-forming toxin pneumolysin in neurons.

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