cholesteatoma. One patient (4%) had displacement of the ossicular prosthesis.

Conclusion: Cholesteatomas restricted to the attic and/or mesotympanum can be removed in a one-stage technique with no residual visible at 1 year and closure of ABG by 50%.

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Inflammation in the middle ear: initiation, regulation and pathophysiology (K823)

ID: 823.1

Inflammation in the middle ear: Initiation, regulation and pathophysiology

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Learning Objectives: Inflammatory reactions in the middle ear (ME) are significant contributors to otologic disease, including cholesteatoma and otitis media. A major source of ME inflammation is the activation of pattern recognition receptors (PRRs), either by bacteria, viruses or damage-associated molecules patterns (DAMPs) released from dying cells. Ligand binding to PRRs, including Toll-like (TLR), NOD-like (NLR) and C-type lectin receptors, in turn activates pro-inflammatory signaling pathways including the NFkB and JNK cascades. This leads to the production of pro-inflammatory cytokines, chemokine leukocyte chemoattractants, and growth factors that enhance tissue hyperplasia. Studies in mice with deletion of genes encoding PRRs, downstream signaling molecules and their major transcriptional targets clarify the relative roles of PRRs in mediating ME inflammation. These studies implicate TLR signaling via MyD88 and NOD receptor signaling via RIPK2 as major mediators of ME inflammation. They further indicate that the cytokines TNF alpha and IL-1 beta, and the chemokine CCL3, are critical effector molecules downstream from PRRs. Transcriptome analysis of the ME following activation of PPRs further clarifies the nature and timing of ME inflammatory events, with a large number of PRRs and pro-inflammatory mediators rapidly up-regulated. Expression profiles also highlight the role of anti-inflammatory genes, which are activated in response to PRR activation with similar kinetics to that observed for pro-inflammatory mediators. These serve to blunt inflammation and prevent bystander injury to ME tissues. Inflammation also down-regulates tissue growth suppression genes in the ME, including the transmembrane oncogene ecrg4. ECRG4 protein is also enzymatically cleaved in response to inflammation, further eliminating growth suppression and releasing an extracellular fragment with growth-promoting activity. In addition, the fragment complexes with the TLR4/CD14/MD2 endotoxin receptor, forming another link between tissue growth and inflammation. The inflammatory pathways activated in cholesteatoma include up-regulation of TLRs, NLRs and their downstream signaling molecules. This includes TLR4, which has been linked to cholesteatoma pathogenesis. TLR4 functions not only as a receptor for bacteria that may disperse from cholesteatoma biofilms but also for DAMPs released from necrotic cells, such as S100A and HMGB1 both of which are up-regulated in cholesteatoma. Understanding the complex intracellular web that regulates ME inflammation provides potential targets for manipulation as pharmacological interventions. Supported by grants DC000129 and DC012595 from the US NIH/NIDCD.

Inflammation in the middle ear (ME) contributes to disease including cholesteatoma and otitis media. Activation of pattern recognition receptors (PRRs) by bacteria, viruses or damage-associated molecules patterns (DAMPs) activate PRRs, including Toll-like (TLR), NOD-like (NLR) and C-type lectin receptors These in turn activate pro-inflammatory signaling including the NFkB and JNK cascades, inducing pro-inflammatory cytokines, chemokines, and growth factors that contribute to pathogenesis.

Studies in gene deletion mice clarify the roles of various PRR signaling molecules in ME inflammation, while transcriptome analysis following PPR activation further reveals the nature and timing of ME inflammatory events, with a large number of PRRs and pro-inflammatory mediators rapidly up-regulated. Anti-inflammatory genes are activated with similar kinetics, to blunt inflammation and prevent bystander injury to ME tissues. Inflammation also down-regulates tissue growth suppression genes in the ME, including the transmembrane oncogene *ecrg4*. The ECRG4 protein is also enzymatically cleaved in response to inflammation, further eliminating growth suppression and releasing an extracellular fragment with growth-promoting activity. In addition, the fragment complexes with the TLR4/CD14/MD2 endotoxin receptor, forming another link between tissue growth and inflammation.

Inflammatory pathways in cholesteatoma include TLRs, including TLR4 which has been linked to cholesteatoma pathogenesis, NLRs and their downstream signaling molecules. TLR4 functions not only as a receptor for bacteria but also for DAMPs released from necrotic cells, such as S100A and HMGB1 both of which are up-regulated in cholesteatoma.

Understanding the complex intracellular web that regulates ME inflammation provides potential targets for manipulation as pharmacological interventions.

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Genetics in Otology (R831)

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Genetics of Cholesteatoma Project

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Learning Objectives: The support of BSO to identify affected families is sought.