ISOLATE-SPECIFIC DIFFERENCES IN MACROPHAGE RESPONSE TO GROUP B *STREPTOCOCCUS*

I12

Larisa Janžič, Lucija Levstek, Sara Petrin, Alojz Ihan, Andreja Nataša Kopitar

University of Ljubljana, Faculty of Medicine, Institute of Microbiology and Immunology, Department of Cell Immunology, Ljubljana, Slovenia

E-mail: larisa.janzic@mf.uni-lj.si

Although Streptococcus agalactiae (Group B Streptococcus, GBS) is primarily an opportunistic pathogen that colonizes the gastrointestinal and genitourinary tracts of 15-30 % of healthy individuals, it remains a major cause of invasive disease in neonates [1]. The latter can occur in the first week of life and usually manifest as sepsis or pneumonia (i.e., early-onset-disease), or at 1 week to 3 months of age, which usually manifests as meningitis (i.e., late onset disease) [2]. To date, 10 different serotypes (Ia, Ib, II – IX) have been described, distinguished by their virulence and the immune response they elicit [3]. Since intrapartum antibiotic prophylaxis can only prevent early-onset, but not late-onset disease and infections in the elderly and immunocompromised individuals, further studies are needed to investigate GBS-associated pathogenesis. Because adaptive immunity is underdeveloped in neonates, cells of innate immunity play a critical role in protection against pathogens [4]. Of the latter, macrophages are particularly important as they are involved in pathogen recognition, phagocytosis, and elimination [5]. Because disease severity depends on both the GBS isolate and the immune status of the individual, we investigated possible isolate-specific differences in the immune response of THP-1 macrophages to 12 different previously genotyped GBS isolates [6]. Significant isolate-specific differences were observed in phagocytic uptake and expression of macrophage polarization markers [7]. Furthermore, by measuring inflammatory and anti-inflammatory cytokines and chemokines at the protein level, as well as expression of genes involved in antimicrobial activity and inflammation at different time points, we observed that different isolates have different potential to become invasive or remain colonizing. In addition, by measuring IL-1B, IL-18, and caspases 1 and 3 at the mRNA and protein levels, LDH secretion, and caspase-1 activity, we demonstrated that some isolates were significantly more cytotoxic to macrophages and induced pyroptosis. By measuring glycolysis and oxidative phosphorylation using Seahorse extracellular flux analyzer and analyzing the expression of glycolytic genes, we have shown that different GBS isolates activate macrophage metabolism differently and that differences in metabolism lead to differences in macrophage effector functions [7].

References:

1. Armistead B, Oler E, Adams Waldorf K, Rajagopal L. The Double Life of Group B *Streptococcus*: Asymptomatic Colonizer and Potent Pathogen. J Mol Biol 2019;431(16):2914-31.
2. Korir ML, Manning SD, Davies HD. Intrinsic Maturational Neonatal Immune Deficiencies and Susceptibility to Group B *Streptococcus* Infection. Clin Microbiol Rev 2017;30(4):973-89.
3. Pietrocola G, Arciola CR, Rindi S, Montanaro L, Speziale P. *Streptococcus agalactiae* Non-Pilus, Cell Wall-Anchored Proteins: Involvement in Colonization and Pathogenesis and Potential as Vaccine Candidates. Front Immunol 2018;9:602.
4. Kumar SK, Bhat BV. Distinct mechanisms of the newborn innate immunity. Immunol Lett 2016;173:42-54.
5. Zhang L, Wang CC. Inflammatory response of macrophages in infection. Hepatobiliary Pancreat Dis Int 2014;13(2):138-52.
6. Perme T, Golparian D, Bombek Ihan M, Rojnik A, Lucovnik M, Kornhauser Cerar L, et al. Genomic and phenotypic characterisation of invasive neonatal and colonising group B *Streptococcus* isolates from Slovenia, 2001-2018. BMC Infect Dis. 2020;20(1):958.
7. Janzic L, Repas J, Pavlin M, Zemljic-Jokhadar S, Ihan A, Kopitar AN. Macrophage polarization during *Streptococcus agalactiae* infection is isolate specific. Front Microbiol 2023;14:1186087.