PHOSPHORYLATED BACTERIAL GLYCOLIPIDS AND MIMETICS WITH A ROLE IN INNATE IMMUNITY

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Innate immunity-related factors play an important role in the development of various malignancies, and several components are currently being investigated as potential therapeutic targets or adjuvants. 100 years ago, Dr. William B. Coley achieved remarkable success in the treatment of advanced solid cancers by using mixtures of killed bacteria to induce local and systemic acute inflammation [1, 2]. It is now understood that the anti-tumour effects of the 'Coley vaccine' were related to the activation of pattern recognition receptor (PRR)-mediated innate immune responses, including NF-κB-mediated cytokine release and NLRP3 inflammasome activation, triggered by bacterial pathogen-associated molecular patterns (PAMPs). In recent years, considerable efforts have been made to revive bacterial-mediated cancer therapy [3,4]. However, identifying a strain that achieves the optimal balance between effective immune stimulation and safety remains a challenge, as overly attenuated bacterial strains may not sufficiently activate the immune system—an essential factor for tumor regression and healing, according to W. Coley. Preclinical development of LPS-based cancer therapies has also been hampered by adverse effects or lack of clinical efficacy due to LPS microheterogeneity and detoxification [5].
Identifying the structural factors characteristic of certain bacterial PAMPs that contribute to antitumor effects could open new therapeutic avenues for cancer adjuvant treatment. Synthetic bacterial glycolipids and glycan fragments are perfect candidates for studying the involvement of bacteria-sensing PRRs in cancer biology [6,7]. The library of synthetic phosphorylated bacterial glycans, glycolipids, and their mimetics was assessed for interaction with several PRRs in vitro with particular emphasis on structural aspects and immunomodulatory effects, while selected molecules showed therapeutic potential in targeting experimental tumours. The structural basis for ligand-protein interactions of several glycolipids with picomolar activity was studied using Cryo-EM. Providing in-depth insight into the recognition of structurally different glycolipids by innate immune receptors, including species-specific sensing and correlation with biological activity, paves the way for the design and development of novel adjuvants and immunotherapeutics.

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