Conclusions: Hypoxic-induced cell malignancy strongly depends on both the type of hypoxia (SH vs. MIH/SIH) and the cancer cell type. Therefore, our results provide critical insights for further clinical studies aimed at studying the relationship between lung cancer and respiratory diseases with different hypoxic patterns and severities such as COPD, OSA, obesity reduced ventilation, and overlap syndrome.

Efficacy and Safety of Different Doses of Neuraminidase Inhibitors for the Treatment of Hospitalized Adults with Influenza: Systematic Review and Meta-Analysis

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Introduction: Efficacy and safety of different doses of neuraminidase inhibitors (NAIs) for hospitalized influenza patients have not been established.

Objectives: Our aim was to develop a systematic review and meta-analysis of randomized controlled trials (RCT) on the efficacy and safety of different doses of NAIs regimens in hospitalized adults with influenza.

Methods: The Cochrane collaboration searching methods was followed in Cochrane Library, PubMed and Web of Science databases (2008-2018). Eligibility criteria were limited to RCT comparing different regimens of NAIs in hospitalized adults (>16 years) for influenza therapy. Primary outcomes were 28-day overall mortality and time to clinical resolution (TTCR).

Results: Three RCTs (with 902 patients) among 217 RCTs evaluated were included. Two RCT compared two different regimens and/or doses of intravenous peramivir and another compared two different doses of intravenous zanamivir with oseltamivir. The meta-analysis of mortality showed no significant differences with different dose regimens of systemic NAIs (Odds Ratio [OR]: 0.61; 95% Confidence Interval [CI]: 0.26-1.39). There were no virological or clinical (TTCR) advantages. No differences were observed (OR: 1.03; 95% CI: 0.66-1.61) in severe adverse events. The certainty of evidence (GRADE) was very low.

Conclusions: The evidence does not support the use of different doses of systemic NAIs, even as salvage therapy.

Haemophilus influenzae Glucose Respiration Assisted Fermentation Leading to Production of the Immunometabolite Acetate Has a Key Contribution to the Host Airway-Pathogen Interplay

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Introduction: Glucose homeostasis at the human lung lumen contributes to maintain a nutrient-depleted environment to limit the growth of pathogens. In healthy airways, glucose concentrations are maintained 3-20 times lower in the airways surface liquid (ASL) than in plasma. However, the ASL glucose concentration is elevated in sputum samples of patients with chronic obstructive pulmonary disease (COPD), which facilitates the proliferation of bacteria able to use glucose as carbon source. COPD is characterized by abnormal inflammatory responses and impaired airway immunity, which provides an opportunistic platform for nontypeable Haemophilus influenzae (NTHi) infection. This results in a vicious-circle where large inflammation due to multiple interactions between airway immune cells and NTHi results in worsening of the disease clinical status. NTHi glucose metabolism is a respiration-assisted fermentation. We hypothesized that such specialized glucose catabolism may be a bacterial pathoadaptive trait with a pivotal role in airway infection.

Objectives: Generation and characterization of bacterial mutants unable to produce acetate, formate or succinate, main products of NTHi glucose metabolism.

Methods: Inactivation of the NTHi ackA, pfA and frdA genes. In vitro and in vivo mutant phenotypic characterisation, in terms of bacterial fitness, growth, immunometabolite production and cell signalling, gene expression, and pulmonary infection.
Results: Inactivation of the ackA gene impaired acetate production, and led to slow bacterial growth, production of lactate under low oxygen tension, and bacterial attenuation in vivo. Bacterially produced acetate resulted in increased airway epithelial inflammatory responses, supporting that the COPD lung provides NTHi with elevated glucose concentrations. Bacteria use it and produce fermentative end-products acting as proinflammatory metabolites at the site of infection.

Conclusions: This information has important implications for developing non-antibiotic antimicrobials, given that airway glucose homeostasis modifying drugs could help preventing microbial infection associated to chronic lung disease.

HIGH GENOMIC HOMOGENEITY AMONG HAEMOPHILUS INFLUENZAE SEROTYPE F

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Introduction: Haemophilus influenzae is an opportunistic pathogen highly adapted to the human respiratory tract which is often reported as the etiologic agent of infectious diseases. After the introduction of serotype b vaccine, non-typeable H. influenzae (NT-Hi) has become the most frequent cause of respiratory infection, followed in frequency by serotype f strains (Hi-f).

Objectives: To analyse by whole genome sequencing the genomic diversity among invasive and colonizing Hi-f isolates.

Methods: A total of 37 Hi-f isolated from Portugal (n = 3). The Netherlands (n = 18) and Spain (n = 16) were sequenced using Illumina technology. A core-based phylogenetic tree was constructed with Parsnp from the Harvest suite. The MLST was determined and the core and accessory genome analysis was done by Roary and roProfile. The single nucleotide analysis was done through Snippy to detect polymorphisms (SNPs) among bacterial genomes.

Results: Thirty-one isolates were ST124 and the remaining six isolates were single locus variant of ST124 (ST106 (n = 1), ST1736 (n = 2) and a new ST (n = 3)). Although all strains were closely related two major clusters were observed in the phylogenetic tree. The estimated core genome was 92% and 12.825 core-SNPs were detected. A total of 1,853 genes were predicted, of them, 1,891 were present in more than 95% of the strain and 162 were accessory genome (present in less than 95% strains). Regarding to allelic variation, 952 core genes were monomorphic. The fifteen most polymorphic genes were secA, nmg, maeb, ftsh, emIA, huxA, bgpC, HifGL_000293, dnaA, hgbO, HifGL_000294, HifGL_000920, prob, murD and alaS. This variation was mostly due to a cluster containing the colonizing Hi-f strains.

HUMAN SURFACTANT PROTEIN A BINDS THE HUMAN ANTIMICROBIAL PEPTIDE CATHLECIDIN INHIBITING ITS CYTOTOXIC EFFECT ON ALVEOLAR EPITHELIAL CELLS

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Introduction: Human cathelicidin (LL-37) is a multifunctional component of innate immunity with direct antimicrobial activity against several microorganisms. However, LL-37 also binds to host membranes causing a cytotoxic effect. Secretion of LL-37 by alveolar epithelial and immune cells is increased after infection or tissue injury. Surfactant protein-A (SP-A) is an abundant protein in the alveolar space with important immune defense functions.

Objectives: To evaluate whether SP-A binds to LL-37 and to analyze whether SP-A is involved in the local regulation of LL-37 activity.

Methods: SP-A binding to LL-37 was analyzed by tryptophan fluorescence and dynamic light scattering. Antimicrobial activity of LL-37 in presence or absence of SP-A was studied through killing assay. Cytotoxic activity of LL-37 was measured in alveolar epithelial cells by crystal violet staining and WST-1 cell viability assay.

Results: SP-A bound to LL-37 with high affinity (Kd = 0.01 ± 0.006 pM) in physiological conditions of pH and sodium chloride. SP-A/LL-37 interaction results in reduction of LL-37 cytotoxicity on alveolar epithelial cells at high LL-37 concentrations, without affecting LL-37 antimicrobial activity against the respiratory pathogens. However, at low LL-37 concentrations, SP-A significantly decreased LL-37 antimicrobial activity against non-typable Haemophilus influenzae, Klebsiella pneumoniae K2, and Pseudomonas aeruginosa O1, which is consistent with SP-A/LL-37 interaction that block LL-37 activity.

Conclusions: Our data indicate that SP-A protects lung epithelium from tissue injury caused by high LL-37 concentrations. These data suggest that in conditions of tissue damage or infection, when LL-37 secretion increases, SP-A protects from cytotoxic local high concentrations of LL-37, without interfering with LL-37 antimicrobial activity.

IDENTIFICATION OF NOVEL GENETIC ASSOCIATIONS WITH THE RESPONSE TO INHALED CORTICOSTEROIDS IN CHILDREN WITH ASTHMA

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