THE ROLE OF THE ACUTE PHASE PROTEIN PTX3 IN THE VENTILATOR-INDUCED LUNG INJURY

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WINNING ABSTRACT: The pentraxin 3 (PTX3) is an acute phase proinflammatory protein produced by fibroblasts and alveolar epithelial cells. We have previously demonstrated that PTX3 is a key modulator of inflammation. Mechanical ventilation (MV) is a life saving therapeutic approach for patients with acute lung injury that, nevertheless could lead to an inflammatory response and tissue injury (ventilator-induced lung injury: VILI), representing a major cause of iatrogenic lung damage in intensive units. Our objective was to investigate the role of PTX3 in VILI. PTX3 transgenic, knockout and Wt control mice (n=12/group) were ventilated (45ml·kg⁻¹) until respiratory system Elastance increased 50% (Ers150%), an indicator of VILI. Histological analysis demonstrated that using a Ers150% was appropriate for our analysis since identical degrees of inflammation were observed in Tg, KO and Wt mice as assessed by leukocyte infiltration, oedema, alveolar collapse and number of breaks in alveolar septa. However, Tg mice reached Ers150% faster than Wt controls (p=0.0225). We also showed that the lack of PTX3 does not abolish the occurrence of VILI in KOs. Gene expression profile of PTX3, IL-1beta, IL-6, KC, IFNgamma, TGFbeta and PCIII were investigated by QPCR. MV drastically up modulated PTX3 as well as IL-1beta, IL-6, IFNgamma and KC. Alternatively, mice were ventilated for 20, 40 and 60 min. The faster kinetics of Tg mice to reach Ers150% was accompanied by an earlier augmentation of IL-1b and PTX3 expression. The kinetics of local PTX3 expression in the lungs of ventilated mice strongly suggests the involvement of this pentraxin in the pathogenesis of VILI.

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SYNOPSIS OF MY JOB AND THE ROLE OF THE UNIT IN WHICH I WORK

I am a graduate MSc student at the Oncology Program from Hospital AC Camargo, São Paulo, Brazil. The 54-yr-old Hospital AC Camargo is the largest not-for-profit cancer hospital in Brazil,

diagnosing 6,000 new cancer cases a year, with >800,000 attendances and 9,000 operations carried out each year. Due to its philanthropic status, 60% of the patients treated at the hospital are from the public health programme Sistema Único de Saúde. The hospital has 241 beds, of which 31 are intensive care beds. The staff at the hospital is comprised of 30 doctors, half of them with a Masters degree or PhD, and 1,200 other staff members. Hospital AC Camargo has a long-standing reputation for its teaching and research activities. Its 50-yr-old residency programme has trained 50% of the country's oncologists. Its graduate course in oncology, issuing Masters and PhD degrees, is one of two programmes in medicine with the highest possible rank awarded by the Brazilian Ministry of Education. Due to this grade, all hospital graduate students are funded by federal or state agencies and we have 30 federal fellowships for undergraduate students who wish to begin their career in science early. The research activities of the AC Camargo's International Center of Research and Education, within the AC Camargo Hospital, had a crucial role in the human cancer genome project, which led to the world's second largest contribution, to our knowledge, about human transcriptome, by cloning and sequencing over a million cDNA expressed sequence tags. These clones have been used to generate our own microarray platform, which has been successfully used to address clinically relevant issues in oesophageal, gastric and breast cancer. The research developed in the hospital supports the focus in evidence-based medicine of care for patients and the development of new initiatives to increase awareness of early diagnosis and prevention of cancer in Brazil. The institution also focuses on changes in life habits that can help to decrease the burden of cancer.

STATEMENT OF INTEREST: None declared.

SYNOPSIS OF MY RESEARCH AND HOW IT FITS IN WITH THE OVERALL RESEARCH OF MY WORKING GROUP

My work was carried out under the supervision of Dr Daniel Deheinzelin and Dr Adriana Abalen M. Dias at the Laboratory of Inflammation Research (Hospital AC Camargo).

The main focus of Dr Dias' studies is the functional characterisation of genes modulated by the pro-inflammatory cytokines tumour necrosis factor- α and interleukin-1 β . Of special interest is the investigation of the role of acute-phase protein pentraxin 3 (PTX3) in inflammation. PTX3 is a glycoprotein secreted in response to primary inflammatory signals by many different cell types, including fibroblasts, macrophages, dendritic cells and alveolar epithelial cells. The PTX3 transgenic mice generated in our laboratory [1] have been used as models and provide important data about the crucial role of PTX3 in innate immunity [1, 2], and in the response orchestrated by the host against infectious agents or pro-inflammatory signals [3, 4] with a profound impact on the outcomes of acute inflammation. Of special relevance to the rationale of my project are the results showing the central role of PTX3 in acute lung injury following ischaemia and reperfusion [3], and in the response to *Klebsiella pneumoniae* [4] pulmonary infection.

While involved in clinical studies [5], Dr Deheinzelin is interested in animal models of ventilator-induced lung injury (VILI) [6, 7]. The study of transgenic animals under these experimental conditions seemed relevant for a better understanding of VILI modulation.

In this scenario, since January 2005, I have been working on my MSc project with the objective of understanding the role of PTX3 in the inflammatory process in lungs in response to mechanical ventilation.

During my study, PTX3 knockout and PTX3 transgenic mice, as well their respective wild-type mice were subjected to mechanical ventilation. The time taken to develop VILI, as well as the morphological and molecular features of the injured lungs were analysed. We observed that augmented production

of PTX3 is associated with an earlier development of lung damage. In addition, a different profile of gene response of VILI modulators was observed.

HOW WILL MY RESEARCH IMPACT ON CLINICAL OR RESEARCH PRACTICE?

So far, clinical studies have demonstrated that only mechanical ventilation strategies which lessen ventilator-induced lung injury impacted prognosis. A better understanding of ventilator-induced lung injury mediators may point to different intervention approaches.

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