Signaling Pathways in Multiple Organ Failure

Mary F. McGuire, MSc[1]*, M. Sriram Iyengar, PhD[1], David Mercer, MD[2]
[1] University of Texas School of Health Information Sciences, Houston, USA
[2] Trauma Research Center, Department of Surgery,
University of Texas Medical School at Houston, Houston, USA
*email: mary.f.mcguire@uth.tmc.edu

Introduction

Multiple organ failure (MOF) is the leading cause of in-hospital mortality in critically injured trauma patients (Ciesla *et al*, 2005). In this setting, organs remote from injury location, including liver, heart, lungs, and kidneys, cease functioning. Pro and anti-inflammatory cytokines are implicated as signaling messengers in this process (Moore *et al*, 1996) and their cellular signaling pathways may elucidate novel therapeutic strategies to improve outcomes.

Method

We analyzed BioRad immunoassay data for eleven serum cytokines from 48 patients sustaining major torso trauma (excluding severe head injuries) who met standardized criteria (Mercer *et al,* 2007). Cytokine levels were measured every four hours from the start of resuscitation. Data for the first 24 hours post-injury were grouped by time period (4 hour spans starting at 2 hours) and by patient outcome of multiple organ failure (MOF) or not (NMOF) using a standardized score.

For each time period t, a *Significance set,* S(t), the statistically significant cytokines differentiating MOF and non-MOF (NMOF) groups, was generated using the one-sided Wilcoxon Rank Sum Test with $p < 0.05$ (Hollander and Wolfe, 1973). GenBank identifiers for S(t) and their pmol/L values for each outcome for each time period were uploaded into the Ingenuity Pathways Analysis system (IPA) to generate molecular networks from the Ingenuity Pathways Knowledge Base (Ingenuity, 2007). The networks were then analyzed to gain insights into temporal variation within the MOF patient group as well as temporal variation between MOF and NMOF patients.

Discussion and results

Searching large, richly connected pathway knowledge bases with multiple inputs can yield very large result sets. Using significance sets for IPA input decreases the size of result sets and enhances their relevance. The significance set should be generated using statistical methods appropriate to the nature of input data. In our case, small sample size and a large variation in cytokine levels suggested using non-parametric methods to differentiate between outcome groups.

The significance set, S(t), showed considerable variation across time. Median levels of seven to eight of the eleven cytokines were greater in MOF outcomes through 22 hours. The primary canonical pathways were IL-10 and IL-6 in all time periods. Molecular networks generated by IPA for each time period were different for MOF and NMOF outcomes.

A striking example is for the time period 10 to 14 hours from time of incident. IPA generated four networks, two for each outcome. MOF1 and NMOF1 networks are identical. However, MOF2 and NMOF2 networks have only 20 of 35 molecules in common (Figure 1). IPA identifies the biological functions of MOF2 as cell cycle, tissue morphology and cancer while NMOF2 is associated with cellular growth and proliferation, cellular function and maintenance, and hematological system development and function.

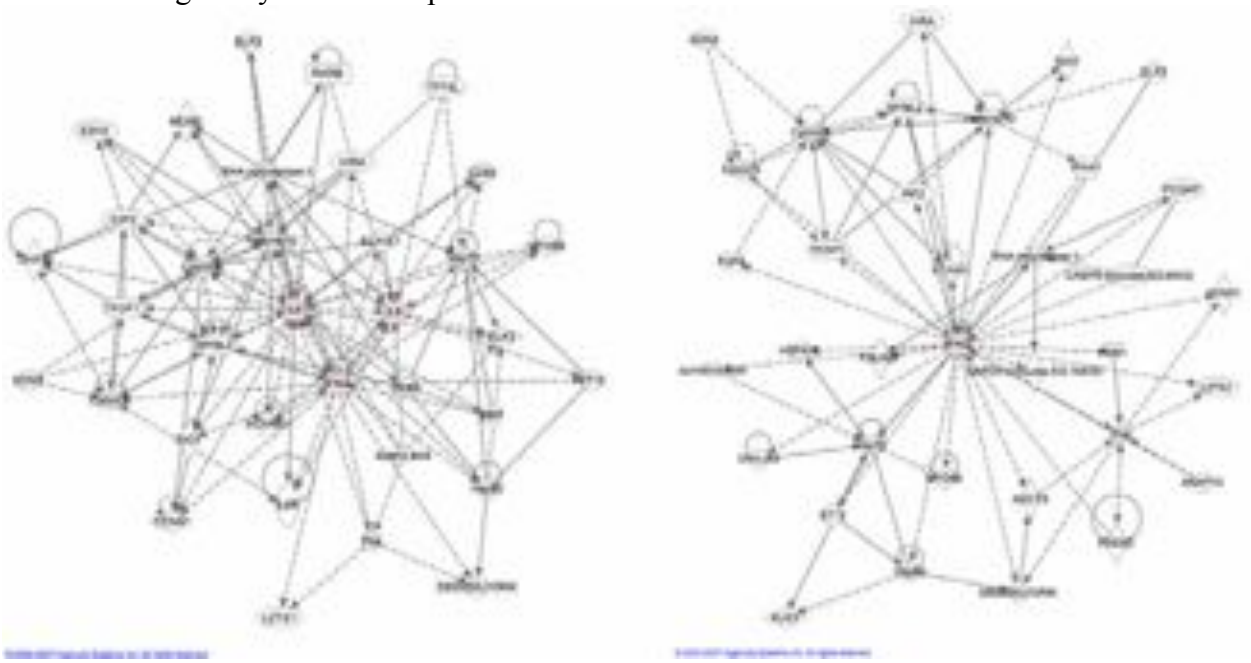

Figure 1 Cytokine-activated signaling networks 10 to 14 hours from trauma.
Left: a generated network for patients with outcomes of multiple organ failure (MOF2).
Right: the corresponding network for patients without multiple organ failure (NMOF2).

Conclusions

Statistical analysis identifying a significance set S(t) of biomolecules, followed by Ingenuity Pathways Analysis based on S(t), can yield useful insights into cytokine mediated networks implicated in multiple organ failure. These results could lead to the development of novel therapeutic strategies to decrease the incidence of MOF and improve patient outcomes.

References

Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A (2005) A 12-Year Prospective Study of Postinjury Multiple Organ Failure: Has Anything Changed? Arch Surg 140: 432-440

Hollander M, Wolfe DA (1973) Nonparametric Statistical Methods. John Wiley & Sons, Incorporated, New York, NY

Ingenuity® Systems (2007) www.ingenuity.com

Mercer DW, Adams SD, Suliburk JW, Gonzalez EA, Kozar RA, Sriram Iyengar M, McGuire MF, Moore FA (2007) Can Cytokines Predict Multiple Organ Failure in Critically Ill Trauma Patients. 7th World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany

Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC (1996) Postinjury multiple organ failure: a bimodal phenomenon. J Trauma 40(4):501-510