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Nutritional Metabolomics in Critical Illness

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Abstract

Purpose of review—Disruption of metabolic homeostasis is universal in the critically ill. Macro- and micronutrients are major environmental regulators of metabolite production through their gene regulation effects. The study of large numbers of circulating metabolites is beginning to emerge through the comprehensive profiling of the critically ill. In the critically ill, metabolomic studies consistently show that changes in fatty acids, lipids and tryptophan metabolite pathways are common and are associated with disease state and outcomes.

Recent findings—Metabolomics is now being applied in research studies to determine the critical illness response to nutrient deficiency and delivery. Nutritional metabolomics approaches in nutrient deficiency, malnutrition and nutrient delivery have included single time point studies and dynamic studies of critically ill patients over time. Integration of metabolomics and clinical outcome data may create a more complete understanding of the control of metabolism in critical illness.

Summary—The integration of metabolomic profiling with transcription and genomic data may allow for a unique window into the mechanism of how nutrient deficiency and delivery alters cellular homeostasis during critical illness and modulates the regain of cellular homeostasis during recovery. The progress and the challenges of the study of nutritional metabolomics are reviewed here.

Keywords

Metabolomics; Nutrition; Malnutrition

Introduction

Metabolomics is the broad profiling of metabolites on the cellular, tissue or circulating level. Metabolite profiles provide a holistic functional view of individual patients. Such metabolite profiles are the final result of cellular function driven by genomic, transcriptomic, proteomic and environmental factors inclusive of nutrition delivery (1) (Figure 1). Advances in mass spectrometry and bioinformatics have allowed metabolomics to become an important tool for the measurement of circulating end products of cellular metabolism (2). The human metabolome is comprised of approximately 6,500 individual small molecule metabolites (3).

Conflicts of interest

The author has no conflicts of interest.

Metabolomics is applied by investigators to define biological markers of chronic and acute diseases, determine the response to intervention and illuminate the mechanistic understanding of disease.

Analysis of the blood metabolome produces a highly coordinated profile of homeostasis (3). Loss of metabolic homeostasis is common in critical illness and characterized by a severe disruption of multiple metabolic pathways (4). Disrupted metabolic homeostasis is important in both the pathogenesis and progression of critical illness. Proteomic and transcriptomic patterns in peripheral blood show systematic changes with critical illness that are reflected in blood plasma metabolites (5, 6). In critical illness, plasma metabolic profiles are the products of the cellular response to inflammation and nutrients. Macro- and micronutrients are major environmental regulators of gene expression by affecting the concentrations of other metabolic substrates or intermediates involved in gene regulation and alteration of signal transduction pathways. Nutrition delivery affects a large number of biological processes vital to the immune response, including gene expression, protein synthesis, modification and degradation, metabolism, signal transduction, and cellular proliferation (7).

Malnutrition present at ICU admission can serve as a marker of illness severity and outcomes in critically ill patients (8). Pre-existing protein-energy malnutrition is a risk factor for the development of sepsis and for mortality in patients with sepsis (8). Malnutrition results in lower neutrophil recruitment to sites of inflammation, related to decreases in integrin expression and altered chemokine production (7). Malnutrition decreases cellular immunity, decreases CD8+Tcell number and function and substantially reduces cytokine production and phagocytosis (9). Malnutrition and the response to nutrient delivery, which can be characterized in the metabolome, may explain a significant proportion of the risk of critical illness development due to altered innate immune responses. By combining metabolomic approaches with clinical, nutritional, and genomic data from critically ill patients, it is possible to link nutrition-gene interactions to specific metabolites and pathways. To date, the metabolomic study of critical illness is limited with regard to malnutrition and nutritional delivery.

In experimental critical illness, early parenteral nutrition suppresses autophagy and is associated with more severe mitochondrial damage and greater organ dysfunction (10). Experimental studies indicate that the maintenance of homeostasis during the cellular stress of critical illness depends on cross talk between autophagy and the inflammasome (11, 12). Experimental stimulation of autophagy is protective against organ failure and mortality, while inhibition of autophagy results in heightened organ dysfunction and mortality (13, 14). Autophagy deficiency in liver and skeletal muscle is noted following early parenteral nutrition in experimental critical illness (10). Inhibition of autophagy via early parenteral nutrition leads to an increase in muscle weakness and decreased muscle recovery (15, 16). Further, autophagy suppression related blunting of innate immunity may contribute to the higher infection rate noted with early parenteral nutrition in the EPaNIC trial (17).

Critical illness is influenced by genetic factors, especially by genes that regulate the immune response. Polymorphisms of many genes related to innate immunity, inflammatory cytokines, and coagulation likely play a large role in determining susceptibility to and

outcome of critical illness. Specifically, polymorphisms in mannose binding lectin, lipopolysaccharide binding protein, bacterial permeability increasing protein, CD14, Toll-Like Receptors, IgG receptors, tumor necrosis factor, Lymphotoxin alpha, IL-6, macrophage migration inhibitory factor, IL-10, plasminogen activator inhibitor-1 may be important in development and outcomes of critical illness (18).

Metabolite concentrations are quantitative, phenotypic traits controlled by a DNA sequence termed the quantitative trait locus (19). Integration of metabolomics and genomics may create a more complete understanding of gene function and the control of metabolism in critical illness (20). Transcriptionally distinct subclasses related to early versus late parenteral nutrition might account for some of the heterogeneity seen in critical illness outcomes. Nutrition-genomic interaction effects via post-transcriptional events are likely more important for driving the metabolic response in critical illness than genetics alone (21). Further, it is likely that metabolites specific to host defense in critical illness have a strong genetic component, given genome-wide association study findings at the FER locus (22).

Critical Illness Metabolomics

The use of emerging metabolomics tools able to examine dynamic responses at a system level holds promise for complex conditions such as critical illness and the response to nutritional interventions. A number of studies are published on metabolomics of critical illness (5, 6, 23, 24, 25, 26, 27, 28*, 29*, 30, 31, 32, 33*, 34**, 35, 36*, 37*). Circulating metabolic signatures showing alteration in fatty acids, lipids and tryptophan pathways are prominent in cohorts of critically ill patients. While these initial studies have shown the potential of metabolomics to distinguish between patients with and without sepsis, limitations do exist regarding small sample size, relatively low metabolite numbers, and the number of time points measured. The integration of metabolic derangements and their contribution to the pathogenesis of critical illness are incompletely understood. Further, there is limited data the influence of protein-energy malnutrition or nutrition delivery on the critical illness metabolome (34**, 36*).

Fatty acid metabolism has been linked to immune responses in critical illness. Fatty acid synthesis has also been implicated in the activation of dendritic cells and the differentiation of B lymphocytes and human monocytes (38). The NLRP3 inflammasome is unique in its ability to recognize molecular patterns associated with host-derived metabolites, such as saturated fatty acids (39). Differences in fatty acid metabolite profiles are prominent in the metabolomic phenotype of adverse versus favorable critical illness outcomes (5).

Lipidome alterations are prominent in critically ill patients (23, 25). NLRP3 mediated inflammasome activation is regulated through lipid synthesis (39). Decreased plasma level of phosphatidylcholines and lysophosphatidylcholines are prominent in critical illness non-survivors (28*). Lysophosphatidylcholine alters innate immunity through inhibition of lipopolysaccharide-induced nitric oxide which is important to reduce levels of inflammation (40). Further, the endogenous carnitine pool is important in the effective immune and inflammatory response towards invading pathogens (41). Carnitine esters are the most pronounced metabolites that differ between critical illness nonsurvivors and survivors (5). Studies show that an early indicator of critical illness outcomes is mitochondrial biogenesis,

a peroxisome proliferator-activated receptor (PPAR)-regulated phenomenon (42). NLRP3 mediated inflammasome activation is regulated through lipid synthesis, autophagy and via release of mitochondrial DNA into the cytosol (39, 43). It is hypothesized that mitochondrial dysfunction may lead to problems in β -oxidation and the increase in circulating acyl-carnitines (44).

Accelerated tryptophan catabolism along the kynurenine pathway occurs with critical illness. Bacterial products and proinflammatory cytokines upregulate indoleamine 2,3-dioxygenase (IDO), the enzyme responsible for kynurenine production. IDO is critically involved in CD4+ and CD8+ effector T cell suppression as well as in generation and activation of regulatory T cells (45). Kynurenine plasma level is predictive for the development of sepsis in major trauma patients (46). Modulation of kynurenine is associated to 28-day mortality in critical illness (24, 27). Increased production of kynurenine has been proposed to contribute to hypotension and is associated with impairment in the immune response and in microvascular reactivity (46).

Nutritional Metabolomics Studies: Static Profiling

In a cohort study of 85 critically ill adult patients both metabolic profiles and nutrition status determined by Registered Dietitian evaluation were determined early in an ICU course (36*). 308 known metabolites were measured in plasma. The combination of five metabolites were significantly associated with malnutrition with good discrimination (AUC=0.76). Pathway enrichment analysis demonstrated that glutathione and purine metabolism was significantly altered with malnutrition as determined by Registered Dietitian evaluation. Elevations in kynurenine and tryptophan pathway metabolites were found in critically ill patients with malnutrition. Further, addition of metabolites related to nutrition status was noted to improve 28-day mortality classification in statistical models (36*).

In a cohort study of 65 adult patients with SIRS, sepsis or sepsis ARDS, differences in metabolic profiles were determined early in the course of critical illness with regard to vitamin D status (37*). This cohort is a subset of patients from the nutrition cohort above (36*). 308 known metabolites were measured in plasma. Utilizing several analytic strategies, the metabolic profile of critically ill patients was demonstrated to differ based on the ICU admission vitamin D status. The evidence showed that differences in metabolite profiles related to vitamin D status were most prominently associated with glutathione and glutamate metabolism as well as with glucuronidation (37*).

Nutritional Metabolomics Studies: Dynamic Profiling

In a cohort study of 20 critically ill adult trauma and surgical patients, differences in metabolic profiles were determined early in the course of critical illness with regard to enteral versus parenteral nutrient delivery (34**). Ten critically ill patients received enteral nutrition and 10 received parenteral nutrition with type of nutrition determined per care team discretion. Post operative patients and those with cancer or chronic organ dysfunction were excluded. Plasma metabolomics were performed at day 0 (before feeding) and day 3 and 7 (after feeding began). 214 known metabolites were measured. Patients treated with EN had

dynamic increase in plasma amino acids, urea cycle products and ribonucleic acid synthetic products. Those treated with PN had dynamic increases in concentrations of plasma amino acids but dynamic decreases in concentrations of urea cycle metabolites and essential fatty acids. Though there were differences between those that received EN versus PN and the bioinformatic analysis limited by small sample size, the repeated sample design following nutritional intervention is an important design element to incorporate into further study.

Currently, the metabolome of plasma samples at multiple time points from the VITdAL-ICU randomized clinical trial (47) are being determined and analyzed (NIH R01GM115774). The VITdAL-ICU trial was a randomized, double-blind, placebo-controlled, single center trial of 475 critically ill medical and surgical subjects with 25(OH)D $\leq$ 20 ng/ml, showed in a secondary outcome that high dose enteral vitamin D3 improved mortality in patients with severe vitamin D deficiency (47). Metabolomics profiles will be produced on the plasma collected from VITdAL-ICU trial patients randomized to high dose enteral vitamin D3 or placebo over three time points. The conceptual model assumes that plasma is an integrative biofluid that reflects the systematic changes of critical illness. The VITdAL-ICU trial plasma metabolites will be studied using bioinformatic approaches including primary metabolomic profile analyses, longitudinal metabolic analysis and canonical pathway analysis. Both the metabolite profile of differential critical illness outcomes observed with pre-existing vitamin D deficiency (48) and dynamic changes in metabolites and metabolite pathways associated with critical illness influenced by vitamin D supplementation will be studied.

Conclusion

As metabolism is a dynamic process, time-series studies of systematic metabolomics may be an advantageous approach to study critical illness pathogenesis and the elucidation of the complex network of metabolomic processes in the context of nutrient deficiency and delivery. Such dynamic metabolomics study designs can produce insights into the depth and breadth of metabolite changes over time in response to intervention. The application of nutritional omics study to the disrupted homeostasis of critical illness can define malnutrition-associated metabolomics signatures, the dynamic response to nutritional intervention and the mechanisms underlying nutritional interventional trial results.

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References

1. Patti GJ, Yanes O, Siuzdak G. Innovation: Metabolomics: the apogee of the omics trilogy. *Nat Rev Mol Cell Biol.* 2012; 13(4):263–269. [PubMed: 22436749]
2. Rinehart D, Johnson CH, Nguyen T, et al. Metabolomic data streaming for biology-dependent data acquisition. *Nature biotechnology.* 2014; 32(6):524–527.

3. Wishart DS, Jewison T, Guo AC, et al. HMDB 3.0--The Human Metabolome Database in 2013. *Nucleic acids research*. 2013; 41(Database issue):D801–807. [PubMed: 23161693]
4. Kiehntopf M, Nin N, Bauer M. Metabolism, metabolome, and metabolomics in intensive care: is it time to move beyond monitoring of glucose and lactate? *Am J Respir Crit Care Med*. 2013; 187(9): 906–907. [PubMed: 23634857]
5. Langley RJ, Tsalik EL, van Velkinburgh JC, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med*. 2013; 5(195):195ra195.
6. Langley RJ, Tipper JL, Bruse S, et al. Integrative "omic" analysis of experimental bacteremia identifies a metabolic signature that distinguishes human sepsis from systemic inflammatory response syndromes. *Am J Respir Crit Care Med*. 2014; 190(4):445–455. [PubMed: 25054455]
7. Afacan NJ, Fjell CD, Hancock RE. A systems biology approach to nutritional immunology - focus on innate immunity. *Molecular aspects of medicine*. 2012; 33(1):14–25. [PubMed: 22061966]
8. Mogensen KM, Robinson MK, Casey JD, et al. Nutritional Status and Mortality in the Critically Ill*. *Critical care medicine*. 2015; 43(12):2605–2615. [PubMed: 26427592]
9. Takele Y, Adem E, Getahun M, et al. Malnutrition in Healthy Individuals Results in Increased Mixed Cytokine Profiles, Altered Neutrophil Subsets and Function. *PLoS One*. 2016; 11(8):e0157919. [PubMed: 27548305]
10. Derde S, Vanhorebeek I, Guiza F, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. *Endocrinology*. 2012; 153(5):2267–2276. [PubMed: 22396453]
11. Martins JD, Liberal J, Silva A, et al. Autophagy and inflammasome interplay. *DNA Cell Biol*. 2015; 34(4):274–281. [PubMed: 25757059]
12. Rodgers MA, Bowman JW, Liang Q, et al. Regulation where autophagy intersects the inflammasome. *Antioxid Redox Signal*. 2014; 20(3):495–506. [PubMed: 23642014]
13. Gunst J, Derese I, Aertgeerts A, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. *Crit Care Med*. 2013; 41(1):182–194. [PubMed: 23222264]
14. Lo S, Yuan SS, Hsu C, et al. Lc3 over-expression improves survival and attenuates lung injury through increasing autophagosomal clearance in septic mice. *Annals of surgery*. 2013; 257(2):352–363. [PubMed: 22968077]
15. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med*. 2013; 1(8):621–629. [PubMed: 24461665]
16. Preiser JC, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care*. 2015; 19:35. [PubMed: 25886997]
17. Yuk JM, Yoshimori T, Jo EK. Autophagy and bacterial infectious diseases. *Exp Mol Med*. 2012; 44(2):99–108. [PubMed: 22257885]
18. Chung LP, Waterer GW. Genetic predisposition to respiratory infection and sepsis. *Crit Rev Clin Lab Sci*. 2011; 48(5–6):250–268. [PubMed: 22185617]
19. Robinette SL, Holmes E, Nicholson JK, et al. Genetic determinants of metabolism in health and disease: from biochemical genetics to genome-wide associations. *Genome Med*. 2012; 4(4):30. [PubMed: 22546284]
20. Fan TW, Lorkiewicz PK, Sellers K, et al. Stable isotope-resolved metabolomics and applications for drug development. *Pharmacol Ther*. 2012; 133(3):366–391. [PubMed: 22212615]
21. Man M, Close SL, Shaw AD, et al. Beyond single-marker analyses: mining whole genome scans for insights into treatment responses in severe sepsis. *Pharmacogenomics J*. 2013; 13(3):218–226. [PubMed: 22310353]
22. Rautanen A, Mills TC, Gordon AC, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. *Lancet Respir Med*. 2015; 3(1):53–60. [PubMed: 25533491]
23. Schmerler D, Neugebauer S, Ludewig K, et al. Targeted metabolomics for discrimination of systemic inflammatory disorders in critically ill patients. *J Lipid Res*. 2012; 53(7):1369–1375. [PubMed: 22581935]

24. Seymour CW, Yende S, Scott MJ, et al. Metabolomics in pneumonia and sepsis: an analysis of the GenIMS cohort study. *Intensive Care Med.* 2013; 39(8):1423–1434. [PubMed: 23673400]
25. Rival T, Cinq-Frais C, Silva-Sifontes S, et al. Alteration of plasma phospholipid fatty acid profile in patients with septic shock. *Biochimie.* 2013; 95(11):2177–2181. [PubMed: 23954620]
26. Mickiewicz B, Duggan GE, Winston BW, et al. Metabolic profiling of serum samples by ¹H nuclear magnetic resonance spectroscopy as a potential diagnostic approach for septic shock. *Crit Care Med.* 2014; 42(5):1140–1149. [PubMed: 24368342]
27. Rogers AJ, McGeachie M, Baron RM, et al. Metabolomic derangements are associated with mortality in critically ill adult patients. *PLoS One.* 2014; 9(1):e87538. [PubMed: 24498130]
- 28*. Ferrario M, Cambiaghi A, Brunelli L, et al. Mortality prediction in patients with severe septic shock: a pilot study using a target metabolomics approach. *Sci Rep.* 2016; 6:20391. Dynamic targeted metabolomic study of patients with severe septic shock. This study describes early changes in glycerophospholipids and kynurenine were associated with mortality. [PubMed: 26847922]
- 29*. Parent BA, Seaton M, Sood RF, et al. Use of Metabolomics to Trend Recovery and Therapy After Injury in Critically Ill Trauma Patients. *JAMA Surg.* 2016; 151(7):e160853. Dynamic targeted metabolomic study of patients with severe blunt trauma. This study describes ongoing oxidative stress, impaired nucleotide synthesis, and suppression of protein metabolism followed by increased nitrogen turnover over time. [PubMed: 27223119]
30. Peltz ED, D'Alessandro A, Moore EE, et al. Pathologic metabolism: an exploratory study of the plasma metabolome of critical injury. *The journal of trauma and acute care surgery.* 2015; 78(4): 742–751. [PubMed: 25807403]
31. D'Alessandro A, Nemkov T, Moore HB, et al. Metabolomics of trauma-associated death: shared and fluid-specific features of human plasma vs lymph. *Blood Transfus.* 2016; 14(2):185–194. [PubMed: 27177401]
32. Park DW, Kwak DS, Park YY, et al. Impact of serial measurements of lysophosphatidylcholine on 28-day mortality prediction in patients admitted to the intensive care unit with severe sepsis or septic shock. *Journal of critical care.* 2014; 29(5):882, e885–811.
- 33*. Banoei MM, Vogel HJ, Weljie AM, et al. Plasma metabolomics for the diagnosis and prognosis of H1N1 influenza pneumonia. *Crit Care.* 2017; 21(1):97. Static metabolomic study of H1N1 versus bacterial community-acquired pneumonia. This study shows that metabolite profiles can differentiate H1N1 from bacterial pneumonia and H1N1 pneumonia survival. [PubMed: 28424077]
- 34**. Parent BA, Seaton M, Djukovic D, et al. Parenteral and enteral nutrition in surgical critical care: Plasma metabolomics demonstrates divergent effects on nitrogen, fatty-acid, ribonucleotide, and oxidative metabolism. *The journal of trauma and acute care surgery.* 2017; 82(4):704–713. Dynamic metabolomic study of critically ill patients with metabolome measured before and after either parenteral or enteral nutrition. This study showed differences in protein metabolism and antioxidant repletion when metabolome of patients with parenteral or enteral nutrition were compared. [PubMed: 28129265]
- 35*. McPhail MJW, Shawcross DL, Lewis MR, et al. Multivariate metabotyping of plasma predicts survival in patients with decompensated cirrhosis. *Journal of hepatology.* 2016; 64(5):1058–1067. Static metabolomic study of patients with decompensated cirrhosis. This study showed lipid and amino acid dysregulation associates with increased severity of illness and mortality. [PubMed: 26795831]
- 36*. Mogensen KM, Lasky-Su J, Rogers AJ, et al. Metabolites Associated With Malnutrition in the Intensive Care Unit Are Also Associated With 28-Day Mortality. *JPEN J Parenter Enteral Nutr.* 2017; 41(2):188–197. Static metabolomic study of adult MICU patients with sepsis. This study showed differences in glutathione and purine metabolism in patients with and without evidence of malnutrition on registered dietitian evaluation at ICU admission. [PubMed: 27406941]
- 37*. Lasky-Su J, Dahlin A, Litonjua AA, et al. Metabolome alterations in severe critical illness and vitamin D status. *Crit Care.* 2017; 21(1):193. Static metabolomic study of adult MICU patients with sepsis. This study showed differences in glutathione and glutamate metabolism in patients with and without vitamin D deficiency at ICU admission. [PubMed: 28750641]

38. Everts B, Amiel E, Huang SC, et al. TLR-driven early glycolytic reprogramming via the kinases TBK1-IRAK4 supports the anabolic demands of dendritic cell activation. *Nat Immunol*. 2014; 15(4):323–332. [PubMed: 24562310]
39. Moon JS, Lee S, Park MA, et al. UCP2-induced fatty acid synthase promotes NLRP3 inflammasome activation during sepsis. *J Clin Invest*. 2015; 125(2):665–680. [PubMed: 25574840]
40. Oliveira BL, Morais M, Mendes F, et al. Re(I) and Tc(I) complexes for targeting nitric oxide synthase: influence of the chelator in the affinity for the enzyme. *Chem Biol Drug Des*. 2015; 86(5):1072–1086. [PubMed: 25894011]
41. Waagsbo B, Svardal A, Ueland T, et al. Low levels of short- and medium-chain acylcarnitines in HIV-infected patients. *European journal of clinical investigation*. 2016; 46(5):408–417. [PubMed: 26913383]
42. Scarpulla RC, Vega RB, Kelly DP. Transcriptional integration of mitochondrial biogenesis. *Trends in endocrinology and metabolism: TEM*. 2012; 23(9):459–466. [PubMed: 22817841]
43. Jo EK, Kim JK, Shin DM, et al. Molecular mechanisms regulating NLRP3 inflammasome activation. *Cell Mol Immunol*. 2016; 13(2):148–159. [PubMed: 26549800]
44. Wajner M, Amaral AU. Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animal studies. *Biosci Rep*. 2015; 36(1):e00281. [PubMed: 26589966]
45. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol*. 2013; 34(3):137–143. [PubMed: 23103127]
46. Cambiaghi A, Pinto BB, Brunelli L, et al. Characterization of a metabolomic profile associated with responsiveness to therapy in the acute phase of septic shock. *Sci Rep*. 2017; 7(1):9748. [PubMed: 28851978]
47. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA*. 2014; 312(15):1520–1530. [PubMed: 25268295]
48. Braun AB, Gibbons FK, Litonjua AA, et al. Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. *Crit Care Med*. 2012; 40(1):63–72. [PubMed: 21926604]

Figure 1. From Genomic to Metabolomic Sampling

Individual cells provide source material for determination of genomics (DNA), transcriptomics (RNA), proteomics (protein/enzyme), and metabolomics (metabolites). Such individual cells may comprise organs, tissue, endothelium or be circulating in the bloodstream. Sampling of tissue via biopsy or of the peripheral circulation via blood sampling can provide a window into the omics of specific tissues/cells or circulating elements respectively.