Hycult Scope

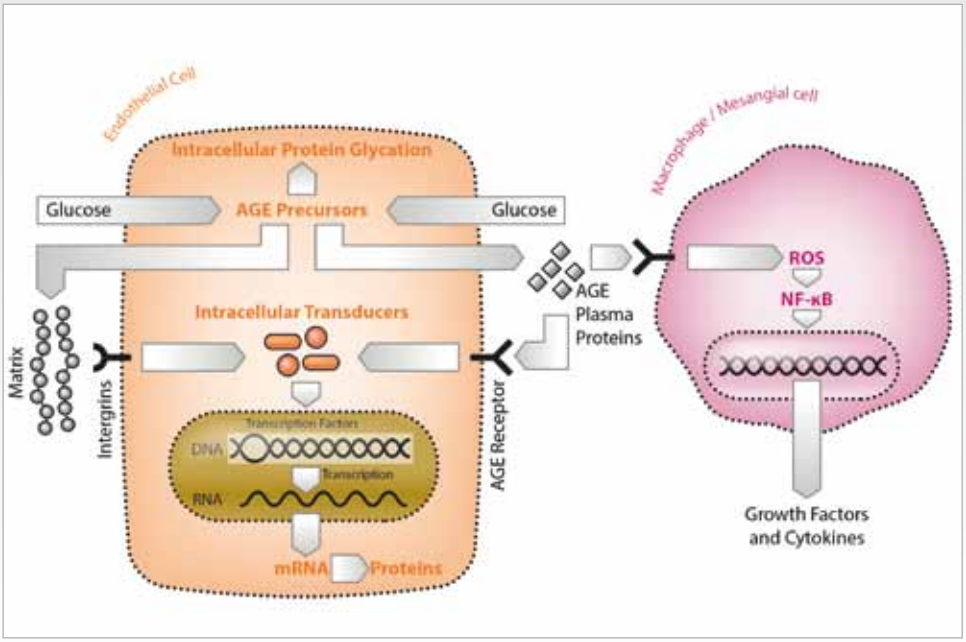
Methylglyoxal: a potent glycating agent in the body

Abnormalities in metabolism such as hyperglycaemia and hyperlipidaemia affect billions of individuals worldwide. Recent data suggest an important role of advanced glycation endproducts (AGEs) and advanced lipoxidation endproducts (ALEs) in the risk for vascular complications in people with metabolic abnormalities. The group of AGEs/ALEs is a heterogeneous family of unavoidable by-products which are formed by reactive metabolic intermediates derived from glucose and from lipid oxidation with the involvement of oxidative stress. Because of the involvement of oxidative stress in the formation of AGEs/ALEs, these compounds are implicated in the development of age-related diseases such as diabetes and Alzheimer disease and are associated with vascular disease such as atherosclerosis. Thus, increased formation of AGEs/ALEs is a core defect derived from abnormalities in both glucose- and lipid-metabolism which can lead to complications.

Of importance for the fast intracellular AGE formation are glycolytic intermediates such as the dicarbonyl compounds. Among these reactive compounds, methylglyoxal (MGO) is believed to be the most potent glycating agent in the body.

Increased levels of MGO and MGO-induced AGEs are found in association with insulin resistance, hypertension and in atherosclerotic lesions. Moreover, MGO targets specific mitochondrial proteins accompanied by an increase in the formation of reactive oxygen species (ROS). MGO-induced ROS production may be an initial event in the pathogenesis of complications. Most importantly, GLO1 overexpression also enhances lifespan in C. elegans, supporting that MGO is involved in ageing. Thus, the above mentioned studies strongly suggest that MGO is a potent glycating agent in the body and is involved in the development of vascular disease.

Schalkwijk, C. Maastricht University



Chronic Inflammation

In this Issue:

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Nitrotyrosine, a biomarker for Arthritis and Joint Injury

This study shows increased nitrotyrosine (NT) in synovial fluid and plasma from patients with arthritis and joint injury.
Plasma NT was increased in Rheumatic Arthritis (RA) patients and decreased when they received anti-TNF therapy after 6 months. The decrease in NT correlates with well-known markers of RA disease activity including MMP-1, MMP-3, CRP and DAS28-3CRP.

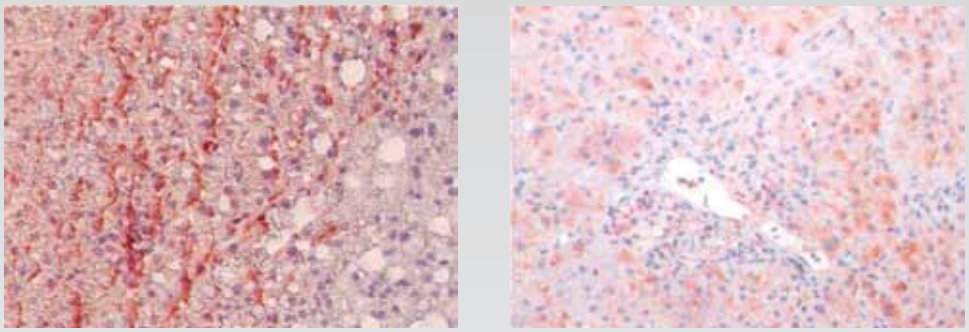
In conclusion, the biomarker NT may alter better selection and gradation scale of individuals with active joint disease.

T.P. Misko et al. Pfizer Research, St. Louis, MO, USA

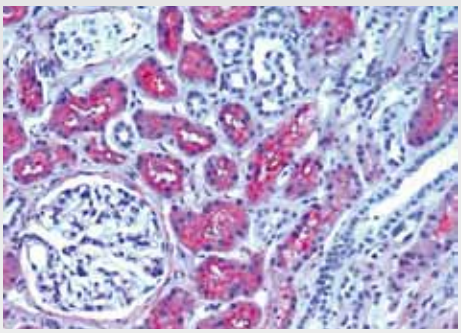
More information can be found in paper:
Osteoarthritis and Cartilage 2013, 21:151

Nitrotyrosine, a biomarker for Obesity

NO synthesis and nitrosative stress are increased in severely obese children and correlated with anthropometric parameters indicative of abdominal obesity, oxidative stress and inflammatory markers. Nitric oxide (NO) is the major endothelium-derived relaxing factor.
Increased NO production in obese children was associated with MRFs; plasma nitrate to waist circumference ($r = 0.388$, $p = 0.003$), uric acid ($r = 0.404$, $p < 0.001$), and tumor necrosis factor α ($r = 0.302$, $p = 0.021$), and plasma nitrite to triglycerides ($r = 0.432$, $p < 0.001$).
More information can be found in paper:
Cordoner-Franch et al, Atherosclerosis 2011, 215:475.



Staining of paraffin embedded liver sections of severely obese patients using monoclonal antibody HM11 directed at nitrotyrosine (magnification 200x).



L-FABP on human kidney paraffin sections (cat.# HM2049)

Oxidative stress products

Product	Cat. #
NO Competitive ELISA, 1x96 det.	HIT501
CML Competitive ELISA, 1x96 det.	HIT502
MGO Competitive ELISA, 1x96 det.	HIT503
Nitrotyrosine, Human, ELISA, 2x96 det.	HK501-02
Nitrotyrosine, mAb HM.11, 100 µg	HM5001
Ethenoadenosine, mAb 1G4, 100 µg	HM5005
BPDE-DNA, mAb 5D11, 100 µg	HM5007
BPDE, mAb 8E11, 100 µg	HM5008
CML, Human, mAb CML26, 100 µg	HM5013
MGO-modified proteins, Human, mAb MGO-1, 100 µg	HM5014
Chlorotyrosine, pAb, 100 µg	HP5002
Oxidized PAPC, 1 mg	HC4035
PAPC, 5 mg	HC4043

LIT score differentiates between surgical NEC and non-surgical NEC infants and survivors and non-survivors

Necrotizing Enterocolitis (NEC) is a gastrointestinal disease that mostly affects premature infants. NEC involves infection and inflammation that causes destruction of the bowel (intestine) or part of the bowel. In view of the high mortality rate, early detection based on a specific or panel of biomarkers could potentially improve the morbidity and mortality of NEC.

The LIT score consist of three plasma markers L-FABP (Liver Fatty Acid Binding protein), I-FABP (Intestinal Fatty Acid Binding protein), and TFF3 (Trefoil factor 3). I-FABP is mainly expressed by enterocytes, L-FABP by enterocytes or hepatocytes. TFF3 is predominantly expressed in intestinal goblet cells and mucin producing epithelial cells.

In this study, plasma concentrations of these three markers were significantly higher in the NEC than in the septicemic (neonatal sepsis without NEC) and the control cases.

The most important finding is that the LIT score can effectively discriminate between surgical and non-surgical NEC infants with a high degree of accuracy. Furthermore, the LIT score is also the best prognostic score for predicting non-survivors in NEC infants.

These results may guide neonatologists and pediatric surgeons in the management of the patients.

E.W.Y. Ng et al. Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong.

More information can be found in the paper:
Annals of Surgery 2013, 258:1111

LPS-binding protein and IL-6 mark paradoxical tuberculosis immune reconstitution inflammatory syndrome in HIV patients

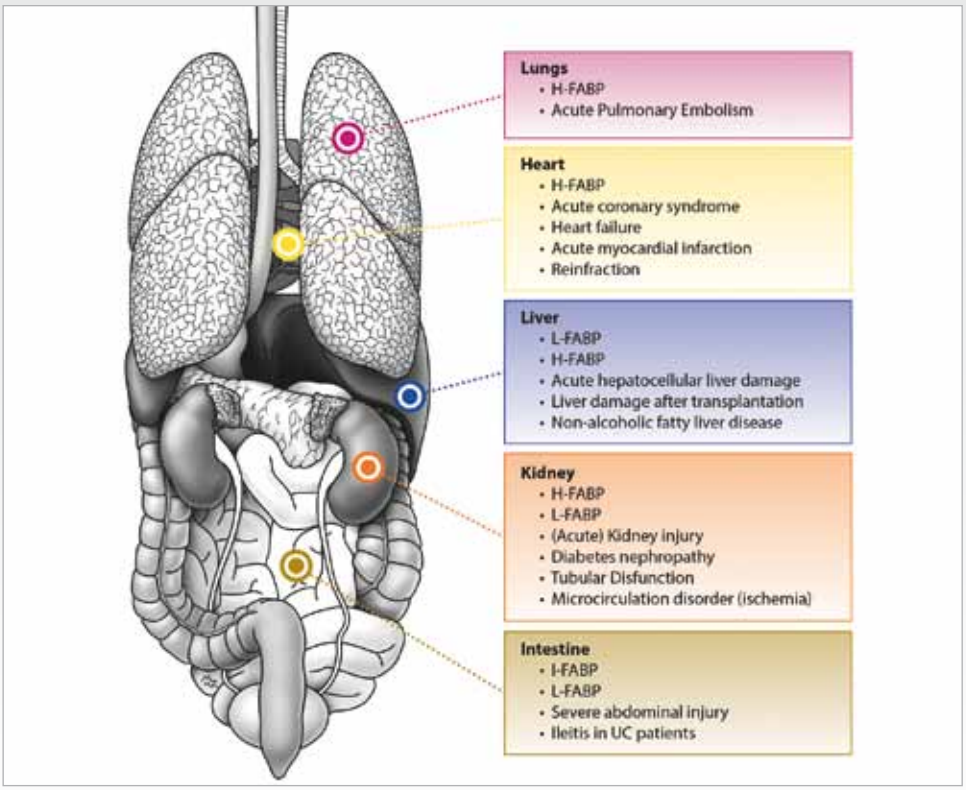
Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) remains a poorly understood inflammatory complication in HIV-TB co-infected patients initiating antiretroviral therapy (ART). The immune reaction and inflammation in response to TB typically involves stimulation of toll-like receptors by antigens such as lipoarabinomannan grouped under the name pathogen-associated molecular patterns (PAMPs).

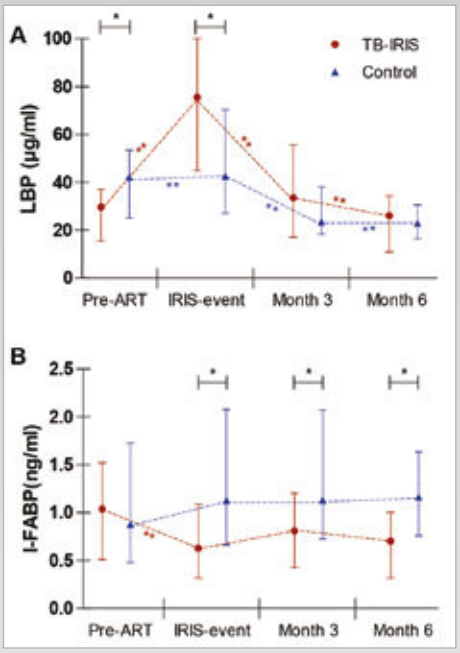
In order to find novel biomarkers of TB-IRIS, we examined whether plasma proteins, capable of binding to PAMPs, are potential candidate biomarkers. In addition, we explored the presence of intestinal permeability (i.e. "leaky gut") as a possible secondary source of other PAMPs such as lipopolysaccharide.

Blood samples were collected from 40 TB-IRIS patients before ART initiation and at IRIS event, 3 months and 6 months on ART. Forty HIV-TB patients that did not develop TB-IRIS served as controls. Plasma concentrations of LBP, sCD14 and markers of a leaky gut, i.e. endotoxin-core antibody IgG (EndoCab) and intestinal fatty-acid-binding protein (I-FABP), were determined by ELISA (Hycult Biotech, Uden, The Netherlands). Dilutions were 2000x (LBP), 100x (sCD14), 100x (EndoCab) and 2x (I-FABP) for each protein respectively. Pre-ART LBP levels were significantly lower in TB-IRIS patient compared to controls ($p = 0.016$). During IRIS event, LBP levels were significantly higher compared to controls ($p = 0.010$). Upon ART, I-FABP levels declined significantly in TB-IRIS patients and remained lower than controls during follow-up ($p \leq 0.049$). Our results show no evidence of a contribution of a leaky gut to TB-IRIS and reveal LBP as a possible biomarker of TB-IRIS.

Odin Goovaerts, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

More information can be found in the paper:
PLoS One 8(11): e81856.





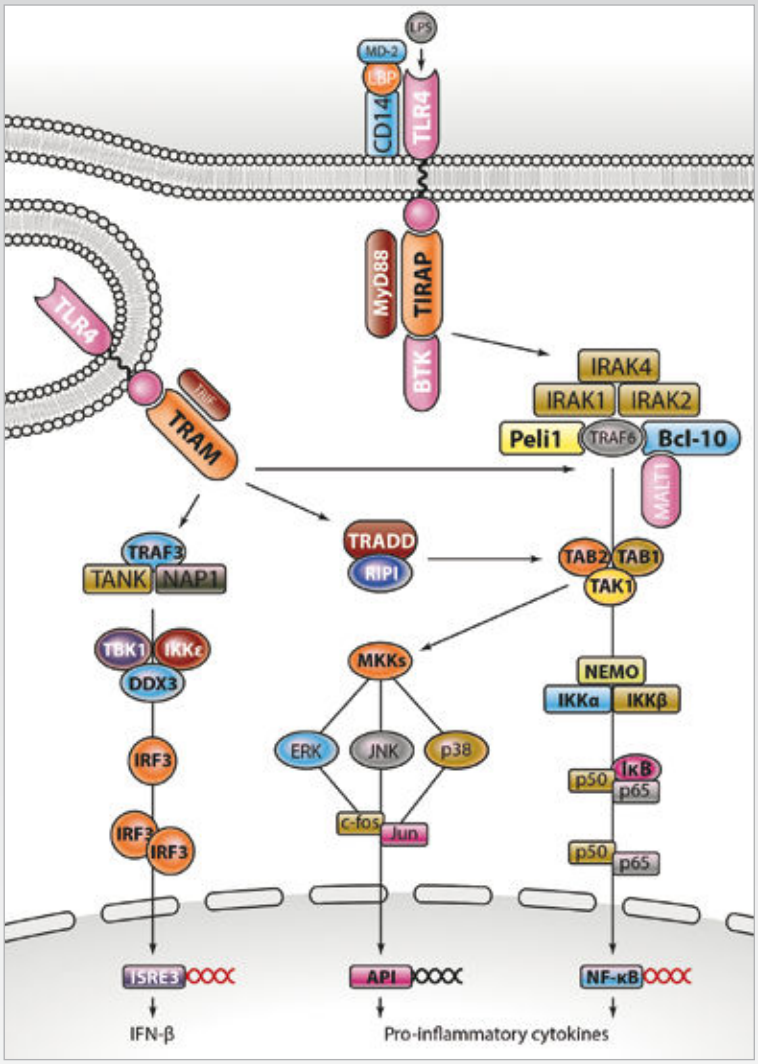
Plasma levels of (A) Lipopolysaccharide binding protein (LBP) and (B) Intestinal-fatty acid binding protein (I-FABP) in HIV-TB patients that did or did not develop TB-IRIS. *○ and △ represent median plasma levels for each patient group at each time point, Dotted lines indicate changes over time per patient-group. ✱ indicate significant differences between groups. ✱✱ represent significant differences between time points of the same patient groups. A Wilcoxon signed-rank test was used to calculate p values with the level of significance set to $p < 0.05$.*

FABP products

Product	Cat. #
H-FABP, Human, ELISA, 2x96 det.	HK402
L-FABP, Human, ELISA, 2x96 det.	HK404-02
I-FABP, Human, ELISA, 2x96 det.	HK406-02
H-FABP, Mouse, ELISA, 2x96 det.	HK413-02
H-FABP, Rat, ELISA, 2x96 det.	HK414-02
H-FABP, Human, mAb 66E2, 100 µg	HM2016
L-FABP, Human, mAb L2B10, 100 µg	HM2049
L-FABP, Human, mAb K5A6, 100 µg	HM2051
B-FABP, Human, mAb 1F5, 100 µg	HM2299
B-FABP, Human, mAb 2D2, 100 µg	HM2300
L-FABP, Rat, pAb, 100 µg	HP8010
IL-FABP, Mouse, pAb, 100 µg	HP8011
I-FABP, Human, pAb, 100 µg	HP9020
L-FABP, Human, pAb, 100 µg	HP9021
A-FABP, Human, pAb, 100 µg	HP9028
B-FABP, Human, pAb, 100 µg	HP9029
E-FABP, Human, pAb, 100 µg	HP9030
IL-FABP, Human, pAb, 100 µg	HP9031
M-FABP, Human, pAb, 100 µg	HP9032
H-FABP, Human, Recombinant, 50 µg	HC2105
B-FABP, Human, Recombinant, 50 µg	HC2106
I-FABP, Rat, Recombinant, 50 µg	HC3101
L-FABP, Rat, Recombinant, 50 µg	HC3102

Systemic T-cell activation and proliferation linked to microbial translocation

The loss in barrier function is a widely accepted feature of both forms of Intestinal Bowel Disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC). The loss of epithelial integrity results in intestinal permeability (CD) or ulceration (UC) that propose that microbial products may enter the underlying lamina properia and transfer to the circulation. In line with this increased levels of LPS are found in serum of IBD patients. The presence of microbial products in the circulation will activate circulating antigen presenting cells and other cells that results in secretion of cytokines, expression of adhesion molecules and activation and differentiation of T-cells.



In this study, the researchers reported increased levels of CRP, IL-6 and IFN-alpha in CD and UC patients. They further demonstrated that increased chronic inflammation in IBD is correlated with increased activation of peripheral blood T cells ((CD38+HLA-DR+) CD4+ and CD8+ T cells).

Circulating LPS may be the driver for T cell activation in IBD. However, no elevated levels of bacterial LPS or sCD14 were measured but they did found elevated levels of LBP that correlated with the activation of CD38+HLA-DR+CD4+ and CD8+ T cells.

They propose that increased levels of LBP is likely contributed to LPS clearance and that this also explains the decline LPS in active IBD.

This study concludes that there is an association between intestinal permeability and systemic immune activation in IBD.

More information can be found in the paper: Circulating CD4+ and CD8+ T cells are activated in IBD and are associated with plasma markers for inflammation. N.T. Funderberg et al. Immunology 2013, 140:87

Related Products

Product	Cat. #
LBP, Human, ELISA, 2x96 det.	HK315-02
sCD14, Human, ELISA, 2x96 det.	HK320-02
Calprotectin, Human, ELISA, 2x96 det.	HK325-02
CRP, Human, ELISA, 1x96 det.	HK358
hsCRP, Human, ELISA, 1x96 det.	HK369
EndoCab, Human, ELISA, 2x96 det.	HK504
LAL Chromogenic Assay, 3x96 det.	HIT302

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