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Monitoring immune modulation by nutrition in the general population: Identifying and substantiating health effects[1]

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Background and Objectives:

Optimal functioning of the immune system is crucial to human health, and nutrition is one of the major exogenous factors modulating different aspects of immune function. In regard to this, there is a need for guidance on the assessment and interpretation of immune modulation by nutrition. ILSI Europe's Nutrition & Immunity and Probiotics Task Forces jointly organised an Expert Group (EG) to develop guidelines for the use of immunomodulation markers applied in nutrition intervention studies in the general population. Three health domains were selected based on the EFSA 2011 Guidance Document[2]: defence against pathogens, control of low-grade (metabolic) inflammation and avoidance or mitigation of allergy. The EG recommendations have been published in the *British Journal of Nutrition*.[1]

Step 1: Criteria for selection and ranking were developed, based on Albers et al 2005[3]:

Ranking Categories:
Biological relevance
Biological sensitivity
Feasibility
Practicality

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Ranking Levels:
Proven (+++)
Strong (++)
Medium (+)
Low (0)

Step 2 /Table 1. Over 75 markers were ranked according to the criteria (illustrating example of allergy):

			Clinical relevance			Biological sensitivity		
Function	Marker	mainly relevant for specific subpopulations	differentially expressed	correlates with clinical endpoint	linked to causal pathway	within subject variation	between subjects variation	*Arbitrary* Marker score[1]
tolerance to allergens	incidence of symptoms	yes (allergic subjects)	++[2]	+++	+++	+	+	■■■
	duration of symptoms	yes (allergic subjects)	+	0	+	+	+	■
	severity of symptoms (e.g. peak flow, SCORAD, ARIA, ACT, TRACK)	yes (allergic subjects)	+++	+++	+++	+	+	■■■
response to allergen challenge	prick test	yes (allergic subjects)	+++	+++	+++	+	+	■■■
	contact hypersensitivity / patch test	yes (allergic subjects)	+++	+++	+++	+	+	■■■
	respiratory (nasal) provocation test	yes (allergic subjects)	+++	+++	+++	+++	++	■■■
	labial/ nasal/oral provocation test	yes (allergic subjects)	+++	+++	+++	+	+	■■■

[1] arbitrary marker score is subjective expert judgement on usefulness of a marker based on weiged evaluation of individual criteria:
•••: high suitability, ••: medium suitability, •: low suitability

[2] +++: proven, ++: strong, +: medium, 0: low

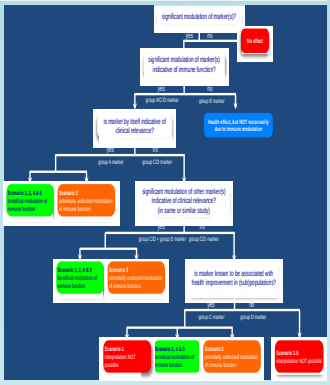
Step 3: Markers were grouped by relationship to immune function (yes/no) and clinical relevance (yes/associated/unknown).

Step 4: Various potential scenarios of marker modulation were defined:

- Modulation within a reference range
- Modulation from outside the reference or control range back into the range
- Modulation from within the reference or control range to outside the range
- Prevention of modulation from within the reference or control range to outside the range
- Modulation from a less favourable reference range into the reference range of a comparator group with a more favourable immune function.

Step 5: A framework for interpretation was developed:

A "flow-chart" was devised to aid the interpretation of changes observed in (combinations of) immune markers, taking into account the type of marker and the changes observed relative to a defined reference range. Within this framework, the 5 scenarios in Step 4 above were considered. The need to consider the quality of individual studies and consistency of effects, is still emphasized, as well as the need to base ultimate conclusions on totality of evidence.



Conclusions:

The EG concluded that there is no gold standard or single marker for immune function. When selecting markers, the following should be considered: 1) the target population, 2) the exact physiological function of the immune system involved and 3) the health benefit of interest. Ideally, markers selected should include those indicating clinical relevance *and* involvement in immune function by themselves, or a combination of markers indicating clinical relevance which are plausibly linked to immune function. It was also concluded that challenge tests and function assays provide stronger results than 'status markers'. Interpretation of marker changes should consider the targets identified and should be in relation to the relevant reference range, as illustrated in the 5 'scenarios'.

References:
1 Albers et al. (2013) Monitoring immune modulation by nutrition in the general population: identifying and substantiating effects on human health. Br J Nutr 110(S2):S4-S22. PDF: http://journals.cambridge.org/bjn/immune.
2 EFSA Panel on Dietetic Products Nutrition and Allergies (NDA) (2011) Guidance on the scientific requirements for health claims related to gut and immune function. EFSA J 9, 1984.
3 Albers et al. (2005) Markers to measure immunomodulation in human nutrition intervention studies. Br J Nutr 94, 452-481.

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