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Selecting for predisposition to cancer cachexia

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Cachexia is a multifactorial syndrome that affects the majority of cancer patients with advanced disease. It is characterized by negative energy balance, chronic inflammation and progressive loss of muscle and fat mass (Fearon et al, 2011). Evidence supports that cytokines, produced directly by cancer cells or by the host's monocytes as a response to the tumour environment, play a key pathogenetic role (Tisdale, 2009). Cachectic patients frequently exhibit decreased tolerance to antineoplastic therapies, diminished quality of life and decreased survival (Dewys et al, 1980; Prado et al, 2009).

Although there are many therapeutic options, including nutritional consultation, exercise, nutritional supplements and drugs, none can be considered satisfactory at present (Kung et al, 2010; Penna et al, 2011). In common practice clinicians use progestagens and short term corticosteroids which may have some positive effect in appetite but it has yet to be proven that this may translate into meaningful clinical outcomes, including increase of muscle mass and improvement in quality of life or overall survival. A major reason for this lack of efficient treatment is the late diagnosis of the syndrome, which is usually, established only when clinical findings are indicative of severe nutritional depletion (Argilés et al, 2008). In obese patients, diagnosis may be further delayed due to the substantial muscle loss under a mantle of fat (Tan et al, 2009). By that time, any therapeutic effort would be not only inefficient but even unethical.

Current notion supports the existence of a 'pre-cachectic stage' which represents the first of the three stages of cachexia (Fearon et al, 2011). Pre-cachectic patients may experience mild or even no weight loss during the 6 months preceding diagnosis and their symptoms and signs may be limited to anorexia and inappreciable metabolic alterations. These patients would probably gain most of the benefit provided by any therapeutic approach. However, our current knowledge does not provide us with the means to select those patients who are at risk to enter and/or progress through the spectrum of cachexia stages. Nor are we able to identify the rate with which weight loss and physical functioning deterioration will eventually occur.

> *» ...C-allele of the rs6136 polymorphism in SELP gene encoding P-selectin, is associated with reduced risk of developing cachexia among cancer patients «*

Thus, our diagnostic criteria and clinical decision-making remain almost solely based on gross disease-related characteristics, such as primary site and stage (Muscaritoli et al, 2006). In addition, patients' medical history and medications, which are directly or indirectly related with the presence of cachexia, are also considered (Lenk et al, 2010).

Previous data from small studies have provided some evidence that genetic polymorphisms of certain cytokine genes may alter the risk for development of cancer cachexia in distinct cancer populations (Tan & Fearon, 2010). The increasing body of evidence of genetic susceptibility to cachexia seems to culminate, so far, to the first large-scale candidate gene association study performed by Tan and coworkers (Tan et al, 2012). In this clinically relevant attempt to explore a potential contribution of genetic factors to the development of the syndrome, which is the first of its kind in terms of population size and variety of single nucleotide polymorphisms (SNPs) tested, Tan et al, 2012 report that the C-allele of the rs6136 polymorphism in SELP gene encoding P-selectin, is associated with reduced risk of developing cachexia among cancer patients of various primaries, including cancers of the digestive tract, lung and pancreas (Tan et al, 2012).

P-selectin is a cell adhesion molecule (CAM) on the surfaces of activated endothelial cells, which line the inner surface of blood vessels, and activated platelets. P-selectin plays an essential role in the initial recruitment of leukocytes to the site of injury during inflammation. P-selectin is also very important

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in the recruitment and aggregation of platelets at areas of vascular injury and has also the ability to attach to the actin cytoskeleton through anchor proteins. In cancer, P-selectin is believed to facilitate adhesion of cancer cells to stimulated endothelial cells, thus inducing inflammatory response (Chen & Geng, 2006). The strong clinical relevance of P-selectin as a contributor to cachexia was also confirmed by the authors in animal (rat) models of LPS- and tumor-induced cancer cachexia.

Although not confirmed in the validation cohort, the study presents a significant risk association between cachexia phenotype and several SNPs of genes involved in other important pathogenetic pathways of the syndrome, including appetite regulation, glucocorticoid signalling and the mitogen activated protein kinases (MAPK) activity (Tan et al, 2012).

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In the light of development of newer agents for the treatment of cancer cachexia, the idea of risk stratification on a personalized basis generates much enthusiasm. This would be of particular interest for patients with various other predisposing factors to cachexia and particularly to those already entering the pre-cachectic stage. However, given the complexity of the pathophysiology of the syndrome as well as the variability of polymorphisms and the diversity across different populations, larger studies are needed in order to confirm the clinical significance of such analysis. Finally, the predictive value of these polymorphisms should be evaluated prospectively. Nevertheless, Tan et al, 2012 have shown us that a clinically oriented approach of looking into constitutional parts of cachexia, including systemic inflammation and weight loss may be the key to reveal contributions of genetic factors to the complexity of the cachectic phenotype in cancer. A simplified model of the contribution of factors to the development and progression of cachexia is presented in Fig 1. There is certainly a long road ahead before discovering the full landscape of cancer cachexia; however, Tan et al, 2012 have possibly put P-selectin on the map as a promising target for rational anti-cachexia drug design.

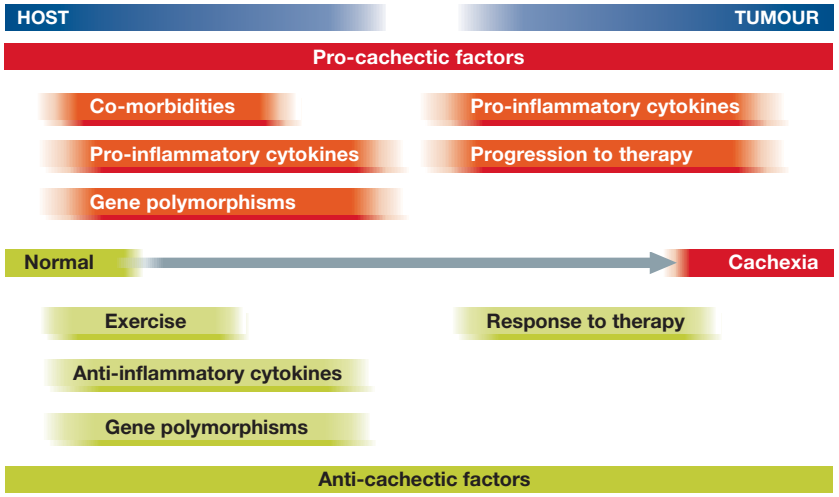

Figure 1. Simplified schema of host- and tumor-related factors that are able to protect against or induce cancer cachexia.

The authors declare that they have no conflict of interest.

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