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Review

Multifunctional targets of dietary polyphenols in disease: A case for the chemokine network and energy metabolism

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ABSTRACT

Chronic, non-acute inflammation is behind conditions that represent most of the disease burden in humans and is clearly linked to immune and metabolic mechanisms. The convergence of pathways involving the immune response, oxidative stress, increased circulating lipids and aberrant insulin signaling results in CCL2-associated macrophage recruitment and altered energy metabolism. The CCL2/CCR2 pathway and the energy sensor AMP-activated protein kinase (AMPK) are attractive therapeutic targets as a part of preventive management of disease. Several effects of polyphenols are useful in this scenario, including a reduction in the activities of cytokines and modulation of cellular metabolism through histone deacetylase inhibitors, AMPK activators, calorie-restriction mimetics or epigenetic regulators. Research is currently underway to develop orally active drugs with these effects, but it is convenient to examine more closely what we are eating. If a lack of relevance in terms of toxicity and substantial effectiveness are confirmed, plant-derived components may provide useful druggable components and dietary supplements. We consider therapeutic actions as a combination of synergistic and/or antagonistic interactions in a multi-target strategy. Hence, improvement in food through enrichment with polyphenols with demonstrated activity may represent a major advance in the design of diets with both industrial and sanitary value.

Contents

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1. Introduction

The goal of acquiring a better understanding of the effects of dietary-derived polyphenols on specific cellular pathways and diseases may impact on the prophylaxis and treatment of some of the most common disorders. This may be associated with their commonly accepted important role in the modulation of oxidative stress and inflammation and, as a consequence, in the regulation of metabolic pathways and bioenergetics. Recent data support the notion that the chemokine (C-C motif) ligand 2 (CCL2)/CCR2 and AMP-activated protein kinase (AMPK) pathways should be singled out, as beneficial effects of dietary polyphenols are most likely linked to this association compared to other pathways (Beltran-Debon et al., 2010; Caligiuri et al., 2008; Declèves et al., 2011; Ewart et al., 2008; Hattori et al., 2006, 2009; Hawley et al., 2012; Herranz-Lopez et al., 2012; Jeong et al., 2009; Joven et al., 2012; Kanellis et al., 2006; Lambernd et al., 2012; Maestre et al., 2010; Miyokawa-Gorin et al., 2012; Roca et al., 2009; Steinberg and Kemp, 2009). Non-acute inflammation and the accompanying altered metabolism are crucial driving forces behind cancer and/or atherosclerosis, among other chronic diseases, that account for most human mortality. In mice, it is generally accepted that macrophages and other types of immune cells that perform key regulatory functions are obligate partners for both tumorigenesis and atherogenesis (Libby et al., 2011; Condeelis and Pollard, 2006). Whether the manipulation of inflammation may be effective in humans remains uncertain and is difficult to interpret because available agents may also possess off-target activity (Choi et al., 2012; Paul et al., 2000; Raes et al., 2005; Tous et al., 2004, 2005a,b) but the inflammatory response is widely accepted as paramount in the pathogenesis of atherosclerosis. In cancer, this was initially viewed as the body's attempt to destroy the tumor cells, but in fact immune cells may foster tumor development (Daniel et al., 2003). Rather, the immune system can promote disease at some times, and in other cases help keep it in check. Chemokines and mechanisms that link inflammation to metabolism play a multi-faceted role in the pathogenesis of chronic diseases through macrophage-related pathways (Declèves et al., 2011; Ewart et al., 2008; Hattori et al., 2006; Lim and Kwon 2010; Qian et al., 2011; Roca et al., 2009; Rull et al., 2010). CCL2 is known to recruit monocytes and macrophages to sites of inflammation, to inhibit AMPK phosphorylation and to activate the production of active and relevant molecules such as growth factors, enzymes that may either promote atherosclerosis or help cancer cells escape from tumors, substances that inhibit apoptosis, molecules contributing to drug resistance and lesion maintenance, and even proteins that stimulate the formation of blood vessels (Kanellis et al., 2006; Miyokawa-Gorin et al., 2012). We will review the evidence linking CCL2 and energy sensors (AMPK) to chronic diseases and how dietary polyphenols provide effective dietary manipulation to modulate the function of both CCL2 and AMPK. We will also discuss why drugs that target single genes are unlikely to be effective in multi-factorial diseases and how dietary polyphenols target multiple genes. Although polyphenols seem to be effective and generally non-toxic, this may be an artefact due to the lack of long-term studies. Also, the action of metabolites is unknown and the process of bioactivation may provide unexpected elements. Consequently, toxicological relevance may be considered an unresolved issue.

2. The action of chemokines on macrophages: rationale for a therapeutic target?

2.1. Modulation of oxidative stress and inflammation

Many of the important pathways underlying inflammation-related diseases resulting in metabolic alterations have been uncovered, but the precise molecular mechanisms and interconnecting pathways remain obscure (Joven et al., 2012; Mantovani, 2010). A vicious cycle between oxidation and inflammation leading to complications has been implicated in a growing number of disease states. Oxidative damage and endoplasmic reticulum (ER) stress-induced apoptosis are both relevant to atherosclerosis and cancer; targeting the redox balance is a powerful way to inhibit the development of atherosclerosis and to induce selective tumor cell death (Calvano et al., 2005; Camps et al., 2009). We have described that almost every tissue expresses the genes for chemokines, chemokine receptors and the antioxidant paraoxonases (PON). Such wide tissue distribution suggests that these molecules are produced constitutively, and not necessarily after selective induction. Their unique effects clearly suggest an important role in the regulation of the inflammatory response. A systemic and coordinated role also seems possible, suggesting that antioxidant and anti-inflammatory treatments may be synergistic in most conditions (Rodriguez-Sanabria et al., 2010). This choice of targets is likely to be safe, because both CCL2- deficient and PON-1 deficient mice exhibit an essentially normal phenotype, except when metabolically challenged (i.e. energy excess) (Chow et al., 2006; Rozenberg et al., 2003). Surprisingly, most plant-derived polyphenols have shown a modulatory effect on both oxidative stress and inflammatory responses (Kostyuk et al., 2011; Vitaglione et al., 2010).

2.2. The role of macrophages in atherosclerosis and cancer

In current models of atherosclerosis, endothelial cells are damaged as a result of persistently elevated levels of oxidized cholesterol. If PON fails to limit the lesion, circulating monocytes are drawn into the subendothelium, where they differentiate into macrophages which become activated and secrete chemoattractants and growth factors that build the atherosclerotic plaque. CCL2 and CCR2 greatly contribute to this situation (Libby et al., 2011) and increased plasma levels of CCL2 predict accelerated atherosclerosis (Coll et al., 2007a,b; Rovin et al., 1999). Macrophages also seem to be involved in myocarditis, ischemia/reperfusion injury, heart transplant rejection, cardiac repair and ischemic angiogenesis (Charo and Taubman, 2004; Gerard and Rollins 2001;