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TSG-6: A Hyaladherin Associated with Inflammation
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TNF-stimulated gene 6 (TSG-6) is activated in a variety of cell types by the proinflammatory cytokines TNF-α and IL-1. The TSG-6 gene encodes a secreted 35 kDa glycoprotein abundant in synovial fluids of patients with various forms of arthritis and detectable in sera of patients with different inflammatory or autoimmune disorders. TSG-6 protein consists of two structural domains. The N-terminal domain, a link module, defines TSG-6 as a member of the hyaladherin family of proteins and provides TSG-6 with affinity for hyaluronic acid. The link module is followed by a C-terminal CUB domain, a module shared by a variety of structurally and functionally diverse proteins. TSG-6 forms a stable complex with components of the plasma protein inter-a-inhibitor (lal), a Kunitz-type serine protease inhibitor that is also a hyaluronan-binding protein. Recombinant human TSG-6 protein exerts a potent antiinflammatory effect in a murine model of acute inflammation. Site-directed mutagenesis was used to target amino acid residues potentially involved in the interaction with hyaluronan. TSG-6 mutants were examined for their interaction with hyaluronan, their antiinflammatory activity and their ability to form a stable complex with lal. Activation of the TSG-6 gene by proinflammatory cytokines, the presence of TSG-6 protein at sites of inflammation and its antiinflammatory effect suggest a role for TSG-6 as a negative feed-back regulator of the inflammatory response.

E1

Introduction: Importance of oestrogen, xenoestrogen and phytoestrogen metabolism in breast cancer risk?

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The role of endogenous oestrogens in breast cancer is widely recognised. Oestrogen metabolism to form the biologically active oestrone, oestradiol, involves the action of enzymes including sulphatase, oestradiol 17β-hydroxysteroid dehydrogenase and aromatase. The activity of these enzymes is clearly of importance in relation to breast cancer risk and to strategies of breast cancer control. Conversion of oestradiol to its metabolite 4-hydroxyoestradiol predominates over 2-hydroxyoestradiol formation in neoplastic breast tissue compared to normal breast tissue. An elevated 4-hydroxyoestradiol/2-hydroxyoestradiol ratio may be a useful marker of malignant breast tumours. Similarly the ratio of genotoxic 16α-hydroxyoestrone to protective 2-hydroxyoestrone, may be a useful marker of breast cancer risk that can be measured, for example, in urine. Some xenoestrogens, including environmental oestrogens, for example, some pesticides, can increase the 16α-hydroxyoestrone/2-hydroxyoestrone ratio and are thus likely to increase breast cancer risk, whereas others such as the antioestrogen drug tamoxifen, used successfully in both the treatment and prevention of breast cancer, and its 4-hydroxy metabolite are protective. Dietary phytoestrogens such as the soya isoflavones genistein and daidzein are weak oestrogens that antagonise the action of oestradiol at the oestrogen receptor in breast cells and appear to protect against breast cancer. Daidzein can be metabolised by gut microflora to equol, a more potent oestrogen and a better antioxidant than daidzein, which is likely to be of importance in relation to breast cancer risk. Furthermore, sulphoonoximates of daidzein, daidzein-4-O-sulphate and daidzein-7-4'-di-O-sulphate are potent inhibitors of steroid sulphatase, and this may contribute to the protective effect of dietary isoflavones.

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Mode of action of hyaluronate enhancement of hemopoiesis
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In recent years it became more and more evident, that components of the extracellular matrix (ECM), such as collagen, fibronectin and laminin are not only structural constituents but influence cell fate via binding to specific receptors and inducing signaling cascades resulting in changes of the genetic program. An important constituent of the bone marrow ECM is hyaluronate (HA). In long term bone marrow cultures (LTBMC) we have shown that HA differentially stimulates gene expression in cells of various lineages. Furthermore, binding of HA to macrophages results in release of IL-13 and IL-6. Interestingly, CD44 specific antibodies that abolish HA binding via the CD44 receptor abrogate IL-1β induction, but not the induction of IL-6, suggesting that two different receptors mediate the HA effect on macrophages. This concept of two distinct receptors is further corroborated by the observation that two different signaling cascades are triggered by HA binding to macrophages. One results in the activation of p38 kinase and is inhibited by CD44 specific antibodies, the other one leads to activation of ERK kinase and is independent of CD44. Thus, the ECM component HA has a decisive effect on hemopoiesis and induces signaling in bone marrow macrophages via two different receptors which result in the release of the two cytokines, IL-1β and IL-6.

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Oestrogen and phytoestrogen metabolism: role of the gut microflora

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The isoflavone phytoestrogens genistein and daidzein are found in soy beans and soy products, where they are present mainly in the form of their glucosidic conjugates, genistin and daidzin. When ingested, the latter are hydrolysed and further metabolized via reactions catalysed by the intestinal flora. Genistin can be converted to the hormonally inert p-ethyl phenol, whilst daidzin can be reduced to the isoflavonoid quinone and o-desmethylgeniopenol (o-DMA). The biological consequences of this metabolism are not fully elucidated. The lignan phytoestrogens secoisolariciresinol and matairesinol glycosides, derived from cereal brans and flaxseed, undergo analogous microflora-mediated reactions and are converted to enterolactone and enterodiol. There is marked interindividual variation in phytoestrogen metabolism in human subjects. For example, in a recent study in our laboratory, 8/23 subjects (35%) excreted large amounts of equol, mean 10905 ± 2147 nmol/24 h, (approximately 200 times that of poor equol producers). Subjects who were good equol producers also had high levels of o-DMA in plasma indicating that equol and o-DMA do not represent alternative pathways of daidzein metabolism. There did not appear to be any correlation between good equol producers and good enterolactone and enterodiol producers, suggesting that the different phytoestrogens are metabolized by different members of the gut microflora. The interindividual variation appears to be a consequence of interactions between diet and the gut microflora.

We thank the EC (FAIR CT-95-0894) for financial support.