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Letter to the Editors

Unconjugated pteridines and the activation of macrophages by interferon gamma

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Sirs,

Webber and Nazarbaghi [12] are to be commended for their studies on the transport of unconjugated pteridines in CCRF-CEM human lymphoblastic cells. However, the discussion relating to the occurrence of certain pteridines during the activation of immune response mechanisms deserves some comments.

It is now well recognized that among the several pterins excreted, e. g., in human urine, only the concentration of D-erythro-neopterin is associated with activated human macrophages, because these cells produce large quantities of neopterin upon induction by interferon gamma, derived from activated T cells [11]. A multitude of clinically oriented investigations by a multitude of research groups have shown that measuring neopterin in human body fluids enables sensitive monitoring of a variety of diseases, all being characterized by the involvement of macrophage activation. These issues have recently been reviewed [11].

Importantly, studies conducted on neopterin and biopterin levels in diseases involving macrophage activation have failed to demonstrate a similar association of biopterin with the immune response [2]. In contrast, measurements of biopterin derivatives are essential in the rare group of metabolic diseases caused by failure to synthesize tetrahydrobiopterin, the well-known cofactor of certain monooxygenases, notably, in the differential diagnosis of the variants of atypical phenylketonuria [3].

It has previously been claimed that 6-hydroxymethylpterin was excreted in raised amounts by tumor cells in culture and was thus suited for clinically relevant discrimination between cancer patients and healthy subjects [8]. Doubts have been raised against this statement, and the original authors themselves corrected their finding a few years later, reporting that urinary concentrations of 6-hydroxymethylpterin in cancer patients were not different from those in healthy individuals [9]. Rather, the authors noted raised neopterin concentrations in urine from cancer patients, in agreement with previous observations of our group [10].

Meanwhile, there is agreement that among the pteridines found in human body fluids, neopterin is most consistently raised in certain tumor types [11]. Furthermore, several independent studies [1, 4–7] have demonstrated that high neopterin concentrations in the urine and serum of cancer patients are significantly associated with a poor prognosis. The suppressed immune responsiveness of cancer patients that can be measured by, e. g., skin test anergy or a reduced in vitro proliferative response of T cells, does not exclude the presence of circulating cytokines in these patients. This seems to indicate that a persistent macrophage activation can be found in malignant disease.

Little is known at present concerning the function of immune response-associated neopterin production by human monocytes/macrophages. The notion of an efficient interferon gamma-induced degradation of tryptophan via the kynurenine pathway [13] by induction of indoleamine 2,3-dioxygenase may be helpful for further research on this unresolved question.

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