RELATIONSHIPS BETWEEN PTERIDINE SYNTHESIS AND TRYPTOPHAN DEGRADATION

E.R. Werner, G. Werner-Felmayer, D. Fuchs, A. Hausen, G. Reibnegger, and H. Wachter

Institute of Medical Chemistry and Biochemistry
University of Innsbruck
6020 Innsbruck
Austria

INTRODUCTION

In 1979, a fluorescent substance occurring in increased amounts in urinary specimens of patients suffering from viral infections or malignant diseases was characterized as D-erythro-neopterin (neopterin; Wachter et al. 1979). Extended studies of neopterin excretion in diseases revealed that the enhanced excretion of neopterin is coupled to clinical conditions characterized by activated cell-mediated immunity (reviewed by Fuchs et al., 1988; Wachter et al., 1989). Studies investigating the cellular background of these observations in vitro confirmed that immunological activation of the host’s peripheral blood mononuclear cells leads to release of neopterin into the culture medium. Surprisingly, large amounts of an unidentified fluorescent substance were always formed together with neopterin by the cells (Fuchs et al., 1982; Huber et al., 1983). The chemical identification of this substance as the tryptophan metabolite 3-hydroxyanthranilic acid (Werner et al., 1985a) initiated our work on the relationship between tryptophan degradation and pteridine synthesis, which is summarized in the present contribution.

INTERFERON-GAMMA INDUCES HUMAN MACROPHAGES TO DEGRADE TRYPTOPHAN

Detailed analysis of the observations in peripheral blood mononuclear cells indicated that the macrophages are the cells responsible for formation of neopterin (Huber et al., 1984) and 3-hydroxyanthranilic acid (Werner et al., 1985b). Interferon-gamma derived from activated T-lymphocytes could be demonstrated as a physiological inducer of the formation of both compounds by macrophages. Subsequently, we showed that the formation of 3-hydroxyanthranilic acid reflected a degradation of tryptophan by macrophages (Werner et al., 1987a). Metabolites formed from tryptophan were kynurenine, anthranilic acid and 3-hydroxyanthranilic acid. It was striking to see that the concentrations of neopterin in the supernatants of macrophages were strictly correlated with the extent of the degradation of tryptophan.
Cleavage of tryptophan induced by interferon-gamma is not specific for macrophages, but had also been observed in a variety of other cultured human cells (Pfefferkorn, 1984; Werner et al., 1987b; Ozaki et al., 1988; Takikawa et al., 1988; Werner-Felmayer et al., 1989). In our experiments, all cells reactive to interferon-gamma by enhanced MHC antigen expression were also triggered to degrade tryptophan. We concluded therefore that induction of tryptophan degradation by interferon-gamma is a general aspect of the action of this lymphokine on human cells (Werner-Felmayer et al., 1989). In addition to cleavage of tryptophan, several of the cells also showed kynureninase.

**Fig. 1.** Schematic presentation of pteridine and tryptophan metabolism of unstimulated (top) and interferon-gamma stimulated (bottom) human cells in vitro. Mo: peripheral blood derived macrophages; fibro: normal dermal fibroblasts; A 498: kidney carcinoma; A 549: lung carcinoma; U 138: glioblastoma; SkHep 1: liver carcinoma; A 431: epidermoid carcinoma; T 24: bladder carcinoma. Open circles indicate that a small amount of neopterin was detected in the supernatant. Pteridine synthesis was observed by GTP-cyclohydrolase activity, intracellular neopterin and biopterin concentrations (see Fig. 2).