drug resistant *MDR-1* transfected HeLa cells, cultures were PKC-depleted by prolonged exposure to bryostatin. This resulted in reduced activity of the Pgp as determined by the efflux of the Pgp substrate rhodamine 123. However, bryostatin was equally efficient in reducing the rhodamine efflux in experiments, where cells were exposed to the drug for 10 min, a condition which activates PKC and does not yet deplete the enzyme, or in cells where PKC was depleted by prior treatment with TPA. These findings suggest that bryostatin acts independently of PKC, probably by a direct interaction with the Pgp.

Thus, inhibitors of enzymes involved in signal transduction appear to be useful in tumour chemotherapy, but in some cases, the precise targets of the putative signal transduction modulators inside the cells still have to be elucidated.

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Retinoids in Oncology

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VITAMIN A (RETINOL) is an essential component of our diet and deficits can lead to visual and fertility problems, as well as loss of integrity of epithelia and mucus secreting cells [1]. Retinoids are vitamin A congeners and have changed the therapy of many skin diseases, such as acne and psoriasis [2, 3]. Their use in oncology stems back to the work of Rowe and Gorlin, Bollag and Lotan who showed their efficacy in preclinical models, developed thousands of derivatives and determined their anti-proliferative action [3, 4].

Retinoids are absorbed from the gastrointestinal mucosa in the form of chylomicrons (although some synthetic forms pass directly into portal circulation) and delivered from liver storage bound to retinol-binding proteins. Their growth modulation and differentiating action on cells which absorb them (disputed mechanism) is through modulation of gene expression, where nuclear retinoic acid receptors (RARs: alpha, beta, gamma) play a key role [5]. Resistance to the effects of retinoids seems to be a multi-step process. For all-*trans* retinoic acid, at least, this seems to be mainly the result of accelerated catabolism of the agent through cytochrome-P450 induction, increased oxidative cofactors and increased expression of cellular retinoic acid binding proteins (CRABP), all of which will ultimately lead to decreased effective concentrations of the retinoid.

All-*trans* retinoic acid and 13-*cis* retinoic acid are naturally occurring retinol derivatives, and many others (e.g. fenretinide (4-HPR), etretinate, acitretin) have been synthesised. These agents differ in their pharmacological properties in terms of bioavailability, half-life and spectrum of toxicity. Skin and mucous membrane toxicity is usually the limiting factor in the clinic; central nervous system toxicity can be manifested by headaches or even pseudotumour cerebri syndrome. Abnormal lipid metabolism occurs, and hepatic toxicity is common. Cardio-respiratory toxicity syndromes have been described in the treatment of promyelocytic leukaemia (PML) with all-*trans* retinoic acid [6].

PML is the first disease in oncology for which retinoids have been shown to be effective, although most responses are transitory. Acute promyelocytic leukaemia is an interesting model as there is a translocation which disrupts the gene encoding for RAR alpha, which fuses with the PML gene on chromosome 15. Sporadic reports on the use of retinoids in other haematological malignancies have appeared, and possibly juvenile chronic myelogenous leukaemia is a target for the use of 13-*cis* retinoic acid.

Initial attempts at treatment of solid tumours with retinoids have not been successful, but the combination of 13-*cis* retinoic

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acid with alpha-interferon has been shown to have some effiacy in squamous cell carcinomas of the skin (68% response rate in one study, with confirmatory data in another independent report), squamous cell carcinoma of the cervix (50% objective responses among 26 patients treated, but with short response durations), but not in squamous cell cancer of the head and neck. A study in non-small carcinoma of the lung is difficult to evaluate because of poor patient tolerance. The rare responses observed in various reports with single agent retinoids are, nevertheless, encouraging, and while the 13-*cis* retinoic acid interferon-alpha combination is of interest, other combinations will have to be explored.

Cancer chemoprevention is a term coined by Sporn and associates [7]. There has been considerable interest in this area since the first studies of Mathé showing a reduction in premalignant changes in the upper airways of smokers treated with preventative retinoids. For skin cancer, exciting results were obtained by a group showing that xeroderma pigmentosum patients treated with 13-*cis* retinoic acid had a disappearance of new basal cell carcinomas. Four studies are on-going in Italy and the USA, looking at the effect of various retinoids and other agents in the prevention of basal or squamous cell cancer in various high-risk populations. In head and neck cancer, trials of primary chemoprevention as well as secondary chemoprevention have been started.

The first type of study looks at the possible reduction in incidence of cancers in patients with precancerous lesions, while the second type is conducted in patients who had been treated for head and neck cancer previously. Pilot studies have shown higher efficacy of isotretinoin compared to beta-carotene in decreasing the incidence of oral leukoplakia, and the efficacy of 13-*cis* retinoic acid in the prevention of secondary tumours, while a study with etretinate is reported to be negative [8].

The first randomised trial of secondary lung cancer prevention has been conducted at the National Cancer Institute of Milan, and has shown the efficacy of vitamin A in preventing secondary tumours in these patients]9]. The Finnish alpha tocopherol and beta-carotene study to decrease the incidence of cancers in smokers has failed to provide positive results [10]. These data, from a well-nourished country, contrast with those from China, where dietary supplementation including retinoids has been shown to decrease the overall mortality of the treated population, mainly through a reduction in gastric cancers [11, 12]. Many other studies in the primary or secondary chemoprevention of lung cancer are on-going.

Transitional cell cancer of the bladder is another target of chemoprevention studies with retinoids, and low-dose etretinate may have some activity in the prophylaxis of superficial bladder cancer. Breast cancer chemoprevention studies have been pioneered by the National Cancer Institute in Milano, using fenretinide. More than 3000 patients have been randomised into this study, which recruits stage I oestrogen-receptor positive patients, with the aim of reducing the incidence of contralateral cancers. Several years of follow-up will be needed before any meaningful conclusion can be drawn from this exciting study.

In conclusion, retinoids are agents which have profound biological effects. There are many different types of retinoids with different activity levels, and it is not possible to describe their properties as those of a group. They hold promise both in therapy and prevention of many malignancies [13, 14].

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