Letter to the editor(1992): Book-Chapter 8 -

To the molecular mechanism of the pathogenesis of psoriasis vulgaris

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In the white population, there is worldwide an about three per cent incidence of psoriasis vulgaris. This disease is a multifactorial condition. A genetic component has been demonstrated in 50 to 65 percent of the patients and the disorder may be triggered by various somatic factors. We are especially interested in the pathogenesis and therapy of psoriasis (1).

More than 30 years have passed since the biochemist Schweckendick in 1959 discovered by successful treatment of his own psoriatic lesions the fumaric acid therapy (2). Since then some investigators found with high dosages of fumaric acid in 5 out of 6 patients an anti-psoriatic activity accompanied by pathological kidney parameters. To find a plausible explanation for the effect reported after treatment with fumaric acid we investigated the related purine nucleotide levels in the blood cells of 20 psoriatic patients and 13 healthy controls (3).

The concentration of the purine nucleotides cAMP, ADP and ATP in the sera of the psoriatic patients were normal, which is contrary to the whole blood-nucleotide levels. Mean blood ATP level in psoriatic patients was 187 µM vs 309 µM in controls, mean ADP level 212 µM vs 292 µM and mean ADP plus ATP concentrations 399 µM vs 600 µM. The change in the described nucleotide concentrations manifests entirely in the cell. The ATP/(ADP+ATP) ratio remains unchanged and makes clear that ATPase/synthetase and PGK (3phosphoglycerate kinase) are not involved in alterations of the nucleotide levels.

As expected, the ADP plus ATP concentrations during the 4 weeks of oral fumaric acid treatment remained unchanged. ATP values increase significantly while ADP levels decrease according to the increasing fumaric acid dimethylester concentrations. A slow rise to a dosage of 120 to 240 mg fumaric acid dimethylester results in clearing of the patients skin after 4 weeks therapy. There is a clear-cut correlation between raise in ATP concentration and clearing of the skin. No changes in the urine and blood parameters were noticed.

It is suggested, that a generalized defect in the purine nucleotide metabolism is responsible for the changed nucleotide concentration in the patients. ATP and GTP were used in RNA and DNA synthesis, cAMP and cGMP control protein biosynthesis activity. cAMP levels in psoriatic epidermis were higher than in the normal skin. The measured cellular concentrations of ADP, ATP, cAMP and cGMP make the suggestion most probable and imply the measurements of the remaining purine nucleotide levels (figure 1).

It has been shown, that in adult human epidermis low levels of cAMP stimulated proliferation, whereas high levels inhibited growth. On the other hand, it has been postulated that an increase in the steady state level of cGMP may be associated with an enhanced rate of cellular proliferation. The nucleotide concentrations in our patients favor a high rate of cellular proliferation, via acceleration of the protein biosynthesis activity. Fumaric acid accelerates Krebs cycle, respiratory chain as well as ATPsynthetase and then elevates ATP- and consequently cAMP-levels. Another important result of elevated fumaric acid is its endproduct inhibition which slows down purine nucleotide synthesis, especially of cGMP. It should be

remembered, fumaric acid dimethylester alone can cross membranes and only its hydrolysis in mitochondria makes it a substrate for the Krebs cycle.

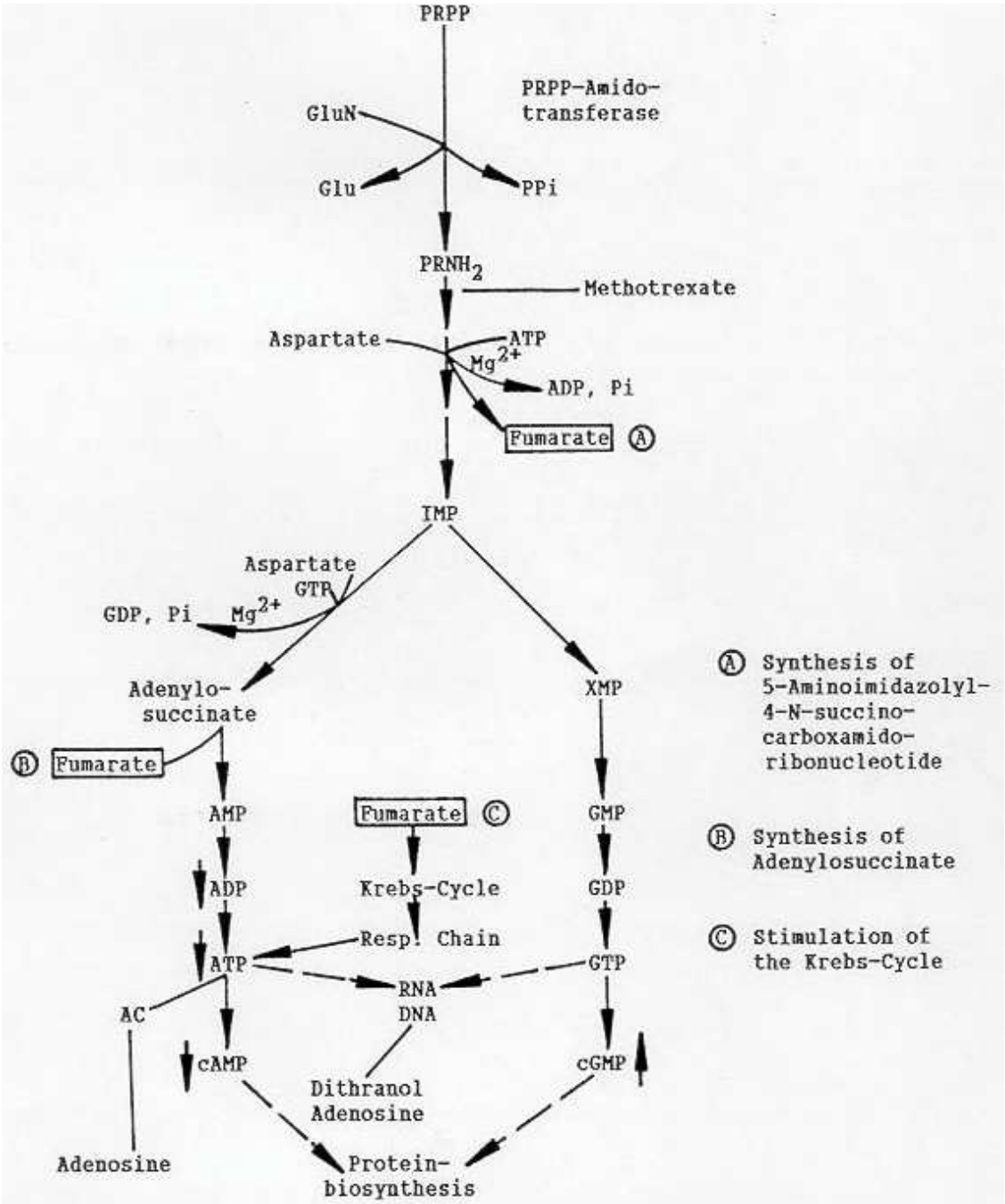

FIG. 1. PURINE NUCLEOTIDE SYNTHESIS PATHWAY

Explanations: PRPP = 5-Phosphoribosyl-1-pyrophosphate;
$PRNH_2$ = 5-Phosphoribosyl-1-amine;
GluN = Glutamine; Glu = Glutamate;
AC = Adenylate cyclase

Figure 1 suggests, that the genetic defect leading in psoriatic manifestations may be localized at the level of adenylosuccinate formation. In this diagram adenylosuccinate and XMP were synthesized out of IMP. The low cAMP, ATP and ADP concentrations imply low concentrations of adenylosuccinate and IMP. High concentrations of cGMP on the other site lets think about elevated GTP, GDP, GMP and IMP. Crossover point is IMP. The IMP concentration cannot be elevated or decreased at once. Only a shift in synthesis to the direction of cGMP resolves this contradiction. Now remains the question how this shift may be acquired by the system.

Elevation of fumarate (c) raises ATP and cAMP levels. Since the cAMP concentration is very small [3] and the adenylate cyclase limited in their synthesis capacity, ADP and presumably AMP were the favored compounds raised in concentration by elevation of the ATP concentration. Remains the adenylosuccinate synthase as probable candidate for the shift and this is even more the possible candidate since fumarate is normally synthesized by this enzyme out of aspartate. Back pressure of AMP and fumarate at this step should lead in elevated IMP levels which contradicts the already concluded shift in synthesis at this crossover point. Adenosine is not able to raise the cAMP concentration significantly (but may be able to block the synthesis by intracellular "supplementation"). The only explanation for regulation of the cellular proliferation rate is then at the adenylosuccinate synthase level.

This conclusion is supported or even proven by studies on the adenylosuccinate synthetase of S.Cerevisiae (4). Polyamines play no role, as originally suggested in analogy to cancer patients(5).

Many triggering factors (6) are acting via adenylate cyclase, including psychogenic stress and associated elevated norepinephrine levels (7). These factors are not only triggering the development of secondary infections. Adenosine may counteract (3) and relaxation therapy (+/- psychotherapeutic attendance) restore the abnormal distribution of the α- and ß-receptors, the associated low concentrations of membrane bound adenylate-cyclases and of cAMP (8).

In summary: The molecular mechanism of the pathogenesis of psoriasis vulgaris has been explored on psoriatic patients. We found a defective purine nucleotide synthesis pathway accompanied by a changed energy metabolism. The genetic defect leading to former manifestations is most likely localized at the level of the adenylosuccinate synthase. Raise in ATP concentration by fumaric acid dimethylester, measured in my laboratory, correlates with cleaning of the skin. The results make it now easier to develop new therapy concepts.

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FULL REVIEW FOR AUTHORS

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The author has incompletely repeated the data which he had published with his co-author G. Ionescu in Acta Derm Venereol in 1992. Any new experimental results are not presented except some speculative statements in the last 2 paragraphs and a figure on the purine nucleotide synthesis pathway. Nevertheless, the author now addresses the genetic defect in psoriasis to the level of adenylosuccinate formation. It remains unclear, however, which are the facts in favour of this new interpretation or - in other words - why are other hypothetical items on the pathogenesis of psoriasis given in the 1992 report no more valid in this letter although based on identical results. These aspects confirmatory to or correcting former scientific interpretations should be discussed, informally.

Kommentar von R.Kiehl: ???