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Peptidoglycan synthesis in eucaryotic cells and its possible roles

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Résumé.–ROTEN C.-A. H. et KARAMATA D., 1992. De la synthèse du peptidoglycane dans la cellule eukaryote et de ses rôles éventuels. *Bull. Soc. vaud. Sc. nat. 82.1*: 87-89.
Des évidences de présence du peptidoglycane, considéré comme un marqueur bactérien spécifique, ont été découvertes chez les plantes et chez les animaux. Nous discutons de la possible synthèse endogène du peptidoglycane qui expliquerait la présence de composés du peptidoglycane dans le cerveau, organe protégé par une barrière efficace contre le peptidoglycane exogène. De plus, la quantité de ces composés produite par la flore bactérienne de l'intestin grêle est insuffisante pour expliquer la quantité de ceux présents dans l'urine. Des fonctions possibles de ces composés sont discutées.

Summary.–ROTEN C.-A. H. et KARAMATA D., 1992. Peptidoglycan synthesis in eucaryotic cells and its possible roles. *Bull. Soc. vaud. Sc. nat. 82.1*: 87-89.
Evidence of peptidoglycan, believed to be a specific bacterial marker, is found in plants and animals. We discuss a possible endogenous eucaryotic peptidoglycan synthesis which would explain peptidoglycan components found in brain, where an efficient barrier against exogenous peptidoglycan exists. Moreover, the amounts of such compounds produced by bacterial flora of the small bowel are insufficient to account for those present in urine. Possible functions of these components are discussed.

Key words: diaminopimelate, muramate, muramyl-peptide, peptidoglycan in eucaryotes, synthesis of peptidoglycan, sleep muropeptide, endosymbiosis.

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A fundamental taxonomic criterion defining the bacterial kingdom is the presence of peptidoglycan (PG), the cell wall component and a specific target for antibiotics. Frequently, the basic unit of this polymer is N-acetyl-glucosaminyl-N-acetyl-muramyl-L-alanyl-D-glutamyl-L,D-diaminopimelyl-D-alanine, and thus muramate, as well as L,D-diaminopimelate (DAP) are bacteria-specific taxonomic markers. Although mitochondria and chloroplasts are of bacterial origin (GRAY *et al.* 1989), PG and its components are not believed to be synthesized by eucaryotic cells.

However, several observations on higher organisms call this belief into question. First, DAP containing compounds are excreted in constant daily amounts in human, bovine and swine urine (10, 30 and 70 $\mu g \cdot kg^{-1} \cdot day^{-1}$, respectively) (KRYSCIAK 1980). Second, muramate was reproducibly found in rat brain (50-100 picomole $\cdot g^{-1}$), and liver (100-150 picomole $\cdot g^{-1}$) (SEN and KARNOVSKY 1984). Third, there is a dramatic effect of 1 picomole of urine sleep factor (FSu), the anhydro PG unit. This PG degradation product, extracted from animal urine or brain, induces a slow-wave sleep in rabbits when infused cerebro-intraventricularly (KRUEGER *et al.* 1984). The presence of these compounds in animal cells and urine was hitherto attributed to degradation products of the bacterial intestinal flora or to bacteria engulfed by macrophages (KRYSCIAK 1980, PAPPENHEIMER 1983, SEN and KARNOVSKY 1984).

These explanations are unsatisfactory, however, since the total amount of DAP containing bacteria in the small bowel (10^3-10^7 bacteria/ml) (GOLDIN 1986), where amino acid absorption occurs, is insufficient to account for the amount of DAP daily excreted in human urine. The latter being equivalent to the PG content of $6 \cdot 10^{11}$ *E. coli* cells.

Quantitative analysis of muramate contained in rat hepatocytes strongly suggests that muramate is synthesized in a pulse, whose amount is equal to that present in the PG of *E. coli* cells whose total volume is equivalent to the volume of mitochondria present in dividing hepatocytes only. Thus, PG derived compounds, mitogenic for lymphocytes (DZIARSKI 1989), could act as division signals. Since cerebrospinal fluid is protected by a highly specific barrier, presence of exogenous PG compounds in the brain is most unlikely. The very strong effects of FSu (somnogenic and pyrogenic like interleukine 1) suggest that this molecule is part of a biological clock; like in septating bacteria, PG would be synthesized as a pulse (LLEO *et al.* 1990).

In conclusion, we postulate that eucaryotic cells are capable of endogenous PG synthesis; the latter being a trigger for cell division or, in mammals, sleep.

Presence of the PG biosynthetic pathway or parts of it in eucaryotic cells is not surprising. For instance, unlike certain fungi, green plants synthesize lysine in chloroplasts, via a specific bacterial DAP pathway (VOGEL 1965, WALLSGROVE *et al.* 1983), while the cyanelle of *Cyanophora paradoxa*, an organelle related to the chloroplast (URBACH. *et al.* 1992), is surrounded by a PG containing cell wall (KIES and KREMER 1990).

Appearance of the PG biosynthetic pathway in higher organisms could be accounted for by the serial endosymbiosis theory (MARGULIS 1981).

A more complete discussion of a possible endogenous eucaryotic PG will be published in its entirety in a manuscript in review (ROTEN and KARAMATA).

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