Proceedings of the 31st European Peptide Symposium
Michal Lebl, Morten Meldal, Knud J. Jensen, Thomas Hoeg-Jensen (Editors)
European Peptide Society, 2010

A regulatory role for the muramyl peptide (GMDP) in a murine model of allergic asthma

Svetlana V. Guryanova[1], Marina A. Shevchenko[1], Ivan G. Kozlov[2] and Tatyana M. Andronova [1]

[1]Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, 117997, Russian Federation; [2]Russian State Medical University, Moscow, 117997, Russian Federation.

Introduction

N-acetylglucosaminyl-N-acetylmuramyl dipeptide (GMDP) – fragment of bacterial cell wall peptidoglycan is known to possess immunomodulatory activity against viral and bacterial infection [1, 2].

Positive effect of based on GMDP pharmaceutics Licopid application was shown at the treatment of children with bronchial asthma and atopic dermatitis [3]. Previously we reported that ***in vitro*** studies on periphery blood mononuclear cells of allergic bronchial asthma patients demonstrated the ability of GMDP to shift Th1/Th2 balance towards Th1 and IFN-γ production [4].

In the present study we evaluated the ability of GMDP to modulate allergic airway inflammation both on the stage of sensitization and during ongoing of airway inflammation. These results suggest that antiasthmatic activity of GMDP in OVA-induced lung inflammation may occur in part *via* downregulation IgE production and eosinophil airway infiltration.

Results and Discussion

The standard well-characterized OVA-induced mouse model of asthma [5] (OVA/OVA) was utilized to assess the immunomodulatory effect of GMDP. Mice were immunized with GMDP on the stage of sensitization (GMDP/OVA/OVA) – two days before each intraperitoneal (i.p.) OVA/Alum injection or during effector stage of the airway inflammation - three consequent i.p. injections between the second and the last OVA challenge (OVA/OVA/GMDP).

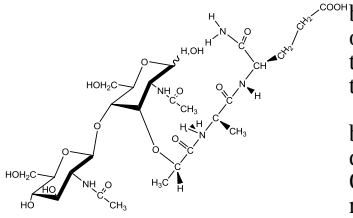

Fig.1.N-acetylglucosaminyl-N-acetylmuramyl dipeptide (GMDP)

Twofold decrease of serum total IgE and broncho-alveolar lavage fluid (BALF) IgA was detected in GMDP/OVA/OVA mice compare to the OVA/OVA group (Figure 2B). At the same time such route of GMDP application didn't alter the IgG1/IgG2a balance, hence didn't promote Th1 response (Figure 2A). Application of GMDP on the stage of ongoing airway inflammation increased OVA-specific IgG2a serum level (Figure 2A), which correlated to our previous ***in vitro*** results [4]. However this IgG2a elevation wasn't accompanied by serum

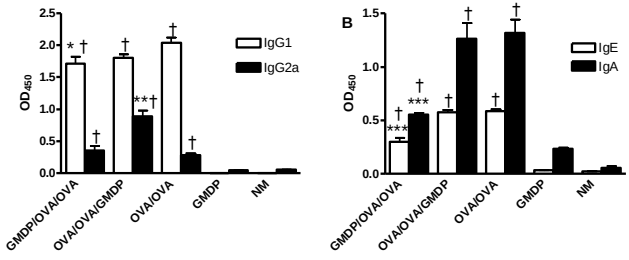

*Fig. 2. Immunoglobulin production. For IgG detection sera were diluted 1:1000, for IgE 1:10. IgA was detected in BALF (1:1). *P < 0.05, **P < 0.01, ***P < 0.005 vs. OVA/OVA; † P < 0.005 vs NM.*

Table 1. Differential cell counts in BALF.

	Macrophages* ($\times 10^5$ *cells)	***Neutrophils* ($\times 10^5$ *cells)***	***Lymphocytes* ($\times 10^5$ *cells)***	***Eosinophils* ($\times 10^5$ *cells)***
GMDP/OVA/OVA	0.88±0.03*	0.12±0.02	0.235±0.003	2.46±0.005***
OVA/OVA/GMDP	2.33±0.13	0.94±0.16*	0.31±0.005	0.54±0.004***
OVA/OVA	**1.68±0.284**	**0.27±0.07**	**0.29±0.008**	**1.74±0.006**
GMDP	1.74±0.36	0.08±0.04	0.2±0.004	0.02±0.001***
NM	1.12±0.01	0.8±0.07	0.18±0.003	0.08±0.001***

*Results are expressed as means (n=8 for each group) ± SEM. *P < 0.05, ***P < 0.005 vs OVA/OVA.*

total IgE or BALF IgA decrease (Figure 2A, B), and therefore couldn't be considered as an allergic response protection.

Analyses of total cell infiltration to the airways of mice from GMDP/OVA/OVA and OVA/OVA/GMDP group didn't reveal significant alteration of inflammation compare to OVA/OVA mice (data not shown). Comparison of infiltrating cells population composition showed significant eosinophilia decrease in group of mice, received GMDP during OVA challenge compare to OVA/OVA mice (Table 1). Neutrophil level in this group was significantly higher then in mice with allergic airway inflammation. Application of GMDP during the sensitization phase, which revealed protective decrease of serum IgE level, induced however a rise of eosinophil infiltration, the level of which was significantly higher then in OVA/OVA mice (Table 1).

Thus, GMDP application during sensitization phase reduced the proallergic IgE production, but was impotent to decrease airway eosinophilia. GMDP treatment of ongoing allergic airway inflammation initiated Th1-mediated decrease of eosinophil airway infiltration. These data point to a dual protective effect of GMDP: preventive application reduces IgE production whereas treatment with muramyl peptide of ongoing airway inflammation suppress eosinophilia.

Acknowledgments

This work was supported by joint stock company PEPTEK.

References

1. Kozlov A., Klimova RR, Shingarova LN, et al.*Mol Biol (Mosk)*, **39(3),** 504-512 (2005).
2. Turánek J, Ledvina M, Kasná A., et al., *Vaccine*, **12(24)**,Suppl 2:S2-90-1 (2006).
3. Kolesnikova N.V., Kokov e.A., Andronova T.M., et al. *Russian J. of Allergology*, **5,** 5-555 (2008).
4. Guryanova S.V., Kozlov I.G., Mesheryakova E.A.,et al. *Immunologia (Russian J.)* **5(30)**, 305-308 (2009).
5. Braun A, Lommatzsch M, Mannsfeldt A, et al.*Am J Respir Cell Mol Biol.* **21(**4), 537-546 (1999).