ImmunoTools *special* Award 2017

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The role of MIP-4 in childhood obesity

Obesity during childhood has been demonstrated to exert profound and lasting effects on bone strength and fracture risk (*Bialo SR et al. Curr Osteoporos Rep. 2014*). Furthermore, obesity is characterized by chronic inflammation and oxidative stress, with an increase in the mediators of innate immunity. Despite the clinical relevance, the cellular and molecular mechanisms ruling the bone disease in obesity are not completely clear. Insights into the mechanisms of impaired bone remodeling in pathological conditions, demonstrated by us and other authors, have shown that many cytokines, produced by immune cells, are involved in altered bone cell activity.

Among the cytokines produced by immune cells, it is emerging the chemokine MIP-4 (CCL18), belonging to the family of chemotactic cytokines that act through seven-transmembrane domain G protein-coupled receptors on their target cells. The spectrum of cellular sources for MIP-4 was confirmed in vitro to be mainly restricted to leukocytes, in particular, monocytic cells and dendritic cells. Monocytes/macrophages were shown to constitutively express only low levels of MIP-4 (*Schraufstatter I et al. Am J Physiol Lung Cell Mol Physiol. 2004; Sallusto F et al. Eur J Immunol. 1999; Song E et al. Cell Immunol. 2000)*, but the MIP-4 production could be up-regulated in these cells by the classic macrophage activator LPS (*Schraufstatter I et al. Am J Physiol Lung Cell Mol Physiol. 2004; Sallusto F et al. Eur J Immunol. 1999; Song E et al. Cell Immunol. 2000*) as well as by other microbial compounds (peptidoglycan and mannan) and by the T cell-derived activation signal CD40-L (*Pivarcsi A, et al. J Immunol 2004*).

Serum levels of MIP-4 correlate with body weight, waist circumferences and waist to hip ratio but not with BMI. In obese women it has been found that high levels of MIP-4 were secreted from white adipose tissue and the levels correlated positively with insulin resistance, and plasma triglycerides. In white adipose tissue MIP-4 mRNA was expressed in macrophages and correlated positively with immune-related genes (*Eriksson Hogling D. et al. J Clin Endocrinol Metab. 2016.*). However in literature there are not data about MIP-4 in obese children as well as about MIP-4 levels and markers of bone metabolism.

Hypothesis: in the bone fragility associated to childhood obesity MIP-4 has a key role. Its neutralization could have a beneficial effect both on adipose tissue accrual and bone disease in obese children.

Aims: Thus, based on the above literature reports, we will evaluate:

1) MIP-4 levels in sera from 45 obese children and 45 controls;
2) MIP-4 pro-osteoclastogenic and pro-adipogenic effect.

Methods:

1) MIP-4 levels will be evaluated by ELISA in sera from obese and control children. To obtain the samples informed consent will be given from parents.
2) To study MIP-4 pro-osteoclastogenic effect monocytes from control subjects will be cultured for about 21 days with different concentrations of MIP-4 with or without the well known pro-osteoclastogenic cytokines MCSF and RANKL. At the end of culture period mature osteoclast will be identified as tartrate-resistant acid phosphatase-positive multinucleated cells containing three or more nuclei.
3) To study MIP-4 pro-adipogenic effect mesenchymal stem cells will be cultured for about 2 weeks with different concentrations of MIP-4 with or without pro-adipogenic factors.