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Microparticles-containing microRNAs: new players in the vascular endothelial dysfunction in obese patients

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Microparticles (MPs) play essential roles in cell-cell crosstalk throw carrying bioactive molecules such as proteins and microRNAs (miRNAs). For this study, the MPs profile was explored in order to understand their implication in endothelial dysfunction in a group of obese (n=69, BMI=25±kg/m²) and normal weight subjects (n=46, BMI=25±kg/m²) recruited at F. Hached Hospital (Sousse, Tunisia). Vascular endothelial function was assessed by the exploration of the endothelium-dependent vasodilatation by Laser Doppler Flowmetry. Circulating MPs were quantified by flow cytometry analysis. Firstly, endothelial dysfunction was detected by an impaired cutaneous vascular conductance (CVC) in obese patients in comparison to normal subjects, 0.3±0.03 versus 0.4±0.05 PU/mmHg respectively (p=0.029). Inflammation was significantly increased (CRPus x 3.5) as well as oxidant stress (AOPP, TBARS) in obese patients. On the other hand, enhanced circulating MPs levels were detected in obese patients 14792±1755.6 MPs/μl plasma in comparison to normal subjects 8480.7±1431.9 MPs/μl plasma (p=0.031). Therefore, we explored inflammation associated-miRNAs in MPs of sub-groups of obese (n=10) and normal weight subjects (n=10). The analysis of individual miRNAs (miR-150, miR-146a, miR-320a, miR-124a, miR-223, miR-155, and miR-302a) was assessed by real time PCR. Among them, miR-150, miR-146a, miR-320a and miR-124a were significantly enhanced in the obese group, miR-223 were identical in each group while miR-135a and miR-302a couldn’t be detected in MPs. Multivariate analyses revealed a positive correlation between miR-124a and CVC (r=0.807; p=0.009), and a positive correlation between miR320a and circulating MPs level (r=0.519; p=0.033). Our results are highlighting the importance of considering the MPs-containing miRNAs as effectors in the process of the endothelial dysfunction in obesity, however, more studies are necessary to understand the precise role these miRNAs.

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Is the stem cell antigen 1 involved in the brain natriuretic peptide effect on cardiac precursor cells?

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Cardiac cellular therapy can be intended by stimulation of "endogenous" cardiac precursor cells (CPCs), identified by several markers such as the Stem Cell Antigen 1 (Sca-1) or the stem cell factor c-kit. CPCs are able to proliferate and differentiate into beating cardiomyocytes in vitro and in vivo after brain natriuretic peptide (BNP) treatment.

BNP is a cardiac hormone, whose role in the heart remains to be clarified. Interestingly, BNP treatments, in vivo and in vitro, induced an up-regulation of mRNA coding for Sca-1 and a 2 fold increase of the number of CPCs. In previous work, we showed that Sca-1 KO mice had two times less CPCs, and two times less BNP mRNA expression compared to Wild Type mice.

The aim of this project is to determine whether the effect of BNP on CPCs is linked to Sca-1 expression.

Sca-1 KO mice developed a dilated cardiomyopathy with ageing. To determine whether reduced amount of BNP is responsible for the development of this cardiac disease, neonatal Sca-1 KO mice were treated with BNP for 2 weeks. Mice were sacrificed 13 weeks later, and cardiac parameters were measured by echocardiography. The thickness of the left ventricular posterior wall and the ejection fraction were increased in BNP-treated Sca-1 deficient mice (+15% and +28%, respectively) compared to untreated Sca-1 KO mice.

To explore the cellular mechanisms, in vitro experiments were performed. Non Myocytes cells (NMCs), containing CPCs, have been isolated from the heart of Sca-1 KO mice and cultured with or without BNP in media favouring either cell proliferation or differentiation into cardiomyocytes. BNP is not able to induce Sca-1 KO cell proliferation, whereas CPC differentiation into cardiomyocytes is maintained even in absence of Sca-1 expression.

In conclusion, BNP modulates the cardiomyopathy developed by Sca-1 KO mice. BNP effect on CPC proliferation is linked to Sca-1 expression, but its effect on differentiation is Sca-1 independent.

0109

Increase liposomes cardioprotective activity of pyridostigmine

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Pyridostigmine (PIR), a reversible anticholinesterase, has its cardioprotective effects demonstrated by the reduction of the QT interval of the electrocardiogram ECG in patients with heart deases. Experimentally this QT prolongation is induced by adrenergic stimulation. However, its short half-life and the incidence of side effects are factors that limit its prolongation. This study was aimed to investigate the cardioprotective activity of pyridostigmine conveyed in convetional multimolecular liposomes administered subcutaneously. Two multimolecular liposomal formulations were developed and listed: one consisting of dioleil phosphatidylcholine (DOPC) and cholesterol (CHOL) and the other consisting of diasteroylphosphatidylcholine (DSPC) and CHOL.

The encapsulation efficiency determined was 15.4% and 23.4% respectively. The cardioprotective activity of PIR was evaluated in rats for its ability to prevent cardiovascular disorders, demonstrated, in signs of blood pressure (BP) and ECG induced by IV administration of noradrenaline (NA). After administration of 10 mg/kg NA, the DSPC and DOPC liposomal formulations containing PIR were able to reduce significantly the QT interval, with a maximum inhibition of 76.4% and 73.0% respectively. Both formulations DSPC:CHOL and DOPC:CHOL, attenuated the increase in BP within 12 to 24 hours respectively. As the QT prolongation is a predictor of sudden death and the PIR was able to prevent its prolongation after sympatheter stimulation, it could be suggested that PIR in liposomes administered subcutaneously has cardioprotective activity.

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Microparticles from apoptotic T lymphocytes induce endothelial dysfunction through induction of endoplasmic reticulum stress

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Microparticles (MPs) are small vesicles released from the plasma membrane of activated and/or apoptotic cells. We have previously shown that MPs generated from apoptotic T cells induce endothelial dysfunction through a decrease of nitric oxide production (NO). In this study we hypothesized that the mechanism by which MPs induce endothelial dysfunc-

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