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Objective: High incidence of cardiovascular diseases in the elderly is in part attributable to cardiac remodelling associated to physiological aging. The Receptor for Advanced Glycation End-products (RAGE) is a multi-ligand membrane-bound receptor involved in many inflammatory disorders. RAGE soluble isoform (sRAGE) acts as a decoy molecule being able to block the activation of the membrane-bound protein, and its circulation levels have been found altered in several chronic and acute inflammatory diseases. The aim of this study was to determine whether sRAGE is a biomarker of aging and age-related cardiac remodelling, and evaluate the contribution of RAGE isoforms to cardiac senescence.

Methods: sRAGE levels were evaluated in the serum of healthy subjects from 20-92 years and of 1- to 22-months-old mice by ELISA. Left ventricle (LV) function and remodelling of *Rage*-/- and wild-type (wt) mice were measured by 2D-echocardiography. Immunohistochemistry determined cardiac collagen levels. Protein and gene expression were assessed by Western Blot and RT-PCR, respectively.

Results: We found a significant decrease of circulating sRAGE with age in mice. Notably, serum sRAGE negatively or positively correlates with LV dimensions or function, respectively. Interestingly, no detectable amount of any RAGE isoforms was found in murine LV, however, *Rage*-/- mice displayed a significant increase of LV volumes and diameters in diastole and systole, and a concomitant decrease in Ejection Fraction and Fractional Shortening, compared to age-matched wt animals during aging. Moreover, *Rage*-/- mice exhibited higher deposition of collagen content and heart failure marker genes expression (BNP and Ankrd1) with senescence in respect to the wt counterpart. Finally, human studies confirmed a strong inverse correlation of serum sRAGE with chronological age in healthy subjects.

Conclusions: Our results indicate that circulating sRAGE is a biomarker of healthy aging and age-related cardiac changes. The absence of RAGE in mice exacerbates cardiac remodeling with senescence. Altogether, our data suggest that, among RAGE isoforms, sRAGE may play a pivotal role in determining intrinsic heart ageing.

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First evidence on the novel hypothalamic peptide Phoenixin-14 as cardiac modulator and cardioprotective in normal and obese rats

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Objective: Phoenixin (PNX) is a peptide identified in 2013. It is mainly expressed in the hypothalamus in which it shares a distribution patter comparable to nesfatin-1, a peptide with anorexic and cardiovascular activities. It is able to cross the blood-brain barrier and this suggests that it elicits peripheral functions. Preliminary mass spectrography data indicate that PNX is present in the mammalian heart. This study aimed to quantify PNX in heart and plasma in of normo-weight and obese rats, and to evaluate if the peptide influences the myocardial function under basal condition and in the presence of ischemia/reperfusion (I/R).

Methods: By ELISA, PNX was detected in both hypothalamus and heart.

Results: In the plasma, PNX levels increased during the post-prandial phase in normal but not in obese rats. On the isolated and Langendorff perfused rat heart exogenous PNX determined negative inotropism and lusitropism. Western Blotting of cardiac extracts revealed that Erk1/2, Akt and eNOS phosphorylation increased after exposure to increasing concentrations of PNX. PNX (EC50 dose), administered in post-conditioning, induced a better systolic recovery and a smaller infarct size with respect to hearts exposed to I/R alone. PNX-dependent cardioprotection was mediated by RISK and SAFE cascades and apoptosis inhibition. Preliminary data obtained in obese rats showed that PNX post-conditioning cardioprotection is obtained only at a concentration (1 nM) that is higher than that required in normo-weight rats.

Conclusions: This study represents a first evidence on the involvement of PNX in cardiac modulation, particularly in relation to normal and pathological conditions.

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Are the nanoparticles friends or foes when inhaled?

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Objective: Recent applications in nanomedicine focus on nanoparticles as they are promising tools for site-specific delivery of drugs and diagnostic agents, through the possibility to functionalize their surface with target-specific ligands. Recently, we showed that among the different administration routes, pulmonary delivery is feasible not only for the local treatment of airway diseases but also for the systemic administration. Our results suggest that pulmonary administration could be exploited for delivery of nanoparticles designed for brain therapy. On the other hand a big claim rosed up about the emerging evidence suggesting that living near major roads might adversely affect health. Indeed despite the mounting global effect of cardiovascular and neurodegenerative diseases, their cause remains largely unknown. Concern is growing that exposures associated with air pollution and mainly to the inhaled ambient fine particles might contribute to these pathology. We will try to outline a road map in order to disclose the inner mechanisms by which nanoparticles interact with microvascular endothelial cells thus triggering effects induced at the endothelial level further linking with systemic and site specific inflammation.

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Enhancement of cardiac differentiation of mouse pluripotent stem cells by β3 adrenoceptor stimulation

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