

Matrix glycoproteins and proteoglycans are paramount in cardiac disease

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Valorization

L'ignorance est la plus grande maladie du monde

Despite efforts for decades, HF remains the leading cause of death worldwide. Even though clinical management has improved, resulting in decreased mortality, the incidence of cardiac diseases and HF remains too high. In addition, HF also has a huge impact on the economical society, in terms of health expenditure, as well as by disabling and immobilizing people, making them unable to work. Fundamental research, as described in this thesis, is vital for understanding HF pathophysiology and for the discovery of novel therapeutic strategies that eventually will prevent the onset of HF, and improve quality of life of thousands of people.

In this thesis I highlight the paramount role of the cardiac extracellular environment in the development of systolic and diastolic dysfunction and concomitant HF. The biological diversity of the extracellular protein, OGN, is described in chapter 2 whereas its role during hypertensive- and age- induced cardiac remodelling and in particular its importance during diastolic dysfunction is described in chapter 3. Chapter 4 identifies SPARC as a novel inotropic agent that improves cardiac contraction, both during health and during systolic dysfunction induced by viral myocarditis. And last but not least, a redundant role for WARP in the wound healing process after MI is described in chapter 5. Also highlighted is the importance of breeding strategies in cardiovascular research.

Moreover, this thesis reveals therapeutic potential for OGN and SPARC. HFpEF and diastolic dysfunction represent one of the most challenging clinical problems in cardiology, as modern pharmacotherapies do not improve outcome, in contrast to systolic HF, and the heterogeneity of HFpEF patients further impedes treatment of these patients. Identification of patient-specific structural and functional abnormalities will help in treatment selection to increase therapeutic responsiveness. This thesis identifies OGN as a novel protective factor against diastolic dysfunction of aged-hypertensive origin and hence opens new windows to target/prevent diastolic dysfunction upon hypertension and ageing, by targeting or mimicking compounds of the extracellular matrix, such as OGN. In addition, a specific therapy for suspected myocarditis patients is unfortunately also still lacking, but increasing cardiac contraction through inotropes might be beneficial for these patients. Yet over the last decades, the number of newly developed inotropes has been surprisingly low and hence, current drug selection is limited. Here, SPARC is identified as a possible calcium-sensitizing inotrope.

Unfortunately the pipeline from fundamental research and therapeutic target discoveries, to the development of new therapies is long, and despite the tremendous efforts done so far in fundamental research, we still don't fully grasp HF pathophysiology. To get there, I personally believe an open mind is key. Researchers should not ignore other fields and other opinions. This is especially true since matrix biology is not only of importance in cardiac diseases, but also in other diseases such as cancer. Hence, I believe we will only benefit when we stop ignoring or competing with other research fields and start an open communication with other researchers from various disciplines. In

addition, clear communication towards the general public on our fundamental scientific findings will further increase awareness, increase appreciation for its relevance and value in the search for novel therapeutic strategies, which I believe, will in the end help in our combat against cardiac (and other) diseases.

Aime la vérité mais pardonne à l'erreur

Besides the paramount role of the cardiac extracellular environment in HF and its therapeutic potential, this thesis also highlights the importance of breeding strategy of mice in cardiovascular research. The use of genetically manipulated mice is a widespread tool to study the effects of a specific gene in models of cardiovascular disease and thanks to intercontinental collaborations, air travel is commonplace these days for genetically manipulated mice. Unfortunately, the competitive environment causes numerous labs to breed their KO mice in-house and to purchase the WT mice from a commercial source, in order to save time and money.

In this thesis I stress the important influence breeding strategy and housing environment can exert on research results. However, the literature poorly describes breeding strategies, genetic backgrounds or the continental source of mice studied, thereby making it difficult to estimate how many studies have mistakenly attributed a phenotype. Using the correct littermate controls and respecting good laboratory scientific practices and particularly, conveying this information in publications, will definitely help us not only in limiting false leads for therapies but in unraveling HF (and other) pathophysiology.

Laissez lire, laissez danser, ces deux amusements ne feront jamais de mal au monde

A PhD is more than this reading alone; it is 4 years of pushing boundaries, both boundaries of scientific knowledge, and personal boundaries. A PhD is hard work, where you learn to keep going when things keep on failing, where you overcome your own limits (such as my initial fear for the very aggressive mice), but where you also get the opportunity to build up an international network, and travel the world. In addition, I learned to put things in perspective, to appreciate things (such as reading and dancing). 4 years of pushing boundaries changed my perspective and taught me that I could achieve things I had been dreaming off. And somehow it made the world seem a little bit smaller...