Targeting the heart

Summary

Cardiovascular diseases (CVD) have been the leading cause of death worldwide for around 3 decades. Despite the burden and potential market size, the number of innovative compounds being approved for CVD is minor. This has been attributed to failure of randomized clinical trials due to lack of efficacy, most likely explained by etiology heterogeneity which has commonly not been accounted for in clinical trials.

RNA therapeutics have been raising attention for cardiovascular precision medicine with the recognition of new RNA classes with relevant biological functions. Among these, non-coding RNAs (ncRNAs), are major epigenetic regulators under both physiological and pathological conditions and are therefore very attractive as drug candidates or targets. Nonetheless, systemic delivery of naked RNA is very limited due to RNAse-mediated RNA degradation and large size and negative charge that hinder efficient cellular uptake.

Extracellular vesicles (EVs) are cell secreted nanoparticles that are natural carriers of biomolecules including ncRNAs and mediate their transport between cells. Due to their ease of isolation from different body fluids, engineering and manipulation, EVs have been emerging as powerful therapeutic tools. While their increased internalization profile and capacity to deliver both natural and synthetic ncRNAs including lncRNAs is a competitive advantage over other non-viral RNA delivery strategies, their lack of tropism to the heart is currently their major caveat. Understanding EV biology and devising strategies to enhance their targeting and bioactivity is thus vital to translate their use into clinical practice.

The work reported in this thesis, provides insights into enrichment of EVs with lncRNA H19 through donor cell engineering and presents a novel way to increase EV accumulation in the heart upon systemic administration. We dissected the presence and abundance of the majority of the splice variants of lncRNA H19 in the EVs and their transfer to the main cardiac cell types. In endothelial cells, we further show that lncRNA H19 transferred by EVs induces a pro-angiogenic profile. In broad terms, evidence of different splice variants in EVs may have implications as a biomarker for splice variant specific diseases or as a therapeutic entity. Moreover, future research into the manipulation of lncRNA splice variant content in EVs may finetune their bioactivity progressing towards personalized medicine.

Finally, to address the lack of cardiac tropism of EVs, we report a novel non-invasive approach for the targeted delivery of EVs to the heart. The approach benefits from a destructible carrier of EVs, which upon remote activation promotes the local delivery of EVs. Being a very versatile approach, this technology holds immense potential for the remotely targeted delivery of native or previously engineered EVs to the heart or other organs.

In conclusion, these results provide new insights into EV engineering to manipulate their content and maximize their delivery to the heart, progressing towards their use for cardiac therapy.