Patient-specific bioinformatics linking coronary microvascular structure, function and gene expression

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Project outline

Background

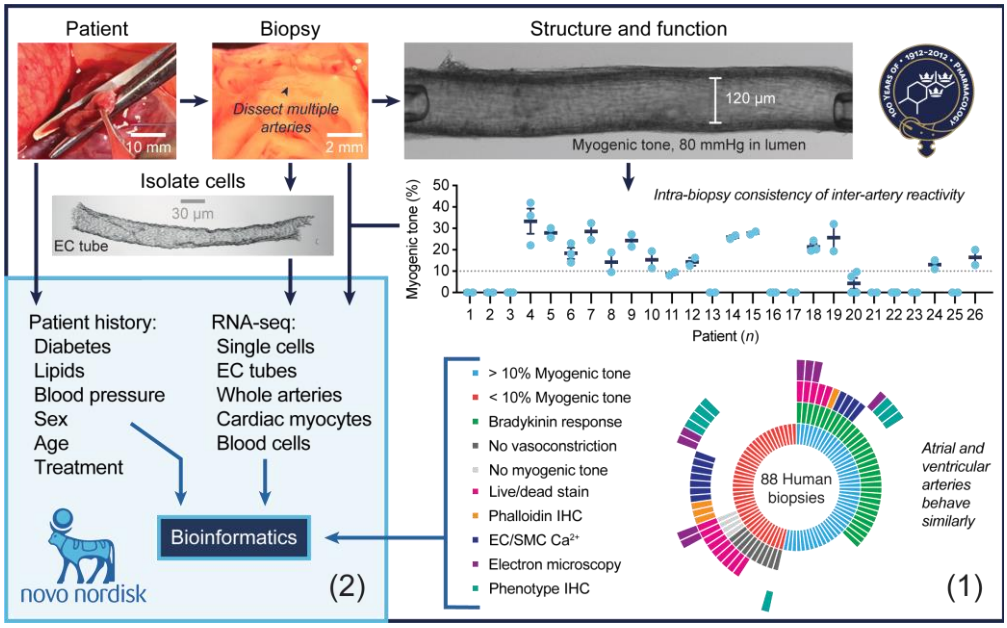
Blood flow to working cardiac myocytes is tightly controlled with every heartbeat. Dysregulation of this blood flow compromises cardiac energetics and contributes to cardiac metabolic diseases and dysrhythmia. Microvascular angina occurs in ~40% of patients undergoing coronary angiography, without visible epicardial coronary artery disease. This non-obstructive coronary microvascular disease, also termed cardiac syndrome X, is a major cause of cardiac events in patients, and is often associated with diabetes, hyperlipidaemia and hypertension. Measurements of human microvascular function *in vivo* are currently limited to low resolution imaging (diameters >300 µm) and calculated microvascular resistance measurements. While these approaches provide much clinically relevant information, and are often associated with biomarkers, the cause of any dysfunction within the microcirculation itself cannot be probed in any detail.

Hypothesis

The ability to study atrial and ventricular arteries from a single patient offers the ability to study structure, function, and with single-cell RNA-seq, the transcriptome to ultimately link to patient-specific medical history and demographics. This unique approach will provide a database that can be utilized for current and multiple ongoing studies.

Aims

To extend our ongoing studies using human coronary micro-arteries by utilizing single-cell RNA-seq and bioinformatics at Novo Nordisk to identify gene targets associated with microvascular contractile dysfunction.



Work flow for patient-specific bioinformatics. Multiple arteries from each biopsy will be dissected for assessment of (1) vascular reactivity and structure in Pharmacology, and (2) cell isolation for transcriptomics in Novo Nordisk. Data will form an information biobank linking structure, function and genetics for each patient.

Description of work to be undertaken

Our cardiac surgery patient studies show that ~50% of micro-arteries studied for vasoreactivity do not develop myogenic tone in response to 80 mmHg luminal pressure. These arteries represent a model of microvascular contractile dysfunction. We know the structure of the arterial wall has changed, the cells are alive and intracellular Ca^{2+} signalling is intact, yet instead of constricting, the smooth muscle cells have changed to a synthetic phenotype in both atrial and ventricular human coronary arteries. The project will develop the use of single-cell RNA-seq using arteries dissected from a human biopsy to link patient history, screening of the transcriptome, and structure and function to identify genes linked to microvascular contractile dysfunction. Access to organ donor atrial and ventricular biopsies lends itself to a unique reference data set. The Fellow will be trained in all aspects of the project in both (1) Pharmacology for vascular reactivity, signalling and structural studies, and (2) Novo Nordisk for single-cell RNA-seq and bioinformatics, with scope for a particular emphasis, and expansion in specific areas.

Supervisor's recent relevant publications:

1. **Dora KA**, Borysova L, Ye X, Powell C, Beleznai TZ, Stanley CP, Bruno VD, Starborg T, Johnson E, Pielach A, Smart N, Ascione R, Microvascular contractile dysfunction associates with synthetic smooth muscle cells in human intramyocardial arteries. *Manuscript under review; available on request by emailing nn.fellowships@rdm.ox.ac.uk.*
2. Herring N, Tapoulal N, Kalla M, *Ye X*, Borysova L, Lee R, Dall'Armellina E, Stanley C, Ascione R, Lu CJ, Banning AP, Choudhury RP, Neubauer S, **Dora K**, Kharbanda RK and Channon KM. Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection fraction following ST-elevation myocardial infarction. *Eur. Heart J.* 40, 1920-1929 (2019). PMID: 30859228
3. Garland CJ, Bagher P, Powell C, Ye X, Lemmey HAL, Borysova L, **Dora KA**. (2017). Voltage-dependent Ca^{2+} entry into smooth muscle during contraction promotes endothelium mediated feedback vasodilation in arterioles. *Sci. Signal*. 10, eaal3806. PMID: 28676489

4. Lucotte BM, Powell C, Knutson JR, Combs CA, Malide D, Yu ZX, Knepper M, Patel KD, Pielach A, Johnson E, Borysova L, **Dora KA**, Balaban RS (2017) Direct visualization of the arterial wall water permeability barrier using CARS microscopy. *Proc Natl Acad Sci USA*114(18):4805-4810. PMID: 28373558
5. Bagher P, Beleznai T, Kansui Y, Mitchell R, Garland CJ, **Dora KA**. (2012). Low intravascular pressure activates endothelial cell TRPV4 channels, local Ca^{2+} events and IK_{Ca} channels reducing arteriolar tone. *Proc. Nat. Acad. Sci. U.S.A* .109 (44), 18174-9. PMID: 23071308