CIM – Centre of Inflammation and Metabolism

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Centre of Inflammation and Metabolism (CIM) is an interdisciplinary research centre with funding from the Danish National Research Foundation for the period 2005-2015. CIM was build on the idea that skeletal muscle is an endocrine organ with the capacity to produce several “myokines” and that such myokines would play important roles in cell-to-cell and organ-to-organ cross talk, e.g. muscle-fat; muscle-liver and muscle-pancreas cross talk. During the past years, we have fulfilled our initial vision of establishing skeletal muscle as an endocrine organ. We have identified the human muscle secretome, including a comprehensive list of approximately 600 potential myokines. However, the regulatory pathways and biological roles of most of these recently identified potential myokine candidates are still totally unknown. It is therefore our aim to characterise the regulatory signalling pathways of selected myokines; their paracrine and/or endocrine biological roles with focus on the effect on metabolism, inflammation, and oncogene proliferation.

Historical background
For most of the last century, researchers sought a link between muscle contraction and humoral changes in the form of an “exercise factor”, which could be released from skeletal muscle during contraction and mediate some of the exercise-induced metabolic changes in other organs such as the liver and the adipose tissue. The idea that signalling pathways from contracting muscles to other organs were not solely mediated via the nervous system was supported by the finding that electrical stimulation of paralysed muscles in spinal cord injured patients induced in essence the same physiological changes as in healthy humans. It was obvious that one or more muscle-derived humoral factors existed. For lack of more precise knowledge, it was called the “work stimulus” or the “work factor”.

The contribution by CIM
In the beginning of this millennium, we were the first to identify a cytokine that was produced and released from contracting muscle cells into the circulation. Following the identification of the

Figure 1. Especially under conditions of obesity, adipose tissue secretes adipokines, which contribute to establish a chronic inflammatory environment that promotes pathological processes such as atherosclerosis and insulin resistance. Skeletal muscles are capable of producing myokines that confer some of the health benefits of exercise. Such myokines might counteract the harmful effects of proinflammatory adipokines (Published with permission, Ref. 1)
first muscle-derived peptides, we suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibres and exert paracrine or endocrine effects should be classified as “myokines”.

In continuation, we have suggested that the interplay between adipokines and myokines represents a yin/yang-balance. Especially under conditions of obesity, adipose tissue secretes adipokines that contribute to establish a chronic inflammatory environment that promotes pathological processes such as atherosclerosis and insulin resistance. However, skeletal muscles are capable of producing myokines that confer some of the health benefits of exercise. Such myokines might counteract the harmful effects of pro-inflammatory adipokines.

Given that CIM was founded in 2005 on the high-risk idea that skeletal muscle is able to produce and release secretory peptides, it is highly rewarding that we are now able to present data showing that skeletal muscle is indeed a secretory organ, capable of producing several myokines with known biological action as outlined in the figure below. The myokine research provides a conceptual basis and a whole new paradigm for understanding how muscles communicate with other organs, such as adipose tissue, liver, pancreas, bones and brain.

Some myokines exert their effects within the muscle itself. Thus, myostatin, LIF, IL-6 and IL-7 are involved in muscle hypertrophy and myogenesis. BDNF and IL-6 are involved in AMPK-mediated fat oxidation, whereas IL-8/CXCL-1 is thought to be involved in angiogenesis. IL-6 also appears to have systemic effects on the liver, adipose tissue and the immune system, and mediates cross talk between intestinal L cells and pancreatic islets.

Other myokines include the osteogenic factors IGF-1 and FGF-2; FSTL-1, which improves endothelial function and revascularization of ischaemic vessels. Irisin has a role in ‘browning’ of white adipose tissue. (Published with permission, Ref.1).

Research achievements
The status on myokines can be listed as follows

- Myokines are cytokines or other peptides that are produced, expressed and released by muscle fibres.
- Myokines may exert autocrine, paracrine or endocrine effects.
- Myokines may balance and counteract the effects of adipokines.

Figure 2. LIF, IL-4, IL-6, IL-7 and IL-15 promote muscle hypertrophy. Myostatin inhibits muscle hypertrophy and exercise provokes the release of a myostatin inhibitor, follistatin, from the liver. BDNF and IL-6 are involved in AMPK-mediated fat oxidation and IL-6 enhances insulin-stimulated glucose uptake. IL-6 appears to have systemic effects on the liver and adipose tissue and increases insulin secretion via upregulation of GLP-1. IGF-1 and FGF-2 are involved in bone formation, and follistatin-related protein 1 improves endothelial function and revascularization of ischaemic vessels. Irisin has a role in ‘browning’ of white adipose tissue. (Published with permission, Ref.1).
The muscle cell secretome consists of several hundred secreted products.

Identified myokines include myostatin, LIF, IL-6, IL-7, BDNF, CXCL-1, IGF-1, FGF-2, FSTL-1 and irisin.

Myokines may mediate protective effects of muscular exercise, with regard to diseases associated with a physically inactive lifestyle.

**From man to molecule strategy**

CIM has established itself as a multi-disciplinary centre with an unconventional strategy, classified as from “bed-to-bench” or more precisely from “man-to-molecule”. We perform integrative, physiological research in humans, using invasive methodologies, but with the aim of unravelling mechanisms of action at the molecular level. We have established a biobank of muscle precursor cells (stem cells or satellite cells) isolated from muscle biopsies obtained from exceptionally well-characterised individuals (n = ~ 600), representing a wide range of body mass, physical activity level, age, and metabolic status. Interestingly, it appears that cultured myocytes retain the in vivo phenotypes of impaired metabolism, insulin resistance, and inflammation. Therefore, we are convinced that this biobank of human primary muscle cell cultures will serve as a useful tool and a basis to unravel a number of mechanisms, by which lifestyle factors influence e.g. the secretome capacity, as well as proliferation and differentiation.

Recently, we have developed electrical stimulation of muscle cells in culture as an in vitro model of acute and chronic exercise in human primary myocytes. These ES models allow for the examination of effects of a physiological stimulus, such as exercise training, in primary myocytes where donor-maintained phenotypes exist. These in vitro models of acute and chronic exercise are now included in several research projects within CIM.

**The possible role of myokines in clinical medicine**

Interestingly, type 2 diabetes, cardiovascular diseases, colon cancer, breast cancer, dementia and depression constitute a cluster of diseases, which defines “a diseasome of physical inactivity”. We are currently working on the hypothesis that physical inactivity is an independent and strong risk factor for accumulation of visceral fat, which again is a source of systemic inflammation. Chronic inflammation is involved in the pathogenesis of insulin resistance, atherosclerosis, neurodegeneration and tumour growth. To some extent the protective effect of exercise may be ascribed to the anti-inflammatory effect of regular exercise,
which may be mediated via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise. The fact that muscles produce and release myokines provides a basis to understand the mechanisms whereby exercise influences metabolism and exerts anti-inflammatory effects. According to our theory, contracting skeletal muscles release myokines, which mediate direct anti-inflammatory effects. Other myokines exert specific endocrine effects on visceral fat or work locally within the muscle via paracrine mechanisms, exerting their effects on signalling pathways involved in fat oxidation.

CIM organization and management

The CIM research plan represents a truly multidisciplinary approach. Our research is based on a concept that links a molecular approach with the whole body in vivo metabolic functions in human beings.

By mid 2012, CIM consists of close to 60 people including technical-administrative personnel and scientific associates at all levels. The CIM management is shared between BKP and Inge Holm (IH) (CIM administrator). As Director of CIM, BKP decides on research strategy, organisational structure, and finances. The administration of CIM is managed by IH, who also serves as financial project manager and HR officer.

CIM applies a highly dynamic organisational structure that presently consists of 9 thematic or methodological research groups, each with a CIM post doc or senior researcher as group leader. The responsibilities of the group leaders include daily supervision and coordination of individual research. This structure ensures that CIM post docs are given the opportunity to develop into independent researchers and junior group leaders, while still contributing to the overall visions regarding “inflammation and metabolism” with focus on muscle as an endocrine organ.

CIM is a popular working site and young researchers are easily recruited. The training of PhD-students has high priority and during our first period of five years, 20 PhD theses were “produced”. Our strategy is to identify potential talents already among graduate students at our faculties and to offer a scholarship to those who appear highly motivated. So far, we have successfully obtained such scholarship grants from the Danish Medical Research Council, the Novo Nordic Foundation, our host institution, and from other granting agencies. However, we also allocate an amount for this purpose from our CIM budget to ensure that we are always in a position to recruit talented pre-graduate students.

Thus, the CIM organisational structure allows young students the opportunity to perform advanced experimental research under close super-
vision, which typically results in publications of original work. Often, students who have spent a year with full-time research in our laboratories will continue their research work in parallel with their studies in medicine or science and graduate with a CV that allows them to compete for PhD grants at the UC faculties or elsewhere.

However, it is also possible to enter a PhD programme in our group without a long publication list. We have allocated money from the CIM budget to make sure that highly motivated young academicians may initiate a research project in CIM while at the same time applying for external PhD grants. We encourage foreign candidates to compete for PhD positions in CIM.

CIM aims at being a research environment, in which potential as independent researchers. We encourage our PhD students to spend time in front line laboratories abroad. We continuously invite leading international researchers to visit CIM to give our PhD-students an opportunity to discuss their research projects face-to-face with such authorities.

Once a year, CIM organises an international one-week PhD-course on “Inflammation and Metabolism”. At these courses, lectures by international “key-opinion leaders” within our field of research are combined with workshops and laboratory sessions. Our invited speakers are asked to participate in as much of the course as possible in order to increase the scientific impact of discussions and promote interaction with the students.

Having young researchers of both gender and of many nationalities stimulates to fully develop their potential as independent researchers. We encourage our PhD students to spend time in front line laboratories abroad. We continuously invite leading international researchers to visit CIM to give our PhD-students an opportunity to discuss their research projects face-to-face with such authorities.

CIM director BKP has regular individual meetings with all CIM associates. However, to secure amble communication at all levels we have implemented a highly structured meeting sequence consisting of

- CIM workshops and journal clubs, alternating every Friday. At the workshops CIM associates present their ongoing research projects, and new findings and future studies are discussed (participants: everyone in CIM).
- Bi-weekly lab meetings (participants: everyone in CIM; practical matters, status of projects and publications; who should apply for which grants).
- Weekly research group meetings (participants: the members of a certain group; research progress).
- Monthly post doc meetings (participants: group leaders and post docs; research progress, collaboration between groups, new methods to be established).
- Bi-monthly “senior meetings” (participants: CIM management, group leaders and post docs; strategy related to research initiatives, funding, personnel, e.g. which of the pre-graduates who should be supported for a research career).

There is strong interaction between the research groups. Typically, the groups conducting human physiological studies will collaborate with the groups, who on a daily basis have “hands-on” molecular biological methods, cell culturing or animal models. In most studies, muscle or fat biopsies are collected from well-characterised individuals who are exposed to various well-defined physiological stimuli. Stem cells are isolated from such tissues and primary human muscle and adipocyte cell cultures are established and used for the study of signal transduction, secretory capacity, etc. Animal models are developed to allow more in-depth studies on muscle-organ cross-talk and the role of individual myokines are studied in knock-out models or by muscle-specific overexpression of individuals myokines.

The impact of CIM : The “Ex-factor”

We believe that research institutions such as CIM have a responsibility to disseminate the knowledge they accumulate and to be players in science and health debates in society. The research of CIM has major health aspects with regard to protection and treatment of chronic diseases and lifestyle-related disorders. CIM therefore provides a solid scientific platform for public health advice to layman and politicians. Thus, CIM affiliates are involved in various committees that directly or indirectly aim at stimulating the political awareness of the importance of physical activity and we continuously provide popular science talks and contribute to radio and television programs and to articles in newspapers, etc.

Moreover, the identification of new myokines will potentially serve as targets for treatment of metabolic disorders and other diseases for the benefit of the population.

References
