EUROPEAN SCIENCE FOUNDATION
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Exploratory Workshop Scheme

Standing Committee for the European Medical Research Councils (EMRC)

Scientific Report

ESF Exploratory Workshop on

Targeting OBesity-driven Inflammation (TOBI)

Vienna, Austria, 22 - 23 February 2007

Convened by:
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ESF-EMRC Exploratory Workshop EW06-007

1) Executive summary

Obesity and associated metabolic disorders such as type 2 diabetes and the metabolic syndrome are most prominent health care issues in Europe and other industrialized countries. Obesity is known to be associated with systemic signs of chronic low-grade inflammation. The inflammatory response strikingly predisposes obese patients to diabetes development and cardiovascular disease. Only very recently it has become evident that the obesity-associated systemic inflammatory reaction primarily originates from the adipose tissue itself. Adipose tissue releases a large number of inflammatory and anti-inflammatory substances into the circulation that are called adipokines that are synthesized by adipocytes and infiltrating inflammatory cells, mainly macrophages. While few adipokines enhance insulin sensitivity, inflammatory adipokines generally disrupt whole body insulin sensitivity and provoke metabolic deterioration. Targeting the obesity-driven inflammatory response by reversing the obesity-driven shift to inflammatory adipokines has the potential to improve insulin sensitivity and prevent metabolic complications in obese patients. Therefore it was the aim of this workshop to set up a concerted European research initiative exploring novel drug targets for the prevention of the insulin resistance by interfering with obesity-associated inflammatory alterations.

On december 22nd, 2006, the European Commission published the framework programme 7 (FP7) that included a call for a collaborative research project covering exactly this issue (HEALTH-2007-2.4.3-4: Pathophysiological mechanisms related to excess fat). Due to this fact, this exploratory workshop not only had a strategic aim for research in Europe but has got a defined operational aim, namely to form and strengthen a consortium for a FP7 project application on this topic.

The program was divided into two sections. On February 22nd, the participants provided their excellent work on different issues of this subject followed by scientific discussions. At the end of this day, the structure of a TOBI collaborative research

proposal to FP7 was explained and the principal structure of a project was presented by the convenor. On February 23rd, the participants explained their suggested work to be performed within the TOBI proposal.

The workshop took place in Vienna, Austria, and was organized by the convenor. The co-convenor, Prof. Waldhäusl had to cancel his attendance few days before the meeting due to an official visit abroad. Most of the participants were highly renowned experts in different issues related to obesity-associated adipose tissue inflammation ensuring a discussion of this topic at the highest level. Dinner discussion on February 22nd were held in a typical Viennese wine restaurant ("Heuriger") where the participants could not only have excellent local food but also relax with typical Viennese music.

As the main result of the workshop, a collaborative proposal for the call HEALTH-2007-2.4.3-4: "Pathophysiological mechanisms related to excess fat" with application deadline on April 19th, has evolved through many discussions. The participants agreed that they will provide their contributions in order to apply for the TOBI collaborative project in time. Hence the exploratory workshop completely met its purpose and fulfilled its aims by allowing discussions on a novel field of research and resulting in a European research project proposal supported by all participants.

2) Scientific content of the event

The workshop started with introductory remarks by the convenor illustrating the enormous burden of obesity for current and even more future health organisations in developed countries including the EU. The current overall understanding of obesity-associated adipose tissue inflammation was illustrated in order to provide a frame for the detailed presentations to follow.

Jens Brüning explained inflammatory signaling in adipose tissue as it occurs during obesity. Dr. Brüning presented the concept of over- and undernutrition related to altered immune response. He emphasized c-jun NH_2-terminal kinase signaling as a mediator of insulin resistance and inflammation. Recent results with mouse lines bearing genetically introduced alterations in signaling molecules revealed insights in the

relevance for obesity development and insulin resistance of signaling pathways in different cell types.

Martin Schröder continued with explaining how the ER stress results in the unfolded protein response (UPR). The UPR is also induced by altered nutrient fluxes and has recently been linked to insulin resistance. He depicted major players of ER stress signaling in yeast as well as their mammalian counterparts. Signaling pathways were defined that either promote restoration of a healthy state or induce inflammatory signaling. The relevance of the findings in yeast where the UPR has been studied in detail for mammalian stress signaling pathways was discussed.

Another interesting aspect of adipose tissue infiltration by macrophages was presented by Saverio Cinti. He showed that adipocyte death is an important stimulus for macrophages to form crown-like structures (CLS) surrounding adipocytes. He showed electron microscopic studies on adipose tissue of obese animals and humans that provided novel insights into mechanisms underlying adipocyte death and monocyte attraction. The importance of CLS formation in contrast to diffuse macrophage infiltration of adipose tissues was heavily discussed by the participants.

The convenor showed novel data on the impact of dietary fatty acid composition on adipose tissue inflammation in obese mice. Inclusion of n-3 polyunsaturated fatty acids as they occur in marine fish oils completely prevented the high-fat diet-induced adipose tissue inflammation. Possible mechanisms underlying this novel mode of action were discussed.

Maximilian Zeyda presented novel data on the nature of adipose tissue macrophages (ATM). He showed that characteristics of ATMs as revealed by very recently published data from mice only partially occur in human ATMs. He showed a panel of surface markers that could be used for characterization of ATMs and that are highly helpful to distinguish ATM from contaminating blood monocytes.

Giulia Chinetti continued with ATM characteristics and showed the impact of nuclear receptors in ATM activation. She demonstrated that inhibitory and stimulatory effects of nuclear receptor agonists can depend on the time of agonist treatment. Sakina Sayah-Jeanne, coworker at the company Genfit, revealed the experience of her company in nuclear receptor research and obesity.

Brian Walker and Nicholas Morton from Edinburgh demonstrated the importance of local glucocorticoid activation in adipose tissue for obesity and insulin resistance. They revealed the concept of 11β-hydroxysteroid dehydrogenase type 1 as the activating enzyme in adipose tissue, liver and the central nervous system. Possible interference by inhibitors of 11β-HSD1 was discussed with respect to alterations in adipose tissue inflammation.

Monika Ehrhart-Bornstein showed that adipose tissue-secreted factors potently alter adrenal production of mineralocorticoids. These changes could underlie obesity-associated hypertension. Systemic alterations in glucocorticoid production could interfere with local glucocorticoid activation in obesity. The interaction of adipose tissue-derived factors on adrenals and their regulation by the HPA axis were discussed in detail.

3) Results of the Meeting

The scientific discussions of these highly renowned experts at the meeting put forward the general understanding of obesity-driven inflammation and elucidated possible modes of interference. Further discussions on a collaborative research proposal yielded a common concept supported by all participants. This project proposal is currently worked out in order to fulfill the requirements of an FP7 collaborative project applications. The participants not only expressed their appreciation of collaborating on various aspects of obesity-associated adipose tissue inflammation but also declared their contribution to the FP7 project proposal. Hence the workshop was highly successful not only in scientific terms but also by initiating a European research initiative. By this means, this exploratory workshop could have enormous impact on European research in this novel and rapidly developing field.

4) Final Programme

Day 1 February 22

10:00 ***Welcome Coffee***

10:30 Introductional Remarks by T. Stulnig

10:45 Presentation of the ESF by K. Polakova

11:00 **Scientific Presentations 1**

Potential triggers of Obesity-driven Inflammation

J. Brüning	Inflammatory signaling
M. Schröder	ER stress and obesity-driven inflammation
S. Cinti	Adipocyte necrosis and macrophage infiltration

12:30 ***Lunch discussions***

13:45 **Scientific Presentations 2**

Adipose tissue macrophages

M. Zeyda/T. Stulnig	Adipose tissue macrophages and the impact of polyunsaturated fatty acids on adipose tissue inflammation
G. Chinetti	Nuclear receptors in adipose tissue inflammation
S. Sayah-Jeanne	Genfit's involvement in obesity and inflammation

15:15 ***Coffee break***

15:30 **Scientific Presentations 3**

Glucocorticoids in obesity

B. Walker/N. Morton	Glucocorticoid activation
M. Ehrhart-Bornstein	Adipose adrenal axis
H. Mascher	pharm-analyt's analytical expertise

16:50 ***Coffee break***

17:05 **Introduction to FP7 and TOBI**

I. Grünert: Introduction to FP7 collaborative project application,

T. Stulnig: Introducing TOBI; arrangement of work packages

19:00 Departure to ***dinner discussions*** at Weingut-Heuriger "Mayer am Pfarrplatz"

Day 2 February 23

07:30 Breakfast (for Hotel Guests)
08:00 ***Welcome Coffee***

08:30 **Presentation of work packages, part 1**
09:00 Discussion
10:10 ***Coffee break***

10:25 **Presentation of work packages, part 2**
11:05 Discussion

12:15 ***Lunch discussions***

13:30 **Presentation of work packages, part 3**
14:00 Discussion
15:10 ***Coffee Break***

15:25 **Concluding plenary discussion and statements**

17:00 Workshop closed

5) Final List of Participants

Name	Affiliation	City, Country	Address, phone/fax, E-mail
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6) Statistical Information on the Participants

Age bracket: 25 to 57 yrs

Gender: 4 female, 9 male

Countries of origin:

Austria	5
Germany	2
United Kingdom	3
France	2
Italy	1