Ageing Research Reviews 41 (2018) 1–17

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Inflammageing and metaflammation: The yin and yang of type 2 diabetes

Francesco Prattichizzo[a,b], Valeria De Nigris[b], Rosangela Spiga[b], Elettra Mancuso[b], Lucia La Sala[a], Roberto Antonicelli[c], Roberto Testa[d,*], Antonio Domenico Procopio[e,f], Fabiola Olivieri[e,f], Antonio Ceriello[a,b,g]

[a] Department of Cardiovascular Research, IRCCS MultiMedica, Milan, MI, Italy
[b] Diabetes and Obesity Research Laboratory, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain
[c] Cardiology Unit, Italian National Research Center on Ageing (INRCA-IRCCS), Ancona, Italy
[d] Clinical Laboratory and Molecular Diagnostics, INRCA-IRCCS National Institute, Ancona, Italy
[e] Department of Clinical and Molecular Sciences, DISCLIMO, Università Politecnica delle Marche, Ancona, Italy
[f] Center of Clinical Pathology and Innovative Therapy, National Institute INRCA-IRCCS, Ancona, Italy
[g] CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Spain

ARTICLE INFO

Keywords:
Type 2 diabetes
Metaflammation
Inflammageing
Immune system
Immunometabolism
Senescence
SASP
Epigenetic alterations
microRNA
Mediterranean diet
Fasting regimen
Microbiota
Antihyperglycaemic agent
Hyperglycaemic memory
Oxidative stress

ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterised by chronic low-grade inflammation, recently referred to as 'metaflammation', a relevant factor contributing to the development of both diabetes and its complications. Nonetheless, 'canonical' anti-inflammatory drugs do not yield satisfactory results in terms of prevention of diabetes progression and of cardiovascular events, suggesting that the causal mechanisms fostering metaflammation deserve further research to identify new druggable targets. Metaflammation resembles ageing-induced low-grade inflammation, previously referred to as inflammageing, in terms of clinical presentation and the molecular profile, pointing to a common aetiology for both conditions. Along with the mechanisms proposed to fuel inflammageing, here we dissect a plethora of pathological cascades triggered by *gluco*- and lipotoxicity, converging on candidate phenomena possibly explaining the enduring pro-inflammatory program observed in diabetic tissues, i.e. persistent immune-system stimulation, accumulation of senescent cells, epigenetic rearrangements, and alterations in microbiota composition. We discuss the possibility of harnessing these recent discoveries in future therapies for T2DM. Moreover, we review recent evidence regarding the ability of diets and physical exercise to modulate selected inflammatory pathways relevant for the diabetic pathology. Finally, we examine the latest findings showing putative anti-inflammatory mechanisms of anti-hyperglycaemic agents with proven efficacy against T2DM-induced cardiovascular complications, in order to gain insights into quickly translatable therapeutic approaches.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic multifactorial disease characterised by metabolic, hormonal, epigenetic, and oxidative imbalances (Di Dalmazi et al., 2012; Donath, 2014; Hotamisligil, 2006; Reddy et al., 2015). The main pathological features of T2DM are chronic hyperglycaemia and dyslipidaemia, which induce a plethora of molecular alterations, eventually leading to the development of complications, i.e. retinopathy, nephropathy, neuropathy, ischaemic heart disease, and peripheral vasculopathy (Donath, 2014; Hotamisligil, 2006). A critical component of T2DM is chronic, low-grade inflammation, recently referred to as 'metaflammation', i.e. metabolism-induced inflammation (Hotamisligil, 2006). This chronic condition involves the same cellular and molecular players of acute inflammatory responses, and accumulating evidence is being provided regarding metaflammation's role in the development of both T2DM itself and diabetes-induced cardiovascular (CV) complications (Hotamisligil, 2017).

Seminal discoveries initially pointed out a role for low-grade inflammation as a major determinant of obesity-induced insulin resistance. In particular, various murine models of obesity and diabetes show TNFa overexpression in fat tissue, with TNFa blockade being sufficient to increase insulin sensitivity (Hotamisligil et al., 1993). Adipose tissue is considered the main source of inflammatory factors in obesity, with enlarged, dysfunctional, or dying adipocytes secreting molecules able to attract immune cells and polarise them into a pro-inflammatory phenotype (Lumeng and Saltiel, 2011). Consistent findings have been presented for other major cytokines and chemokines, such as MCP-1 (monocyte-chemoattractant protein 1) and IL-6 (Fried

* Corresponding author.
E-mail address: r.testa@inrca.it (R. Testa).

http://dx.doi.org/10.1016/j.arr.2017.10.003
Received 1 August 2017; Received in revised form 21 September 2017; Accepted 23 October 2017

et al., 1998; Kanda et al., 2006), supporting the idea that inflammation is the link between obesity and diabetes development (Lumeng and Saltiel, 2011).

1.1. Inflammation can promote T2DM development by inducing insulin resistance and dysfunction of β-cells and the hypothalamus

The role of inflammation in induction of an alteration of metabolism is increasingly being accepted; a number of papers have provided considerable evidence (Hotamisligil, 2017). The observation that chronic infectious diseases can lead to the development of T2DM further reinforces this notion (Hotamisligil and Erbay, 2008). Inflammatory cytokines can directly induce insulin resistance by interfering with insulin signal transduction (Hotamisligil et al., 1996). For instance, TNF-a and IL-6 activate different intracellular Ser/Thr kinases, e.g. Jun NH2-terminal kinase (JNK) and IKK-b. In turn, these kinases catalyse serine phosphorylation of insulin receptor substrate 1 (IRS1), inhibiting its ability to recruit phosphatidylinositol-3-kinase (PI3K) and Akt, thus disrupting the metabolic pathway of insulin (Hotamisligil et al., 1996; Kahn and White, 1988; van Greevenbroek et al., 2013).

In addition to insulin resistance, pro-inflammatory molecules can even induce b-cell deterioration. In particular, both *gluco-* and lipotoxicity can foster the production of IL-1b, IL-6, and IL-8 in pancreatic islets (Ehses et al., 2007). A pro-inflammatory microenvironment can then downregulate insulin gene transcription and promote macrophage infiltration and b-cell apoptosis, overall contributing to the inability of the pancreas to compensate the insulin demand in insulin-resistant patients (Ehses et al., 2007; van Greevenbroek et al., 2013).

Low-grade inflammation is a common phenomenon observed in various tissues in response to glucose and lipid overload (Hotamisligil and Erbay, 2008). Of note, even the hypothalamus manifests pro-inflammatory gene expression after a high-fat diet (HFD) or high-carbohydrate high-fat diet (De Souza et al., 2005; Gao et al., 2017). Hypothalamic inflammation is an early event promoted by an HFD and appears to precede the development of obesity (Thaler et al., 2012). Specific subgroups of hypothalamic neurons control feeding and energy homeostasis, and local or microenvironmental inflammation is sufficient to alter central insulin sensitivity with consequent whole-body alterations resembling diabetes and metabolic syndrome (Horvath, 2005). In certain settings, artificial induction of hypothalamic inflammation is sufficient to trigger diabetes-like features (Arruda et al., 2011). Just as fat and muscle tissues, JNK and IKK-b are emerging as key players determining altered insulin signalling, suggesting that common inflammatory pathways in different organs can promote T2DM development (Zhang et al., 2008). Furthermore, aside from over-nutrition, ageing increases the activity of the IKK-b–NF-kB axis in the hypothalamus, indicating cerebral low-grade inflammation as a common denominator of both conditions (Zhang et al., 2013).

1.2. Non-obese patients with T2DM present systemic, low-grade inflammation resembling 'inflammageing'

Adipose tissue is often regarded as the main and earliest source of low-grade inflammation in obesity-induced T2DM, with noticeable infiltration of both innate-immunity cells and lymphocytes into this tissue, as extensively reviewed elsewhere (Dasu et al., 2012; Glass and Olefsky, 2012; Johnson et al., 2012; Shu et al., 2012). Metaflammation is mainly stimulated by a surplus of nutrients (Hotamisligil, 2006; Hotamisligil and Erbay, 2008). Nevertheless, non-obese patients with diabetes are characterised by an increased inflammatory score, defined as the mean concentration of multiple cytokines in the bloodstream, e.g. IL-6, IL-8, and TNFa (Daniele et al., 2014; Esposito et al., 2003; Herder et al., 2005; Pickup et al., 1997). Thus, over-nutrition should not be considered the only trigger of metaflammation in the case of T2DM, and dysfunctional adipocytes should not be regarded as the main determinant of low-grade inflammation in non-obese patients with diabetes.

Metaflammation shares some molecular features with 'inflammageing', i.e. the chronic, low-grade, systemic, inflammatory state that characterises ageing (Franceschi et al., 2000; Franceschi, 2017). Levels of major circulating pro-inflammatory cytokines, e.g. the IL-1 family, IL-6, IL-8, and TNFa, are increased in both conditions (Prattichizzo et al., 2016a). In particular, IL-6 represents a robust marker able to predict T2DM development in previously healthy subjects (Wang et al., 2013) and CV diseases and mortality in both diabetic and non-diabetic elderly patients (Harris et al., 1999; Danesh et al., 2008; Shinohara et al., 2012). In addition, patients with diabetes experience accelerated ageing and have a shortened median lifespan, thus rendering T2DM a prototypical age-related disease (ARD) (Prattichizzo et al., 2016a). Exposure to high glucose levels decreases the lifespan and fitness in lower organisms (Schulz et al., 2007), while a low-carbohydrate, ketogenic diet extends longevity and healthspan in adult mice (Roberts et al., 2017). The additive effects and redundancy of metaflammation and inflammageing are suggestive of a combined effect of these two phenomena on the resulting short-lifespan phenotype of patients with diabetes.

1.3. Common phenomena fuel metaflammation and inflammageing

Modern research aimed at finding potential sources of low-grade inflammation is now focusing on almost overlapping mechanisms to explain both metaflammation and inflammageing (Franceschi, 2017). Thus, it is tempting to hypothesise a partly shared aetiology for both, with diabetic patients experiencing these phenomena more strongly. In addition, major pathways driving organismal ageing are intimately connected with metabolism (López-Otín et al., 2016). Using the accumulated knowledge regarding inflammatory sources of inflammageing (Franceschi et al., 2017), here, we review the latest findings concerning selected mechanisms proposed to drive low-grade inflammation in T2DM, i.e. prolonged immune-system stimulation, accumulation of senescent cells, epigenetic rearrangement, and a shift in microbiota composition (dysbiosis). Despite the difficulty with identifying the first culprit of these pathological cascades, a holistic view of the phenomena induced by *gluco-* and lipotoxicity could be important for introduction of new therapeutic approaches to low-grade inflammation in T2DM, a still unexploited target considering that current anti-inflammatory treatments only marginally affect diabetes evolution and the development of its complications (Pollack et al., 2016). In addition, we summarise recent data on the ability of specific diets and anti-diabetic medications to control systemic inflammation in the diabetic milieu.

2. Stimulatory role of glucose and lipids in the inflammatory response of immune cells

2.1. Hyperglycaemia induces a pro-inflammatory response in immune cells

A large body of evidence has shown an inflammatory response in immune cells after exposure to high glucose concentrations *in vitro*. Secretion of IL-1b, IL-6, IL-8, MCP-1, and other major cytokines has been demonstrated in both monocytes and macrophages derived from patients with T2DM and in monocytic cell lines exposed to hyperglycaemia (Johnson et al., 2012). Mechanistic explanations include reactive oxygen species (ROS)-mediated activation of p38 and other pro-inflammatory kinases, NF-kB induction, overexpression and activation of TLRs, mitochondrial uncoupling with consequent oxidative stress, and non-enzymatic glycation with over-activation of the AGE-RAGE pathway (Ceriello, 2012; Johnson et al., 2012). Furthermore, many pieces of evidence for a more pronounced pro-inflammatory state of *ex vivo* samples of immune cells from patients with T2DM have been shown, both in the basal state and after stimulation (El-Osta, 2012; Pirola et al., 2010). Glycaemia and the inflammatory state of immune