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Non-traditional roles of complement in type 2 diabetes: Metabolism, insulin secretion and homeostasis

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ABSTRACT

Type 2 Diabetes (T2D) is a disease of increasing importance and represents a growing burden on global healthcare and human health. In T2D, loss of effectiveness of insulin signaling in peripheral tissues cannot be compensated for by adequate insulin secretion, leading to hyperglycemia and resultant complications. In recent years, inflammation has been identified as a central component of T2D, both in inducing peripheral insulin resistance as well as in the pancreatic islet, where it contributes to loss of insulin secretion and death of insulin-secreting beta cells. In this review we will focus on non-traditional roles of complement proteins which have been identified in T2D-associated inflammation, beta cell secretory function, and in maintaining homeostasis of the pancreatic islet. Improved understanding of both traditional and novel roles of complement proteins in T2D may lead to new therapeutic approaches for this global disease.

1. Introduction

The pancreas consists mostly of exocrine tissue, supplying digestive enzymes for secretion into the gut, but approximately 1% of the human pancreatic mass is made up of pancreatic islets, small clusters of endocrine cells which are highly vascularized, receiving about 10–20% of the pancreatic blood flow (Jansson and Hellerstrom, 1983; Lifson et al., 1980). Increased blood glucose concentrations after a meal lead to increased glucose uptake by islet beta cells, enhanced glucose metabolism and an increase in intracellular ATP, causing closure of ATP-sensitive potassium channels, membrane depolarisation and the opening of voltage-gated calcium channels. The resultant increase in intracellular calcium induces mobilisation of insulin granules and secretion of insulin into the blood. Insulin acts on peripheral tissues including muscle, adipose tissue, and the liver, to induce glucose uptake and storage, returning blood glucose levels to normal. Diabetes mellitus is a disease state where blood glucose control is lost. Diabetes can be divided into 2 main types: Type 1 diabetes (T1D), which is autoimmune, and typically has an earlier onset, and type 2 diabetes (T2D), which was traditionally seen as a metabolic disease, and is associated with increasing age and obesity. Until the discovery and therapeutic use of insulin, T1D was a lethal disease, where immune-mediated destruction of beta cells leads to a total loss of insulin production, resulting in hyperglycemia, wasting, ketoacidosis, and death. T2D, which makes up the majority of diabetes cases, has a slower progression. Loss of insulin sensitivity in peripheral tissues is at first compensated for by an increase in insulin secretion, with glycemic control therefore maintained by increased insulin levels. However, with time various factors including islet inflammation, cellular toxicity and endoplasmatic reticulum (ER) stress caused by increased insulin production, lead to death of beta cells and an inability to maintain increased insulin secretion, with the result that blood glucose levels rise (Kahn, 1998) (Fig. 1). T2D is treatable by careful diet regulation, exercise, and drugs such as metformin, which increase insulin sensitivity of peripheral tissues, and sulfonylureas, which increase insulin secretion. At later stages supplementing insulin becomes necessary.

T1D disease progression includes production of auto-antibodies which are capable of fixing complement via the classical pathway, therefore contributing to pancreatic islet inflammation and cell death (Radillo et al., 1996; Rowe et al., 2013). However, it has become clear that inflammation also has an important role to play in T2D (Donath and Shoelson, 2011), and is now understood to

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; IAPP, islet amyloid polypeptide; C4BP, C4b binding protein; MAC, membrane attack complex; ASC, apoptosis-associated speck like protein containing a CARD domain.

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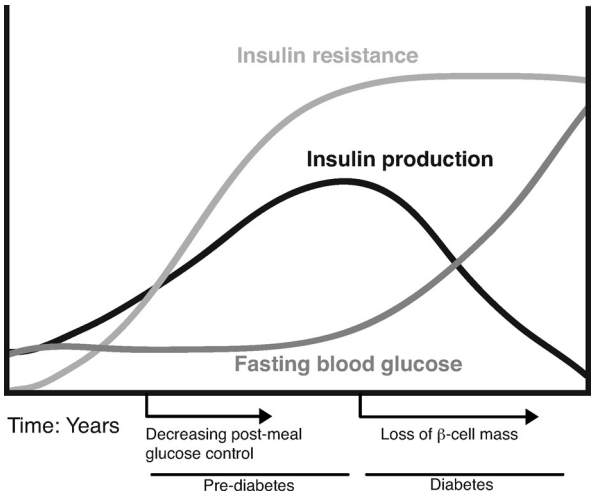

Fig. 1. The development of T2D: Insulin resistance, caused by inflammation in peripheral tissues, is at first compensated for by an increase in insulin secretion from pancreatic islets. However, with time, the development of pancreatic islet inflammation, β-cell stress and IAPP-mediated toxicity causes death of β-cells and the loss of insulin production, leading to increased fasting blood glucose and associated pathologies. A reduction in postprandial blood glucose control occurs already before loss of beta cell mass begins.

contribute to peripheral induction of insulin resistance, as well as contributing to the pathology within pancreatic islets. As an inflammatory mediator, complement has an obvious potential role to play in these processes.

The peripheral complications of prolonged hyperglycemia also include complement-mediated pathology, caused partly by the glycation and resultant inhibition of the cell-surface complement inhibitor CD59 at Lysine 41 (Acosta et al., 2000), leading to enhanced complement-mediated damage. These 'traditional' roles of complement in T2D complications have been covered in a recent comprehensive review (Ghosh et al., 2015). We shall instead focus on roles of complement in homeostasis and cell biology in metabolic tissue and the pancreatic islet, with emphasis on 3 major complement proteins: C3, CD59, and C4BP, which are all expressed in human pancreatic islets. We shall however begin with a brief description of complement's involvement in the periphery, which has been studied in more detail and serves as a good parallel example of processes which may also occur in the pancreatic islet.

2. Complement contributes to insulin resistance and metabolic changes in peripheral tissues

The clinical states of obesity and T2D are associated with chronic low-grade inflammation, as detectable by increased serum levels of inflammatory cytokines and acute phase proteins (Pickup et al., 1997; Spranger et al., 2003; Herder et al., 2005), including complement proteins such as C3 (see Table 1). In an MS/MS proteomics approach comparing over 1300 serum proteins of diabetic and non-diabetic cohorts, the complement system was found to be the most highly upregulated pathway in T2D (Li et al., 2008). In a cohort of over 540 individuals, serum levels of C3 associated with insulin resistance, increased blood glucose levels, and development of T2D over 7 years of follow-up (Wlazlo et al., 2014), and in a second study of over 2800 men, increased serum C3 levels were found to be a risk factor for T2D development, independent of BMI (Engstrom et al., 2005). Increased chronic inflammation is now considered to be a causative factor in the development of insulin resistance in adipose tissues, the first stage of T2D development (Xu et al., 2003). It is now established that obese human patients as well as experimental animals have shifts in populations of macrophages and T cells in

Table 1
Changes in levels of key complement proteins in T2D:.

Protein/Peptide	Effect	Refs.
C3	Increased serum levels in multiple studies of human obesity and T2D, correlates with insulin resistance, risk of T2D development	Li et al. (2008), Wlazlo et al. (2014), Engstrom et al. (2005)
C3a	Increased plasma levels in diabetic rat models Increased plasma levels in human diabetic subjects	Kolev et al. (2015) Li et al. (2008)
FactorD/Adipsin	Decreased adipose expression in multiple rodent models of obesity and T2D Decreased plasma levels in rodent levels Decreased adipose levels in human diabetics	Rosen et al. (1989), Flier et al. (1987) Mamane et al. (2009), Lo et al. (2014) Lo et al. (2014)
C4BP	Increased serum levels in T2D patients	Li et al. (2008)
CD59	Decreased pancreatic islet expression levels in rodent models, decreased human islet levels after high glucose exposure, exposure to IL-1β	Krus et al. (2014)

adipose tissues towards pro-inflammatory phenotypes (Schipper et al., 2012). In particular, resident adipose tissue macrophages increase in number (Weisberg et al., 2003) and undergo a shift from the 'M2' phenotype, which secrete more IL-10, to the more inflammatory 'M1' phenotype, which produce more TNF, in obese compared to lean animals and humans (Lumeng et al., 2007a; Shaul et al., 2010; Lumeng et al., 2007b). TNF was an early identified factor which is upregulated in obesity and which induces insulin resistance in adipose tissue (Hotamisligil et al., 1993), while the anti-inflammatory cytokine IL-10 reverses TNF-induced insulin resistance in adipocytes (Lumeng et al., 2007b). In addition, some trials have suggested that targeting TNF can improve insulin sensitivity in human subjects (Kiortsis et al., 2005; Stanley et al., 2011; Yazdani-Biuki et al., 2004), and could therefore improve blood glucose control in diabetic patients. Alterations also occur in adipose tissue $CD4^+$ T cell populations during obesity, with increases in numbers of infiltrating Th1 T cells (Wu et al., 2007) and decreases in proportions of $FoxP3^+$ Treg cells (Feuerer et al., 2009), the induction of which reduce inflammation and restore insulin resistance (Ilan et al., 2010; Lalazar et al., 2015). It is therefore clear that inflammation and subsequent changes in resident cell cytokine production can regulate insulin sensitivity of adipose tissue (Odegaard and Chawla, 2013). As an inflammatory mediator, complement can be expected to be able to influence this.

The complement system is a proteloytic cascade consisting of many serum proteins and inhibitors and cell surface receptors (see Fig. 2). Most complement proteins are primarily expressed in the liver, with several exceptions, notably that of factor D, which cleaves factor B bound to hydrolysed C3 to initiate the alternative pathway of complement activation. This leads to C3 cleavage, releasing the anaphylatoxin C3a and a larger fragment C3b, which functions as an opsonin. The alternative pathway is unique in that it occurs in the absence of any activating stimulus, with constitutive 'tickover' continuously occuring. As a consequence, expression of the alternative pathway components, C3, factor B, and factor D, is sufficient for low-level complement turnover to occur, with production of C3a which can signal via its receptor, C3aR. Factor D (adipsin) is in fact primarily expressed in adipose tissue, and was the first identified adipokine (Rosen et al., 1989). Cultured adipocytes also express C3, as well as factor B on exposure to pro-inflammatory cytokines, leading to spontaneous alternative pathway activation as detected by production of both C3a and the

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