Chapter 1

Insulin action and beta-cell function: role in metabolic regulation

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Regulation of fuel utilization in health and disease

The normal processing and utilization of fuels is tightly regulated by hormonal, neural, and intracellular mechanisms so that carbohydrates, proteins, and fats supply energy to the brain, muscles, and other tissues, and excess fuel is stored efficiently for use during periods of fasting or increased energy needs. Two key players in the balance of hormones regulating these processes are insulin and glucagon.

Insulin is secreted by the islet beta-cell in response to glucose, amino acids, peptides, and fatty acids and then promotes tissue uptake of glucose and glycogen synthesis. Insulin also acts on lipid metabolism by promoting enzymes involved in de novo lipogenesis, while suppressing those enzymes involved in lipid oxidation and lipolysis, resulting in a decrease in circulating free fatty acids (FFAs). The net result is a shift towards utilization of glucose as the primary fuel. Insulin’s effects are mainly anabolic as insulin levels increase when nutrient availability is high. During times when insulin levels are low, such as during fasting, these processes reverse and fuel selection shifts to preferentially utilize fat. Insulin also acts centrally in the hypothalamus as a satiety signal by interacting with neural centers that regulate food intake.

In contrast to insulin, the hormone glucagon, which is secreted by the islet alpha-cell, acts as a catabolic hormone, stimulating production of glucose via glycogenolysis and gluconeogenesis, primarily in response to hypoglycemia. Glucagon is also important in the regulation of basal and postprandial glucose levels, with the balance of this hormone with insulin being important. Thus,
when insulin levels rise, as occurs after nutrient ingestion, glucagon levels will normally decrease.}

In both type 1 and type 2 diabetes, insulin release is reduced, resulting in disruption of normal metabolism. Type 1 diabetes represents the extreme situation in which a near total deficiency of insulin is associated with marked hyperglycemia and the development of ketosis. In type 2 diabetes the deficiency of insulin is less pronounced, but since subjects with this disease are typically insulin resistant, as discussed in greater detail in the next section, the amount of insulin secreted is insufficient to overcome the tissue’s reduced responsiveness to insulin, resulting in overall insulin action being diminished.

**Insulin sensitivity and beta-cell function: a critical interplay determining glucose tolerance in health and disease**

Insulin resistance has long been recognized as a common feature of type 2 diabetes and has been considered by some to be the major underlying feature of the disease. However, it is now clear that it is the interplay between insulin sensitivity and the beta-cell’s response which is important. Interpreting the beta-cell’s response in the light of concurrent insulin sensitivity is vital and, when doing so, it is apparent that a failure of the beta-cell to release adequate amounts of insulin is the critical determinant of the progression to abnormal glucose tolerance.

Insulin secretion and insulin sensitivity are related in a physiological manner through a feedback loop that ensures maintenance of glucose tolerance. Thus, as insulin sensitivity decreases, insulin secretion increases in a compensatory fashion. The converse is also true so that when insulin sensitivity increases, less insulin is secreted in response to the same stimulus and in this manner hypoglycemia is avoided. This relationship between insulin sensitivity and the acute insulin response to intravenous glucose (AIR glucose or AIR g) has been shown to be hyperbolic in nature [1] (Figure 1.1a). Based on this hyperbolic relationship, the product of insulin sensitivity and the insulin response should remain constant for any level of glycemia (Figure 1.1b). This product has been termed the disposition index and has been used as a measure of beta-cell function.

Evidence that beta-cell dysfunction is present well before the onset of diabetes has been provided using this approach. In subjects with impaired fasting glucose (IFG; fasting plasma glucose 100–110 mg/dL) compared to those with normal fasting glucose levels (< 100 mg/dL), for any given level of insulin sensitivity, there is a relative decrease in the insulin response, so that the hyperbolic curve for the IFG group is shifted leftward and downward relative to those with normal fasting glucose levels [2] (Figure 1.2a). Furthermore, when subjects were divided into quintiles based on their fasting plasma glucose level and plotted relative to each other, a progressive decrease in beta-cell function can be shown
Figure 1.1 (a) The hyperbolic relationship between insulin sensitivity index ($SI$) and the first-phase (acute) insulin response ($AIR_g$) in 93 apparently healthy subjects (55 men [•] and 38 women [□]; log$_e$ regression: $r = -0.62$, $P < 0.001$). The hyperbolic relationship determines that changes in $SI$ are balanced by reciprocal changes in $AIR_g$. The cohort has a broad range of insulin sensitivity and insulin responses. The solid line depicts the mean relationship (50th percentile) whereas the broken lines represent the 5th, 25th, 75th, and 95th percentiles. (Reproduced from Kahn et al. [1], with permission from the American Diabetes Association.) (b) Model of the reciprocal changes in insulin sensitivity that is determined by the hyperbolic relationship between $SI$ and $AIR_g$. As insulin sensitivity falls (1), a normal adaptive increase in the $AIR_g$ occurs. Similarly, if insulin sensitivity improves (2), the $AIR_g$ will decrease in response to avoid hypoglycemia. (Adapted from Kahn et al. [1], with permission from the American Diabetes Association.)
Figure 1.2 (a) The hyperbolic relationship between insulin sensitivity index (\(S_I\)) and the first-phase insulin response (AIR_0) in 219 subjects subdivided based on whether they had normal fasting glucose (NFG; fasting plasma glucose < 100 mg/dL, \(n = 156\), Δ solid line) or impaired fasting glucose (IFG; 100–110 mg/dL, \(n = 63\), ○ broken line).
Figure 1.2 (Continued) The hyperbolic relationship between $S_i$ and $AIR_g$ is shifted to the left and downward in subjects with IFG compared to those with normal fasting glucose, indicating poorer beta-cell function in those with IFG. (Reproduced from Utzschneider et al. [2] with permission from the American Diabetes Association.) (b) The relationship between $S_i$ and $AIR_g$ is plotted relative to a normal healthy population (5th to 95th percentiles) for each quintile of fasting glucose for those subjects with fasting glucose < 110 mg/dL. Beta-cell function declines as the fasting plasma glucose concentration increases quintile 1: 80–91 mg/dL, quintile 2: 91–94 mg/dL, quintile 3: 94–98 mg/dL, quintile 4: 98–103 mg/dL, quintile 5: 103–109 mg/dL. (Adapted from Kahn et al. [1] and Utzschneider et al. [2] with permission from the American Diabetes Association.) (c) The hyperbolic relationship between insulin sensitivity index ($S_i$) and the first-phase insulin response ($AIR_g$) in 219 subjects subdivided by quartiles of the glucose disappearance constant ($K_g$). The hyperbolic relationship between $S_i$ and $AIR_g$ is progressively leftward and downward shifted with decreasing intravenous glucose tolerance (lower $K_g$). (Reproduced from Utzschneider et al. [2] with permission from the American Diabetes Association.)

as fasting glucose increases from below 90 mg/dL to 110 mg/dL [2] (Figure 1.2b). Similarly, division of subjects based on their glucose disappearance constant ($K_g$), a measure of intravenous glucose tolerance, demonstrated a shift of the curves to the left and downward with decreasing glucose tolerance [2] (Figure 1.2c). Thus, even mild changes in glucose levels may herald early evidence of beta-cell dysfunction and increased metabolic risk.
Groups of subjects who are at increased risk for the development of diabetes also demonstrate decreased beta-cell function using this approach. For example, beta-cell dysfunction has been shown in women with a history of gestational diabetes [3–5] or polycystic ovarian syndrome [6], in older subjects [7,8], and in individuals with a family history of type 2 diabetes [6,9]. Similarly, subjects with pre-diabetes, whether isolated IFG or isolated impaired glucose tolerance (IGT), have defects in beta-cell function. The beta-cell defect in isolated IGT is manifest during both intravenous as well as oral glucose testing. In contrast, the defect in isolated IFG is only manifest during intravenous testing and appears to be compensated for during oral testing by an increased incretin response which would act to enhance glucose-stimulated insulin secretion [10].

Examining the insulin response relative to the degree of insulin sensitivity has also been used to demonstrate that progression to IGT and diabetes over time is associated with decreases in beta-cell function as subjects “fall off” the curve. This was first illustrated in Pima Indians using hyperinsulinemic euglycemic clamp data along with measurement of the acute insulin response to glucose. Over time, all subjects became more insulin resistant, but only those who were unable to adequately increase their insulin response developed diabetes [11] (Figure 1.3). We have made similar observations in subjects with a first-degree relative with type 2 diabetes. In these subjects at increased risk of developing hyperglycemia, the decline in glucose tolerance over time was strongly related to a decline in beta-cell function [12]. The process of loss of beta-cell function appears to be slow with a rapid rise in glucose levels into the diabetic range occurring as a late phenomenon. This was illustrated in a study of women with a previous history of gestational diabetes followed over time. The women who progressed to diabetes demonstrated a slow decline in beta-cell compensation to insulin resistance and this was attended by slowly rising glucose levels, followed by a rapid rise in glucose levels once beta-cell function reached approximately 10% of normal [13]. As discussed later, a similar effect can be observed with data obtained using an oral glucose tolerance test (OGTT).

The approach of interpreting the adequacy of the beta-cell response in relation to the degree of insulin sensitivity has also provided insight into the adequacy of changes in beta-cell function in response to interventions. For example, in older men, 10% weight loss resulted in a 57% improvement in insulin sensitivity, with a consequent 19% decrease in the acute insulin response to intravenous glucose. Adjusting this insulin response for the change in insulin sensitivity demonstrated that overall beta-cell function improved with the weight loss intervention [14]. However, a regular exercise training program alone did not enhance beta-cell function in older subjects despite improvements in insulin sensitivity [15], suggesting that the improvement in insulin sensitivity with weight loss has effects that differ from those observed with exercise training.

Examination of beta-cell function by consideration of the adequacy of the insulin response relative to the degree of insulin sensitivity has also demonstrated
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Figure 1.3 Changes in beta-cell function as measured by the first-phase insulin response to glucose (AIR_g) relative to changes in insulin sensitivity as measured by the clamp method at a low insulin concentration (M-low) in 34 Pima Indians studied over several years. Twenty-three subjects maintained normal glucose tolerance (NGT) throughout (non-progressors), and 11 subjects progressed from NGT to impaired glucose tolerance (IGT) and then to diabetes (DIA; progressors). The curvilinear lines represent the mean and upper and lower 95% confidence interval for the regression between AIR_g and M-low based on a population of 277 Pima Indians with NGT. EMBS, estimated metabolic body size. (Reproduced from Weyer et al. [11] with permission from the American Society for Clinical Investigation.)

That beta-cell function can be preserved with the insulin-sensitizing medication, troglitazone. Hispanic women with a previous history of gestational diabetes were administered this thiazolidinedione or placebo in a randomized, double-blinded study. After a median of 30 months on blinded medication, fewer women in the troglitazone arm developed diabetes (12.1% on placebo vs. 5.4% on troglitazone, \( P < 0.01 \)). Protection from progression to diabetes was significantly associated with early improvement in the disposition index at 3 months in the troglitazone group [16].

The series of observations discussed above has made it very clear that the beta-cell is a critical player in determining glucose metabolism and that reductions in the adequacy of insulin release underlie changes in plasma glucose levels even
in individuals who are at risk for developing diabetes. However, these analyses have all been based on intravenous testing. As this approach is not practical in epidemiological and large clinical studies, an important issue is whether oral testing provides similar information and can be used in large, clinical research studies.

**Insulin sensitivity and beta-cell function: insights from oral testing**

Recently, a similar hyperbolic relationship between surrogate measures of insulin sensitivity and the early insulin response derived from an OGTT has been demonstrated [17,18]. When subjects with IFG and/or IGT and diabetes were examined, the curves for these groups were shifted downward and to the left as glucose tolerance declined from normal to IFG and/or IGT and then to diabetes, with those subjects with diabetes demonstrating insulin resistance and a flatter early insulin response. Based on the existence of a hyperbolic relationship, the product of the two variables was calculated to quantify this adjusted insulin response as the oral disposition index. This measure decreased with decreasing glucose tolerance and, importantly, a higher oral disposition index was associated with a decreased relative risk of developing diabetes over a 10-year follow-up period in these subjects [17]. Of further importance, this decrease in beta-cell function with deteriorating glucose tolerance appears to occur similarly in different ethnic groups [19].

Understanding this relationship has highlighted the importance of beta-cell function in determining the magnitude of the glucose excursion during an OGTT. In a large cohort of subjects with varying glucose tolerance, it has been demonstrated that insulin sensitivity is a weak determinant of the magnitude of the glucose excursion during a standard 75-gram OGTT, while beta-cell function was a strong and significant predictor of post-challenge glycemia [19]. Further, data from this analysis demonstrated that while beta-cell function varied tremendously in individuals with normal glucose tolerance, when it was markedly decreased, small changes had dramatic effects on the efficiency of glucose disposal (Figure 1.4) [19].

Using data from OGTTs, subjects with IGT who participated in the Diabetes Prevention Program (DPP) demonstrated improvements in beta-cell function with both the lifestyle intervention (weight loss and increased physical activity) and metformin treatment [20]. From the baseline data in these subjects, the relationship between the measures of insulin sensitivity and insulin release could be plotted as a non-linear function with the mean for all groups being similar. With the two interventions there was a rightward shift which was greater with lifestyle than metformin, while with placebo there was a small change that tended to be to the left of the mean line for the baseline relationship (Figure 1.5). These differences in outcome when examining insulin release and
Figure 1.4 Relationship between beta-cell function, as determined by the early insulin response to oral glucose adjusted for the prevailing insulin sensitivity, the latter determined using the homeostasis model (HOMA), and overall glucose tolerance quantified as the incremental area under the glucose curve in response to an oral glucose challenge (AUC$_g$) in 531 first-degree relatives of patients with type 2 diabetes. The mean value for subjects with normal glucose tolerance (circle, $n = 240$), impaired glucose tolerance (diamond, $n = 191$), and diabetes (square, $n = 100$) are illustrated. As the relationship is non-linear, when beta-cell function is diminished (such as in subjects with IGT and diabetes), small differences in beta-cell function will have a marked effect on the efficiency of glucose disposal compared to similar magnitude differences in subjects with normal glucose tolerance. (Reproduced from Jensen et al. [19] with permission from the American Diabetes Association.)

insulin sensitivity are in keeping with the lifestyle intervention resulting in a 58% decrease in the risk of progression to diabetes, while metformin resulted in a 31% decreased risk [21]. Thus, interventions that improve beta-cell function may explain their ability to delay the progression to diabetes in those at risk.

Effects of insulin resistance and insulin deficiency on regulation of fuel partitioning

One of the major effects of insufficient insulin release in type 2 diabetes is an increase in hepatic glucose production and decreased efficiency of glucose uptake, both resulting in an increase in plasma glucose. This outcome occurs both in the fasting state and following nutrient ingestion when suppression of glucose production is not normal. Insulin, and perhaps other constituents of the beta-cell secretory granule, also acts in a paracrine fashion to suppress glucagon secretion by the alpha-cell; thus, the insulin deficiency in type 2 diabetes is
Figure 1.5  Relationship between insulin sensitivity (1/fasting insulin) and the early insulin response (insulinogenic index; IGR) quantified from an oral glucose tolerance test (OGTT) at baseline and after a year by treatment group in subjects with impaired glucose tolerance (IGT) who participated in the Diabetes Prevention Program. Beta-cell function is described by the relationship between insulin release and insulin sensitivity. The curve represents the regression line of the logarithm of estimated insulin release as a linear function of the logarithm of estimated insulin sensitivity for all participants at baseline. The arrows connect the point estimate for median insulin release and median insulin sensitivity at baseline and after a year of the interventions (lifestyle, metformin, placebo). After one year of intervention, subjects who underwent the lifestyle intervention had the greatest improvement in beta-cell function as evidenced by the greatest shift to the right from the baseline curve. In contrast, those in the placebo group had a slight decline in beta-cell function, while those treated with metformin had an intermediate response. These changes in beta-cell function paralleled the positive effects to reduce the rate of development of diabetes by lifestyle and metformin, which were in contrast to that with placebo that had the highest rate of progression from IGT to diabetes. (Reproduced from Kitabchi et al. [20] with permission from the American Diabetes Association.)

associated with a paradoxical increase in postprandial glucagon levels which further raise glucose levels.

The effects of beta-cell dysfunction are not simply confined to abnormalities in glucose levels, but have broader impacts on lipid metabolism and fuel selection. As tissues take up less glucose and there is less insulin to suppress lipid oxidation, fuel selection shifts towards more lipid oxidation. For example, in conditions such as non-alcoholic fatty liver disease (NAFLD), oxidative and
non-oxidative glucose metabolism are decreased in response to insulin while lipid oxidation remains elevated compared to body mass index (BMI)-matched controls [22].

**Effects of insulin resistance and insulin deficiency on free fatty acids and lipid metabolism**

One of the major effects of insulin resistance at the level of the adipocyte is an impaired ability to suppress lipolysis via lipoprotein lipase (LPL), resulting in increased free fatty acid (FFA) levels. High FFA levels have been shown to be detrimental in many ways. Increased FFAs produce insulin resistance by competing with glucose as a substrate for oxidation, resulting in the inhibition of the activities of pyruvate dehydrogenase, phosphofructokinase, and hexokinase II [23]. In addition to this mechanism, it has been suggested that an increase in delivery of FFAs to the cell or a decrease in their metabolism results in an increase in the cell’s content of metabolites including diacylglycerol, fatty acyl-coenzyme A (fatty acyl-CoA), and ceramides. The increase in these metabolites leads to serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2), which in turn results in reduced activation of PI-3-kinase and diminished downstream signaling [24]. Finally, elevated FFAs in the setting of hyperglycemia may be “toxic” to the beta-cell, thus contributing to beta-cell dysfunction and inadequate insulin secretion [25]. Any decrease in the relative amount of circulating insulin relative to the prevailing insulin sensitivity will thus exacerbate the process by increasing FFAs and impairing glucose clearance.

The metabolic effect of increased FFAs is also frequently manifested as changes in lipid metabolism. The hypertriglyceridemia seen in subjects with the metabolic syndrome and type 2 diabetes is the result of increased export of available triglycerides as very-low-density lipoprotein (VLDL) particles [26]. This occurs mainly as a result of increased FFA flux to the liver, but insulin stimulation of *de novo* lipogenesis via sterol receptor element binding protein 1-c (SREBP1-c) [27] may also contribute. In patients with type 2 diabetes, hyperglycemia also stimulates *de novo* lipogenesis via the carbohydrate receptor element binding protein (ChREBP) [27]. Insulin resistance further contributes to increased VLDL by decreasing the direct inhibitory effect of insulin on apoB secretion. In subjects with low liver fat, an insulin infusion leads to a rapid drop in VLDL apoB and triacylglycerol secretion, but in subjects with high liver fat, including many with type 2 diabetes, the insulin infusion causes no significant change in VLDL secretion [28]. Finally, insulin resistance can decrease degradation of apoB [29,30]. The generation of excess VLDL particles results in subsequent metabolic abnormalities that are associated with an increase in cardiovascular risk, including generation of more atherogenic small dense
low-density lipoprotein (LDL) particles and increased catabolism of high-density lipoprotein (HDL) [31].

**Insulin regulation of amino acid metabolism**

Insulin also has important effects to regulate protein and amino acid metabolism. In the fasted state, insulin levels are low and amino acids are utilized for gluconeogenesis. Using the insulin clamp technique, it has been demonstrated that in the fasting state insulin decreases whole-body protein degradation [32], but does not stimulate protein synthesis in the absence of hyperaminoacidemia [33]. In the fed state the response depends on the composition of the meal. A high-protein meal both stimulates secretion of insulin and increases plasma amino acid levels with a net anabolic effect and positive nitrogen balance [34]. A meal consisting of glucose alone would lead to a prompt increase in insulin and a subsequent fall in plasma levels of many amino acids, with a continued net negative whole-body nitrogen balance.

In uncontrolled type 1 diabetes there is a lack of insulin and counter-regulatory hormones are increased with subsequent increased protein degradation and utilization of amino acids for gluconeogenesis. The net result is wasting of lean body mass, often seen in the early presentation of the disease. In contrast, in type 2 diabetes the deficiency in insulin is not as absolute and these dramatic effects on muscle wasting do not occur and protein metabolism is maintained fairly near normal [35].

**Role of fat distribution and ectopic fat in insulin resistance**

For many years it has been considered that insulin resistance was the result of obesity, as determined simply by body size. While insulin resistance is most often associated with obesity, even lean people have been found to be quite insulin resistant [36]. This finding has been shown to be in part the result of increased intra-abdominal fat (IAF), which may occur in people technically considered lean based on BMI criteria alone. Using computed tomography data to quantify IAF and abdominal subcutaneous fat (SQF), IAF has been most strongly related to insulin sensitivity [36]. In addition to being a determinant of insulin sensitivity, IAF has also been shown to be predictive of the future development of the metabolic syndrome [37], IGT [38], and diabetes [39].

In insulin-resistant states, lipid accumulation frequently occurs at “ectopic” sites including muscle and liver. Fat accumulation in the liver [40] is associated with dyslipidemia [41] and increased risk for cardiovascular disease (CVD) in patients with type 2 diabetes [42]. Further, elevated liver enzymes, as a marker of fatty liver disease in the absence of hepatitis C or excess alcohol intake, have been associated with increased cardiovascular disease [43,44].
Mechanisms for hepatic fat accumulation include (i) dietary excess of fats or carbohydrates such as fructose that are converted into triglycerides in the liver via de novo lipogenesis, (ii) hyperinsulinemia stimulating de novo lipogenesis, (iii) relative decreased lipid oxidation due to low adiponectin levels and/or high insulin levels, and (iv) increased FFAs delivery from adipose tissue due to impaired suppression of lipolysis by insulin. The latter explanation is supported by the fact that addition of basal insulin treatment to patients with type 2 diabetes already on metformin results in reduced plasma FFA levels, a small but significant reduction in liver fat, as well as improved hepatic insulin sensitivity [45]. Thus, relative insulin deficiency may contribute to development of fatty liver.

Increased intramyocellular lipid (IMCL) has been strongly correlated to skeletal muscle insulin resistance in obesity and type 2 diabetes [46]. Interestingly, endurance trained athletes also have increased IMCL despite being highly insulin sensitive [47] and moderate aerobic exercise training that increases insulin sensitivity and aerobic fitness in previously sedentary, overweight to obese, older subjects was accompanied by increases in IMCL [48]. These latter changes were accompanied by favorable alterations in lipid content, specifically with decreases in diacylglycerol and ceramide [48]. Thus it appears that it is not simply the amount of IMCL, but the quality of lipid within the muscle, that may be important.

Accumulation of excess lipid in the pancreas has also been noted and has been suggested to perhaps contribute to the beta-cell dysfunction seen in type 2 diabetes. *In vivo* studies measuring pancreatic lipid content found it to be increased in subjects with type 2 diabetes relative to non-diabetic controls and to be negatively correlated with beta-cell function parameters by oral glucose testing [49]. Adipocyte infiltration of the exocrine pancreas has also been noted in mice in response to a high-fat diet and human autopsy samples have been shown to have variable degrees of adipocyte infiltration in exocrine tissue [50]. Whether this ectopic fat accumulation in the pancreas really contributes directly to beta-cell dysfunction is not clear.

**Insulin resistance, insulin deficiency, and bodyweight regulation**

As has been discussed, insulin is an important regulator of metabolism. In recent years there has been a flurry of scientific inquiry examining the role of insulin along with leptin in regulating energy balance and thus bodyweight. Insulin acts in the hypothalamus to regulate bodyweight by modulating food intake. Thus, impaired insulin signaling centrally could contribute to weight gain and thereby impact metabolic homeostasis [51]. Beta-cell dysfunction resulting in a relative reduction in insulin release could result in further decreased insulin action in this critical brain region and could be associated with weight gain and further
aggravation of insulin resistance. This concept is supported by data from the Pima Indians showing that insulin secretion was inversely associated with the rate of weight gain and relatively reduced insulin secretion was independently predictive of weight gain and adiposity [52].

Summary

Insulin is the major regulator of metabolic processes, including glucose, protein, and lipid metabolism. Beta-cell dysfunction resulting in a relative deficiency in insulin secretion for the prevailing degree of insulin sensitivity can result in metabolic abnormalities and is a marker for increased risk for the future development of diabetes, with a progressive reduction leading ultimately to clinical hyperglycemia and the diagnosis of diabetes. Thus, it is important for clinicians to continue to promote strategies to improve beta-cell function, including lifestyle intervention with weight loss and medications. The net result should be an improvement, not only in glucose metabolism, but overall metabolic regulation.

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References


