

REVIEW

## The current biology of resistin

CLAIRE M. STEPPAN & MITCHELL A. LAZAR

From the Division of Endocrinology, Diabetes, and Metabolism, Departments of Medicine and Genetics, and The Penn Diabetes Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

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Obesity and noninsulin-dependent diabetes mellitus are globally epidemic. Insulin resistance is a major contributor to the pathogenesis of type II diabetes and plays a role in numerous other metabolic disorders including hypertension, dyslipidaemia and atherosclerosis. Obesity, in particular visceral adiposity, is positively correlated with insulin resistance. Although this correlation between adiposity and insulin resistance is well established in human beings

as well as in rodent models, the mechanisms involved in obesity-related insulin resistance are not fully defined. One mechanism is that factors secreted from adipocytes can affect peripheral insulin resistance. One candidate for such a factor is resistin, an adipocyte-secreted hormone that impairs glucose homeostasis and insulin action in the mouse. This review will summarize our current understanding of resistin and will attempt to provide a framework for future study of its role in rodent and human physiology.

**Keywords:** adipokines, adipose, diabetes mellitus, insulin resistance, obesity, resistin.

### Introduction

The discovery of the *retn* gene and the fact that it encodes an adipocyte-derived hormone called resistin is consistent with the recently recognized role of adipose tissue as an endocrine organ. More than 100 research papers on resistin have been published since its initial description in 2001. This new knowledge has not resulted in a consensus about the biological role of this newly identified molecule, and additional experimentation will be required to shed light upon resistin physiology and pathophysiology. This review will provide a summation of the current literature in order to address potential roles for resistin in both human beings and rodents.

### Initial observations of the physiological role of resistin

Three groups discovered resistin independently using modern genomic approaches, albeit with different aims. Our group identified resistin in a screen to identify potential targets of the thiazolidinedione (TZD) class of insulin sensitizers in 3T3-L1 adipocytes [1]. Microarray analyses identified resistin as adipose secretory factor or ADSF by Kim and coworkers [2]. A third group initially found resistin, which they termed 'FIZZ3', as an expressed sequence tag related to a protein they found to be induced during lung inflammation known as 'found in inflammatory zone 1' (FIZZ1) [3].

In mice, the *retn* gene is expressed almost exclusively in white adipose tissue and the protein is detectable in adipocytes and in the blood [1]. This observation suggests that resistin is produced primarily by adipose tissue and may act at sites distant from where it is produced. Serum levels of resistin were found to be elevated in rodent models of obesity and diabetes implicating a dysregulation of resistin in these disease states [1]. Administration of resistin to wildtype mice worsened glucose homeostasis and insulin sensitivity, and antibody neutralization of resistin by injection of antibodies in the diet-induced obese mouse decreased blood glucose levels and improved insulin sensitivity [1]. These studies suggested that resistin could possibly be one of the many factors contributing to the complex disease of insulin resistance.

Kim and colleagues have reported that conditioned media from COS-1 cells expressing resistin has an inhibitory effect upon 3T3-L1 adipogenesis [2]. These authors speculated that resistin is involved in a negative feedback loop and a signal to limit adipose tissue formation.

Although no functional analysis was performed, the group that identified resistin as FIZZ3 implicated a role for resistin in inflammation [3]. Nevertheless, the postulated roles for resistin, one in the regulation of glucose homeostasis, another in the regulation of adipose tissue mass and a third in inflammation, are not mutually exclusive and await additional investigation.

### The role of resistin in glucose homeostasis and insulin sensitivity

#### *Resistin expression in models of obesity and diabetes*

Resistin expression has been analysed in several different rodent models of obesity and diabetes. We have shown that serum resistin levels are elevated in two different genetic models (*ob/ob* and *db/db*) as well as in a diet-induced model of diabetes and obesity [1]. In contrast, Rajala *et al.* reported that resistin protein levels in adipose and serum of *db/db* mice were decreased compared with lean animals [4]. Both groups reported that resistin mRNA levels are decreased in adipose tissue from these animal models [4, 5], whilst Makimura *et al.* reported no change in resistin mRNA levels in *ob/ob* mice when compared with wildtype animals [6]. As mRNA

expression is normalized to total cellular RNA, a measured reduction in resistin expression per adipocyte may still be compatible with an increase in total body resistin gene expression and hence protein secretion in settings of increased adiposity. The reason for the discrepancies in the measured serum resistin levels in obesity are unclear, but are likely related to the methodology for detection and quantitation of resistin, which is still in its infancy and not standardized.

In the fructose-fed rat model of insulin resistance, resistin mRNA levels were decreased [7]. Conversely, in rats made insulin resistant by prenatal ethanol exposure and postnatal high-fat diet, resistin mRNA and protein levels were elevated [8]. Additionally, mice lacking c-Jun amino-terminal kinase 1, which exhibit decreased adiposity and improved insulin sensitivity, have decreased serum resistin levels [9]. These studies are consistent with a role for resistin in regulating insulin sensitivity. By contrast, resistin mRNA levels were unchanged following adrenalectomy of *ob/ob* mice, suggesting that resistin may not play a role in insulin sensitivity in this model [6].

In the insulin resistant Fischer 344 rats, resistin mRNA levels were increased as the animals aged 70–130 days without any apparent change in glucose tolerance yet exhibited increased weight gain when compared with Sprague Dawley rats thereby suggestive of a role of resistin in obesity [10]. In contrast, in two mouse models where obesity is induced by high-fat diet in a transgenic mouse model or injection of gold thioglucose to FVB/n mice, resistin mRNA is decreased indicating that a reduction in resistin is involved in obesity [11]. Resistin expression increases at the onset of diet-induced obesity by high-fat diet in rats [12]. In human beings, resistin mRNA levels in whole adipose tissue were increased in morbidly obese subjects when compared with lean controls [13]. However, this group did not find any correlation of resistin expression in freshly isolated adipocytes and BMI [13].

In sum, it appears that expression of resistin is differentially regulated in various rodent models of obesity and diabetes, and differences amongst models may also reflect direct and indirect mechanisms regulating resistin. Additionally, the role and regulation of resistin may be different in normal physiology when compared with disease states such as

obesity and diabetes. The specific role of changes in resistin gene expression in several different models of obesity and diabetes remains to be determined.

#### *Regulation of resistin expression in response to insulin and glucose*

In addition to studies in which resistin expression was monitored in obesity and diabetes, regulation of resistin expression has been studied in response to insulin and glucose. Resistin mRNA levels were increased in response to acute hyperglycaemia and decreased in response to hyperinsulinaemia in the mouse [4]. Consistent with these findings, resistin mRNA levels were increased by high glucose concentrations and decreased by insulin in 3T3-L1 adipocytes [14–16]. In contrast, insulin stimulated resistin gene expression in Zucker diabetic fatty rats [17] and streptozotocin-treated mice [2] and increased resistin secretion from 3T3-L1 adipocytes [18]. Overall, measurement of resistin in response to acute changes in glucose and insulin levels has not yielded consistent findings.

#### *Regulation of resistin expression in response to glucocorticoids and thyroid hormone*

Glucocorticoid excess, or Cushing's syndrome, causes insulin resistance [19] and recently a local increase in glucocorticoids caused by adipose-specific overexpression of 11 $\beta$ -HSD1 was shown to cause visceral obesity and impairment of insulin sensitivity [20]. Dexamethasone dramatically increased expression of both resistin mRNA and protein levels in 3T3-L1 adipocytes and mouse white adipose tissue [15, 16], although another report did not find an effect of glucocorticoids or thyroid hormone on resistin gene expression in 3T3-L1 adipocytes [21]. Increased serum levels of thyroid hormones can also impair glucose tolerance [22], and a different study found that resistin expression was severely decreased in hyperthyroid rats [23]. Therefore, the role of glucocorticoids and thyroid hormone as regulators of resistin expression is unclear at present.

#### *Resistin expression in different adipose depots*

As excess visceral adipose tissue is highly correlated with insulin resistance, increased expression of

resistin in abdominal depots would be consistent with a role of resistin in obesity-associated insulin resistance. Indeed, we have noted the resistin expression is higher in visceral depots in the mouse with the highest levels of expression in gonadal fat. Similarly, resistin mRNA levels were higher in visceral fat as measured in epididymal and periephric depots when compared with subcutaneous fat in Zucker fatty rats [24]. Recently, Atzmon *et al.* demonstrated an increased expression of resistin mRNA in visceral fat depots in both young rats and old diabetic rats [25]. In human beings, McTernan *et al.* observed higher levels of resistin mRNA expression in abdominal depots when compared with the thigh suggesting that human resistin could be playing a role in obesity-related insulin resistance [26, 27]. Additionally, resistin release from human adipose tissue explants was 250% higher in omental when compared with subcutaneous explants, although the source of resistin was thought to be nonadipocytes [28]. Serum human resistin levels were negatively correlated to waist to hip ratio and positively correlated amount of body fat mass which would be consistent with a role of resistin in insulin resistance [29]. The studies in both mice and human beings are supportive of a potential role of resistin in insulin resistance associated with increased visceral adiposity. Future studies should elucidate whether elevated resistin expression in visceral depots mediates its effects systemically or more locally on the liver through its access to the portal vein.

#### *Resistin expression in response to insulin sensitizing agents*

If resistin were involved in the pathogenesis of insulin resistance, one would predict that insulin sensitizing agents might decrease resistin expression. Consistent with this notion, resistin mRNA and protein are downregulated by antidiabetic TZDs in 3T3-L1 adipocytes [1, 15, 16, 30]. Similarly, PPAR $\gamma$  overexpression in 3T3-L1 adipocytes decreased resistin mRNA and protein [31]. The effects of TZDs on resistin expression *in vivo* has been controversial with reports of both upregulation [17, 32] and downregulation [1, 33, 34]. Additionally, metformin, a different class of insulin sensitizing agent, upregulated resistin protein levels in adipose tissue

in *db/db* mice [35]. Human resistin mRNA levels were unchanged in human monocytes in response to a 24-h treatment with rosiglitazone [13]. More recently, however, human resistin mRNA and protein were found to be expressed in human primary monocyte-derived macrophages, and levels were downregulated after 96-h treatment with rosiglitazone [36].

Analysis of 6.2 kB of the mouse resistin promoter did not reveal any apparent regulation by PPAR $\gamma$  [30]. Although recently, a PPAR $\gamma$  response element within an intron downstream of the stop codon has been identified and functionally characterized [37]. The human resistin gene does not contain this intron [37].

#### *The role of resistin on glucose homeostasis and insulin action*

Two independent studies in which recombinant resistin was administered to rodents both argue that resistin can cause insulin resistance. When resistin protein (32  $\mu\text{g}/\text{mouse}$ ) administered intraperitoneally to C57BL/6J mice, glucose homeostasis and insulin action was impaired [1]. More recently, infusion of resistin protein (5  $\mu\text{g h}^{-1}$ ) into Sprague Dawley rats worsened glucose homeostasis because of increased hepatic glucose production without apparent changes in glucose utilization by skeletal muscle and adipose tissue [38]. Interestingly, circulating levels of counterregulatory hormones such as glucagons and corticosterone were not altered by resistin infusion [38]. Recently, recombinant bacterially produced resistin has been demonstrated to inhibit glucose uptake in L6 skeletal muscle cells following an acute exposure [39]. Previously, we demonstrated that recombinant resistin inhibits insulin-stimulated glucose uptake in 3T3-L1 adipocytes [1]. These studies suggest that resistin may contribute to insulin resistance and, whilst produced in adipose, its effects are being mediated at target tissues such as liver, skeletal muscle and adipose tissue. Therefore, an acute increase in resistin levels of rodents is able to impair glucose homeostasis. Future studies in which resistin is administered chronically will elucidate whether this is a long-lasting effect or if compensatory mechanisms might counter the effects of resistin or alter its secretion. Such counterregulation might explain the differing levels

of resistin expression in various models of rodent obesity and insulin resistance.

#### **The role of resistin in other metabolic processes**

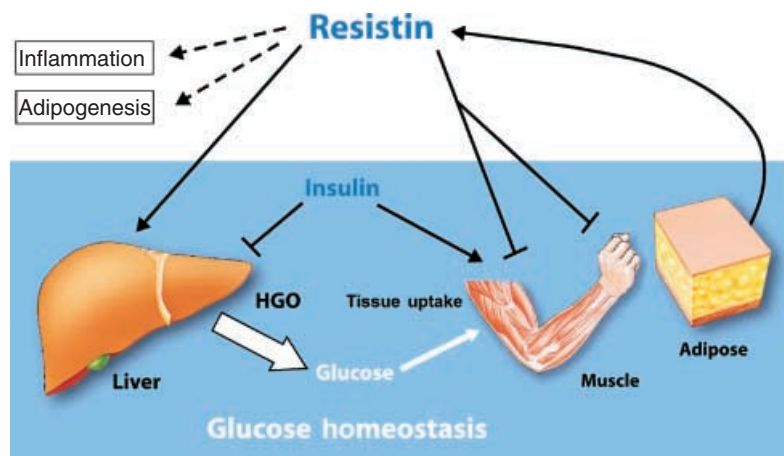
Resistin mRNA levels are significantly decreased by fasting and increased upon refeeding [1, 2, 4]. Resistin mRNA levels were also decreased in rats that were food restricted to 30% *ad libitum* [23]. Resistin mRNA levels show a negative correlation with plasma cholesterol levels suggesting that cholesterol is regulating resistin expression in human white adipose tissue [40]. However, in a recent study, serum resistin levels in human beings were not altered by total caloric intake or the macronutrient composition of diet [29]. On the whole, these studies raise the possibility that resistin play a role in sensing nutritional status and may be involved in the adaptive response to starvation.

#### *Potential central role of resistin*

Intracerebroventricular administration of neuropeptide Y (NPY) to mice increased resistin mRNA expression in white adipose tissue (WAT), suggesting that NPY might have a role in regulating resistin gene expression [41]. As the signalling components mediating resistin actions have yet to be identified, it will be of interest to determine whether resistin actions are mediated either centrally or peripherally or by both. Resistin gene expression was detected by reverse transcription polymerase chain reaction (RT-PCR) in the hypothalamus and cortex of the mouse brain [42], but the level is low and the role of resistin in the central nervous system remains to be determined.

#### **The role of resistin in adipogenesis**

Resistin mRNA and protein are both induced during 3T3-L1 adipogenesis [1, 2, 14]. Resistin inhibits adipogenesis in 3T3-L1 adipocytes [2]. No follow-up studies addressing the potential role of resistin in inhibiting adipogenesis have been published to date. It will be interesting to note whether human resistin possesses this same anti-adipogenic property as mouse resistin. Generation of mice that are null for resistin should conclusively determine whether



**Fig. 1** Physiological roles for murine resistin. Three roles for murine resistin have been postulated. Resistin has been demonstrated to impair glucose homeostasis and insulin action in the mouse. Resistin is able to antagonize the effects of insulin. This antagonism results in a decreased suppression of hepatic glucose output (HGO) and a decreased ability of skeletal muscle and adipose glucose output and a decreased ability of skeletal muscle and adipose to uptake glucose in response to insulin. Thus, the overall net effect of transient elevation of resistin levels in rodents is insulin resistance. Resistin has also been shown to inhibit adipogenesis *in vitro*. Resistin may also be playing a role in inflammation.

resistin is involved in the regulation of adipogenesis in rodents.

### The role of resistin in inflammation

Increased release and action of proinflammatory cytokines have been shown to account for insulin resistance in inflammation. Specifically, tumour necrosis factor alpha (TNF- $\alpha$ ) has been demonstrated to be elevated in insulin resistance and antagonize insulin action [5]. However, regulation of resistin by inflammatory stimuli is not supportive of a role of resistin in insulin resistance. Treatment of 3T3-L1 adipocytes with TNF- $\alpha$  downregulated resistin mRNA and protein levels [4, 15, 43] and interleukin-6 did not alter resistin expression [4]. Studies using another potent proinflammatory stimulus, lipopolysaccharide, have reported both up-regulation in rats and 3T3-L1 adipocytes [34] and downregulation [4] of resistin expression. Studies of resistin expression and serum levels in inflammatory responses should determine whether resistin has a direct role in mediating inflammation.

### Current status of resistin

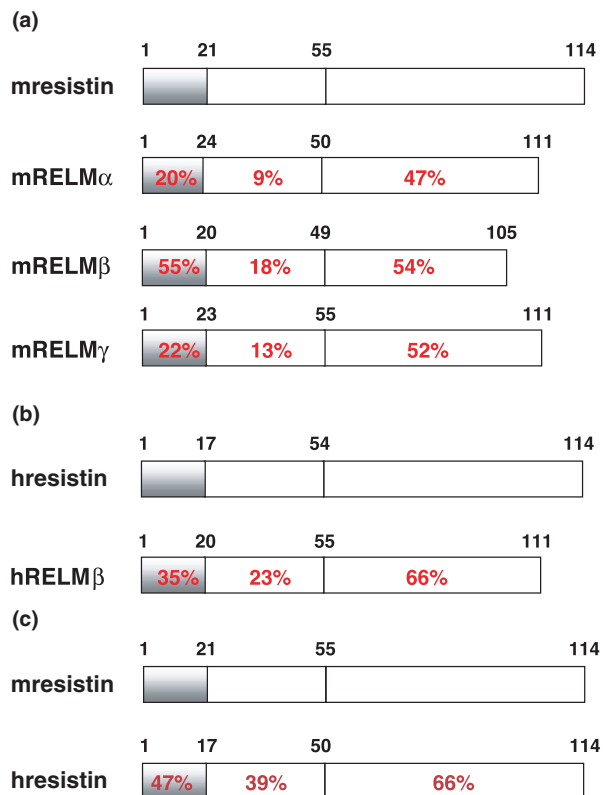
Three physiological roles have been proposed for resistin: a mediator of regulation of metabolism, a regulator of adipogenesis and a relationship to

inflammation (Fig. 1). It should be noted that these postulated roles are not mutually exclusive. Recently, Rajala *et al.* demonstrated that administration of resistin induced hepatic insulin resistance, supporting a role for resistin in glucose metabolism [38]. Future studies must expand on this and mechanisms of resistin action, as well as address the potential role of resistin in adipogenesis and/or in inflammation.

### Comparison of resistin in mice and human beings

Resistin is a member of a new gene family of small cysteine-rich secreted proteins. Resistin, resistin like molecule  $\alpha$  (RELM $\alpha$ ), RELM $\beta$  and RELM $\gamma$  comprise the gene family to date. Comparisons of the amino acid sequences for mouse and human resistin are illustrated in Fig. 2. Surprisingly, there are four genes encoding for the gene family in the mouse and only two identified in the completed human genome [44]. The significance of this observation may explain the apparent differences between mouse and human resistin.

Comparison of the human and mouse resistin mRNA demonstrates that they share 64.4% sequence homology; whereas, the genomic sequence has only 46.7% nucleotide identity [37]. Interestingly, the mouse genomic sequence is



**Fig. 2** (a) Comparison of murine resistin and the RELM family; (b) comparison of human resistin and hRELM $\beta$ ; (c) comparison of mouse and human resistin. Amino acid sequences for mouse and human resistin, and RELM family members were aligned and compared relative with mouse resistin (a, c) or human resistin (b). The overall amino acid sequence was analysed with respect to the signal sequence, variable region and C-terminal signature sequence as indicated.

approximately three times bigger than the human [37]. Alignment of the mouse and human genomic sequences clearly illustrates their diverse organization despite having the same number of introns in the coding region and conserved intron/exon boundaries [37]. The human resistin gene is localized to chromosome 19 and the mouse resistin gene to chromosome 8 which are syntenic regions, thus human *retn* is the orthologue of mouse *retn*.

Human and mouse resistin share 59% identity at the amino acid level (Fig. 2c). The source of circulating resistin in the mouse and human beings is drastically different. Mouse resistin is expressed predominantly in white adipose tissue; whereas, human resistin is expressed at significantly lower levels in adipocytes and in other tissues. A scan of a variety of human tissues by RT-qPCR determined human resistin to be expressed the highest in bone marrow followed by lung with almost undetectable levels in adipose tissue [36]. Consistent with these studies, human resistin mRNA has been detected in the nonfat cells of adipose depots [28] specifically in circulating mononuclear cells and not preadipocytes, endothelial or vascular smooth muscle cells [13, 45]. Additionally, human resistin has been detected in human placental tissue, mainly in trophoblastic cells [46].

Like its murine counterpart, resistin has been detected in human plasma [47]. The highest levels of murine resistin gene expression were found in

SNP/variant	Association	Reference
<b>Positive</b>		
SNP in 3' UTR (+62)	Type 2 diabetes and hypertension	[49]
ATG repeat in 3' UTR	Increased insulin sensitivity	[52]
Promoter region (-394C/G)	Insulin sensitivity in interaction with obesity	[53]
<b>Intronic SNP (191C/T)</b>		
5' flank variants (g. -537, g. -420)	Obesity	[54]
5' flank variant (+181G/A)	Interaction with obesity in conferring risk for type 2 diabetes	[55]
<b>Negative</b>		
Three intronic SNPs (-167C/T, +157C/T, +299G/A)	None with type 2 diabetes	[50]
Coding region (1326G/C)	None with obesity or type 2 diabetes	[51]
Promoter region (-420C/G)	None with polycystic ovary syndrome	[56]

**Table 1** Analysis of single nucleotide polymorphisms (SNPs)/variants with the human *retn* gene

Studies have been performed in which SNPs in the human *retn* gene were analysed for association with obesity and diabetes. These studies are summarized below as being either supportive (positive) for a role of resistin in obesity and/or diabetes or not (negative).

female gonadal fat [1]. Similarly, human serum levels of resistin were found to be higher in females than in males after correction for adiposity [29]. Whether this sexual dimorphism results from differences in body fat distribution or sex steroids is a matter of interest.

### Human genetic studies

Insulin resistance is generally a polygenic disorder, and resistin is an obvious candidate gene. A number of studies have searched for association of single nucleotide polymorphisms (SNPs) in the resistin gene with obesity and diabetes; to date, the results are complex without a clear answer. In a Chinese population consisting of 1102 type 2 diabetic subjects and 743 nondiabetic controls, an SNP at position +62 in the 3'-untranslated region (UTR) [48] was associated with type 2 diabetes and hypertension [49] (Table 1). By contrast, analysis of a Japanese population consisting of 99 controls and 99 type 2 diabetic subjects did not find any associations of three intronic SNPs with type 2 diabetes [50].

One coding region, SNP (G1326C) was examined in 198 obese subjects, 207 diabetic subjects and 186 control subjects within an Italian population study and determined to not be associated with obesity and diabetes [51]. Another Italian study analysing 203 nondiabetic subjects from Sicily and 456 nondiabetic subjects from Gargano identified an ATG repeat in the 3'-UTR of the human resistin gene that was associated with increased insulin sensitivity [52].

Resistin variants examined in a population with northern European ancestry consisting of 68 type 2 diabetic subjects, 61 controls with a family history of diabetes and 118 nondiabetic controls that were not associated with type 2 diabetes suggested an effect on insulin sensitivity in interaction with obesity amongst individuals predisposed for diabetes [53]. Similarly, two 5'-flanking variants were associated with obesity amongst French Canadians in Quebec with the effect being the strongest in nondiabetic subjects [54]. Accordingly, Ma *et al.* presented preliminary evidence that a resistin variant (+181) may interact with obesity in conferring risk of type 2 diabetes [55]. No association was found between an SNP in the promoter region (-420C/G) of the *retn* gene and polycystic ovary syndrome in a population of Caucasian origin [56].

Thus several, but by no means all, genetic analyses have suggested that polymorphisms at the resistin locus are associated with obesity and/or insulin sensitivity. Further studies that include measurements of serum levels in large populations will be required to better understand the potential involvement of resistin in the pathophysiology of obesity and diabetes in human beings.

### Conclusion

We are just beginning to explore the complex biology of resistin. Much more needs to be learned. Identification of the receptor for resistin will shed light on signalling pathways and target tissues by which resistin exerts its biological effects. Genetic mouse models in which resistin is chronically overexpressed or ablated will provide invaluable insight as to the role of resistin in normal physiology. Finally, as human and mouse resistin appear diverse, it will be even more crucial to determine whether the physiology of mouse resistin is pertinent to human beings.

### Conflict of interest statement

No conflict of interest was declared.

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### Note added in proof

Since this review was prepared, several additional studies have described correlations between resistin serum levels in humans and either type 2 diabetes or obesity [57–64].

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Correspondence: Mitchell A. Lazar MD, PhD, University of Pennsylvania School of Medicine, 611 CRB, 415 Curie Blvd., Philadelphia, PA 19104-6149, USA.  
(fax: (215) 898-5408; e-mail: lazar@mail.med.upenn.edu)