

Obesity, insulin resistance, and type 2 diabetes: the fat-muscle connection

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Type 2 diabetes mellitus (T2DM) and obesity are two global epidemics that show no signs of abating. The number of adults with impaired glucose tolerance (IGT) and T2DM is predicted to continue rising over the coming few decades. In children, in addition to the steady overall rise in rates of overweight, obesity, and T2DM, certain groups are identified as having a particularly high risk of developing IGT and T2DM. Considerable progress has been made in understanding the mechanisms in the development of IGT and T2DM; recently, this research has focused on organ interconnections and "cross-talk" among different tissues and cells in the body, and the role of these connections in mediating insulin resistance and T2DM. This issue of *Endocrinology Rounds* reviews current knowledge about adipocyte-myocyte interactions and their role in insulin resistance of obesity, and in the development of IGT and T2DM. Insulin signalling in cells is described and the mechanisms involved in developing adipocyte and myocyte insulin resistance are explained. Finally, the cytokines produced by both of these cell types and by recruited macrophages, acting to modulate cellular responses to insulin, are analyzed.

T2DM and obesity: two global epidemics

T2DM has reached global epidemic proportions with estimates that 4.4% of the population worldwide will be affected in the forthcoming 30 years.¹ The basis of this dramatic increase in T2DM is not completely understood, but it is accepted that nutritional overload and sedentary lifestyle along with genetic factors are important in this evolving crisis; in addition, multiple factors combine to trigger onset and progression. From an etiological viewpoint, insulin resistance and defective insulin secretion from pancreatic β -islet cells are the two key phenomena involved in the development of glucose intolerance and T2DM. Obesity is also rising at alarming rates worldwide, with developing nations rapidly approaching the rates in developed countries. In the pediatric population, the significant rise in rates of obesity are primarily related to sedentary lifestyle and diet. In addition, several pediatric groups are at greater risk of developing obesity and T2DM, including infants who are small or large for gestational age, premature infants, and infants of diabetic mothers. Recent investigations have demonstrated that infants of obese mothers have an increased risk of glucose intolerance.²⁻⁷ The complications of obesity are multiple and IGT and T2DM are significant complications that will have devastating global societal, economic, and individual burdens in all afflicted societies.

Evidence over the past few years reveals that interaction or "cross-talk" among cells of different organs is central to mediating insulin resistance and T2DM. Interactive cellular events over time are modified by multiple genetic, epigenetic, and environmental factors, eventually compromising insulin action and production; subsequently, when a critical threshold is reached, glucose intolerance and T2DM occur. Significant research efforts have focused on understanding insulin signalling in various tissues and how defects in this process lead to glucose intolerance.

Insulin-signalling pathways in adipose and muscle tissue

Insulin is an anabolic hormone with the major function of controlling energy homeostasis in the body. Insulin acts via multiple pathways on hepatic, muscle, and adipose tissues by signalling through the insulin receptor (Figure 1). Insulin binds to the receptor at the surface of hepatocytes, myocytes, and adipocytes, leading to tyrosine phosphorylation (ie, adding a phosphate group to tyrosine residues of a molecule) of insulin receptor substrates (IRS)-1 and IRS-2. Phosphorylation enables the recruitment of the p85 regulatory subunit of the



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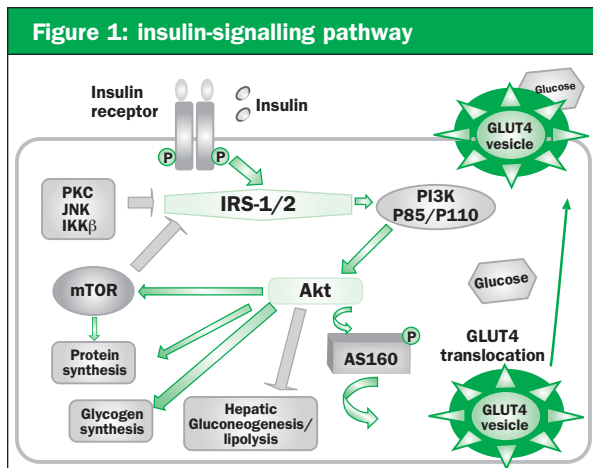
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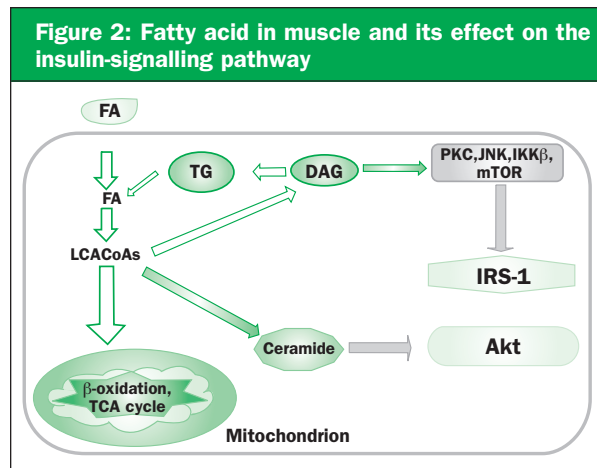
Binding of insulin to its receptor at the hepatocyte, myocyte, and adipocyte leads to tyrosine phosphorylation of insulin receptor substrates 1 and 2 (IRS-1/2). Phosphorylation (P) enables the recruitment of the p85 regulatory subunit of phosphatidylinositol 3 kinase (PI3K) with its associated catalytic p110 subunit, which thereby becomes activated. PI3K recruits and activates the kinase Akt. Akt regulates the insulin-dependent inhibition of gluconeogenesis and glucose output in the liver and inhibits lipolysis in adipose tissue. Akt is also important in protein synthesis and glycogen synthesis. In muscle and fat, Akt phosphorylates the protein AS160 and this step is essential to mobilize glucose transporter 4 (GLUT4) to cell membrane. Glucose is then readily taken up via GLUT4 into the cell. The mammalian target of rapamycin (mTOR) provides a feedback loop that regulates IRS-1/2 activity. When inflammatory pathways (PKC, JNK, IKK β) are activated, they interfere with insulin signalling.

JNK = Jun N-terminal kinase; IKK β = inhibitor of κ B kinase β ; PKC = protein kinase C; PI3K = phosphatidylinositol 3 kinase; P85/P110 = regulatory/catalytic subunits of PI3K.

phosphatidylinositol 3 kinase (PI3K) enzyme with its associated catalytic p110 subunit that then become activated. The product of this enzyme, phosphatidylinositol 3-phosphate (PIP₃), recruits and activates the kinase, Akt. In the liver, this pathway regulates the insulin-dependent inhibition of gluconeogenesis and glucose output. In muscle and fat, Akt phosphorylates the protein Akt substrate (AS160), an essential step in mobilizing glucose transporter 4 (GLUT4) to the cell membrane.⁸ Glucose is readily taken into the cell via GLUT4 and channeled into oxidative (energy generation) and nonoxidative (storage) pathways within the cell (Figure 1). Several mechanisms have been proposed that interfere with this process and lead to impaired glucose uptake and metabolism, thereby causing insulin resistance.

Adipose tissue changes with obesity leading to insulin resistance

Insulin resistance in adipose tissue, skeletal muscle, and liver is a preamble to the development of T2DM.⁹ Obesity is a major determinant of insulin resistance and the risk of insulin resistance and T2DM rises as body-mass index (BMI) increases, approaching certainty with BMI >40 kg/m².¹⁰ In animals and humans, adipose tissue (AT) is composed of multiple fat storage compartments distributed in subcutaneous and visceral depots.¹¹ White AT is the main fat-storage site and has an important role in storing energy excess from food in the form of fatty acids (FAs).¹² In obesity, increased AT mass, especially visceral adipose tissue, occurs through adipocyte hypertrophy and hyperplasia, and is associated with reduced



Fatty acids (FAs) enter cells via dedicated membrane transporters and become conjugated to long-chain acyl coenzyme A (LCACoAs). Normally, LCACoAs go into mitochondria and are recycled through beta-oxidation and tricarboxylic acid (TCA) cycle, or will be further metabolized to diacylglycerol (DAG) and ceramide in case of excess FA. Intermediate lipid metabolites such as DAG will either be used to synthesize triglycerides (TG), thus increasing intracellular TG levels and maintaining insulin sensitivity; if that does not take place, it will then activate proinflammatory pathways within the cells leading to interference with insulin signaling at level of IRS proteins. Ceramide interferes directly with insulin signalling at the level of Akt.

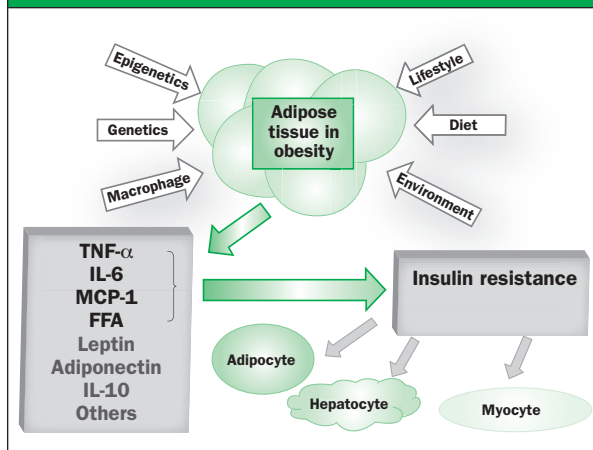
blood flow, reduced glucose and FA uptake, and increased lipolysis in both animals and humans.^{9,13,14}

Obesity-induced inflammation: adipose tissue attraction of macrophages and activation of inflammatory pathways

Sustained lipid overload in AT leads to a chronic low-grade inflammatory state through the production of proinflammatory cytokines (called adipokines), including the tumour necrosis factor- α (TNF- α) causing AT insulin resistance, as well as the monocyte chemoattractant protein-1 (MCP-1) that attracts macrophages to AT. These macrophages are subsequently activated to initiate a number of stress pathways, including the inhibitor of nuclear factor (NF)-kappa B (κ B) kinase- β -NF κ B (IKK β -NF κ B) and Jun N-terminal kinase-activator protein-1 (JNK-AP1) and, in turn, this activates macrophage TNF- α secretion. TNF- α reduces triglyceride (TG) synthesis and storage, and enhances lipolysis in adipocytes, resulting in increased free fatty acid (FFA) release.⁹ Hence, in the first step of obesity-induced insulin resistance, adipocytes are the target of an inflammatory process.

The continued production of cytokines raises their levels in the circulation, and along with the outpouring of FAs, cytokines contribute to the provocation of insulin resistance in muscle and liver. This is the second step in obesity-induced insulin resistance, and is the one that results in whole-body insulin resistance. The molecular mechanisms whereby cytokines and FAs cause insulin resistance in myocytes and hepatocytes are diverse, but most include reductions at various levels of the insulin-signalling cascade. In particular, circulating FFAs entering myocytes and hepatocytes are converted to TGs and ceramides that have inhibitory actions on IRS-1 and Akt, respectively (Figure 2). FAs also contribute to the activation of stress enzymes that alter gene expression and the

Figure 3: Effect of obesity on adipose tissue is mediated via genetic, epigenetic, lifestyle, and environmental factors



When macrophages arrive at adipose tissue, they become activated and produce more proinflammatory cytokines, which leads to insulin resistance. This in turn causes a reduction in amount or activity of other adipokines, which worsen insulin resistance.

TNF- α = Tumour necrosis factor- α ; IL = interleukin;
MCP-1 = monocyte chemoattractant protein-1; FFA = free fatty acid

redox status of a number of pathways, leading to mitochondrial compromise and loss of tissue oxidative capacity.

In mice fed a high-fat diet¹⁵ and in primary skeletal muscle cells from patients with T2DM,¹⁶ the above-described series of events affect a number of insulin responses: GLUT4 translocation and glucose uptake into muscle and fat; glucose output from liver; lipolysis curb in adipocytes; and fat oxidation in all 3 tissues.^{9,15-17} Skeletal muscle cells from obese individuals show reduced insulin-mediated glucose uptake *in vivo* with reductions in insulin signalling along the entire axis from IRS-1 to AS160.¹⁸ This appears to be largely an acquired element with weight gain, since cells from obese, insulin-resistant individuals when grown *in vitro* show no altered insulin response.¹⁹

To review the process, AT in obese individuals produces cytokines and factors that attract macrophages, producing more cytokines; these events render adipocytes insulin resistant, releasing FFAs into circulation. These FFAs and cytokines eventually reach the muscle and liver, where they instigate insulin resistance through metabolic and stress programs (Figure 3). Once whole-body insulin resistance develops, there is expanded demand on β -islet cells of the pancreas to counteract the insulin resistance; this is the third step that causes hyperinsulinemia. Eventually, a fourth step in the process, the exhaustion of β -cell secretory and survival capacities, is exacerbated through the negative effects of circulating FFAs and cytokines, and overt T2DM develops.

Skeletal muscle changes in obesity leading to insulin resistance

Skeletal muscle is the major site of dietary glucose disposal, and a major determinant of glycemia. In both human and animal studies, FFAs cause skeletal muscle insulin resistance by interfering with the insulin-signalling cascade from its initial steps.²⁰⁻²² This is mediated in part through the activation of protein kinases such as JNK,

IKK β , protein kinase C, mammalian target of rapamycin complex-1 (mTORC1), and p70 ribosomal S6 kinase (p70S6K), that phosphorylate various serine residues of IRS proteins and negatively regulate IRS function, as well as downstream insulin effects.²³⁻²⁶

Several factors contribute to the accumulation of fat in myocytes with obesity:

- increased FFA uptake through dedicated membrane transporters due to mass action
- FFA uptake mechanisms themselves may be upregulated
- the large mass of muscle provides a clearance mechanism of circulating lipids.

What is the fate of the FFAs entering muscle during obesity? A prevailing view has held that they are not properly shunted to mitochondria for full oxidation, due to the reduced biosynthesis of enzymes in this organelle and the reduced ability to activate the system that transports FFAs into the mitochondria. Both mitochondrial overload-associated toxicity (through oxidative radicals), as well as mitochondrial insufficiency (through reduced gene expression of its components) occur secondary to increased lipid and cytokine action, effectively lowering the muscle capacity for FA oxidation.^{27,28} It is possible that a combination of these mechanisms contribute to the accumulation of lipids and lipid products within the myocyte.

Intramyocyte lipid metabolites and muscle insulin resistance

A negative correlation between intramyocyte triglyceride [IMTG] content and insulin sensitivity has been reported; therefore, it is conceivable that preventing IMTG conversion to its intermediary metabolites may counteract muscle insulin resistance. Indeed, transgenic mice overexpressing enzymes that increase TG synthesis in muscle present the expected increase in IMTG and reduced lipid intermediary metabolites including long-chain fatty-acid coenzyme A (LCACoAs), ceramide, and diacylglycerol (DAG), as well as improved insulin sensitivity.²⁹

In obese T2DM patients on a weight-loss program with a low-calorie diet, magnetic resonance spectroscopy revealed that IMTG declined with increased insulin sensitivity. Further, interventions that lowered circulating FFAs but failed to change IMTG did not combat insulin resistance.³⁰ Nevertheless, IMTG is elevated in people who exercise and even limited physical activity improves insulin sensitivity;³¹ this indicates that while IMTG is a useful correlate of muscle lipid accumulation and muscle insulin resistance in some conditions, it is unlikely to be the responsible factor. Instead, intermediate products of lipid metabolism including LCACoAs, ceramide, and DAG may be the important factors mediating insulin resistance either directly or via activation of proinflammatory pathways in myocytes [Figure 2]. In fact, DAG is thought to act by reducing IRS-1 activity, while ceramide interferes with insulin signalling at the level of Akt.^{27,28} In summary, shunting the toxic intermediary lipid metabolites to TG synthesis appears to be a mechanism through which muscles are able to maintain insulin sensitivity in the face of elevated FA supplies.

AMP-activated protein kinase [AMPK] pathway: fuel guardian in muscle insulin resistance

FA oxidation is a major function of skeletal muscle, regulated by the enzyme adenosine monophosphate (AMP)-activated protein kinase (AMPK), which is activated in conditions requiring energy supply (eg, exercise), and in response to the adipokines, adiponectin and leptin. AMPK activation reduces the cellular levels of malonyl-CoA, the metabolite that inhibits the enzyme carnitine palmitoyltransferase-1 (CPT-1), which moves FAs into the mitochondria. By inhibiting the production of the inhibitor (malonyl-CoA), AMPK promotes CPT-1 function and shunts lipids from storage into oxidation.³² Although there are conflicting results about the dysregulation of AMPK contributing to lipid accumulation in muscle and insulin resistance, the beneficial actions of AMPK in FA oxidation are supported by many studies.³³ In addition to promoting FA oxidation, AMPK reduces ceramide synthesis, FA-induced activation of the NFκB inflammatory pathway, and mTOR activity in muscle. The latter is an intermediate in a low-level negative feedback loop for insulin signalling (Figure 1). By inhibiting mTOR, AMPK would be expected to remove the low-level inhibition of insulin action built into the signalling pathway, effectively improving insulin action.

Evidence from these studies suggests that lipid accumulation in muscle and impairment of FA oxidation by mitochondria are responsible for insulin resistance in obesity.³⁴ Recent work in rodents and myocyte cell cultures, however, question this conclusion by actually detecting elevated FA oxidation. In fact, excessive oxidative activity was found, as well as a reduction in organic acid intermediates of the tricarboxylic acid [TCA] cycle and a loss of the ability to switch to carbohydrate utilization during the fasted-to-fed transition. From these observations, it was proposed that FA overload in muscle mitochondria and increased oxidation lead to insulin resistance.²⁷

Adipokines and myokines in insulin resistance

One of the most important realizations of the last decade is that AT is an endocrine organ;³⁵ it secretes many cytokines termed “adipokines” that serve a wide variety of functions, including regulation of feeding behaviour, metabolism, energy homeostasis, and insulin sensitivity. Muscles also produce a set of cytokines termed “myokines” that affect multiple processes within muscle. Of particular interest are the adipokines and myokines that are produced by adipocytes or myocytes to regulate FA and TG metabolism; some of these peptides are exclusive to one or the other cell type, while others are produced by both. Two cytokines, leptin and adiponectin, are not discussed, since there are extensive reviews on the topic.^{34,36,37}

TNF-α: TNF-α is produced by adipocytes in obesity, leading to recruitment and activation of macrophages; subsequently, activated macrophages initiate the IKKβ-NF-κB and JNK-AP1 pathways, further enhancing the production of TNF-α, this time by the macrophages. One of the many actions of TNF-α on AT is the downregulation of peroxisome proliferator-activated receptor-γ [PPARγ], a major transcriptional regulator of adipogenesis. This action of TNF-α is mediated by activation of the NFκB pathway that also induces PPARγ mRNA degradation, and activates caspases that degrade the PPARγ protein. The loss of PPARγ impairs TG storage and increases lipolysis in the AT; it also increases circulating FFA and deposition of TG in muscle.^{9,38,39}

Elevated TNF-α levels are observed in skeletal muscle cells and in cultures of human and animal skeletal muscles with insulin resistance and T2DM. TNF-α acts via activation of apoptotic signals and activation of JNK and NFκB pathways; all of these impair key steps in the insulin-signalling pathway. By causing multiple serine phosphorylations, the tyrosine phosphorylation of IRS-1 by the insulin receptor is reduced, and additionally, IRS-1 is degraded. Both actions effectively reduce signalling to PI3K and Akt. TNF-α also reduces phosphorylation of Akt and this causes a reduction in AS160 phosphorylation and insulin-stimulated glucose uptake in muscle. In addition, TNF-α suppresses the AMPK pathway leading to a reduction in FA oxidation in muscle and a rise in DAG.

Interleukin (IL)-6: IL-6 is produced by adipocytes and myocytes and levels are increased in insulin resistance and T2DM. Although at first glance its role in insulin signalling in myocytes is contentious, with studies demonstrating insulin resistance in obese T2DM patients⁴⁰ and increased insulin sensitivity following IL-6 treatment,^{41,42} it appears that IL-6 can provoke insulin resistance in liver and AT, but cause insulin sensitivity in muscle. The balance of such actions may differ depending on the concentrations and duration of exposure to the cytokine, but some differences between mice and humans are also apparent. Further, muscles release large amounts of IL-6 during exercise, suggesting a role in maintaining glucose homeostasis with exercise and possible effects on exercise-induced lipolysis.⁴³ Indeed, human muscle-cell cultures exposed to IL-6 show improved insulin signalling and glucose uptake.⁴⁴ Supporting these data, transgenic mice over-expressing IL-6 are protected from high-fat diet-induced obesity and insulin resistance.³⁸ However, some studies have reported adverse effects of IL-6; for example, one study reported that acute treatment with IL-6 reduced mouse skeletal muscle glucose uptake and increased acyl Co-A levels.⁴⁵ In another study, IL-6 recruited IRS-1 to IL-6 receptors in cultures of skeletal muscle and transiently induced IRS-1 serine phosphorylation, resulting in IRS-1 ubiquitination (degradation) in muscles.⁴⁶ As a result, the tissue

action and whole-body consequences of elevated IL-6 require further examination, taking into account the dynamics of IL-6 in the circulation.

IL-10: IL-10 is an anti-inflammatory cytokine that also reduces insulin resistance in skeletal muscle and liver. In lean mice, it is expressed and secreted by muscle and AT macrophages, and protects adipocytes from TNF- α -induced insulin resistance.⁴⁶ IL-10 also protects against hepatic steatosis in mice. When used in conjunction with IL-6, IL-10 prevents IL-6-induced defects in insulin action and hepatic insulin signalling.⁴⁵

IL-15: IL-15, like IL-10, has positive actions on glucose homeostasis. It is expressed in skeletal muscle and has anabolic effects on skeletal muscle protein dynamics both *in vivo* and *in vitro*; accordingly, this myokine plays a role in weight control and insulin sensitivity. IL-15 inhibits white AT deposition when administered to rats and mice; it also increases GLUT4 expression and glucose uptake in C2C12 mouse muscle cells in culture. IL-15 administration inhibits lipid accumulation and stimulates secretion of adiponectin by 3T3-L1 murine adipocytes in cell culture. In summary, IL-15 functions to enhance communication between muscle and adipose tissue, which modulates body fat distribution and insulin sensitivity.^{38,47}

IL-1 and IL-1 receptor antagonist (IL-1Ra): IL-1Ra is an anti-inflammatory cytokine that antagonizes the binding of the proinflammatory cytokine IL-1 to its receptor. In a recent clinical trial in patients with T2DM, the blockade of IL-1 with the recombinant peptide IL-1Ra improved glycemia, reduced HbA_{1c}, enhanced beta-cell secretory functions, and reduced markers of systemic inflammation.⁴⁸ Previous observations have documented that circulating IL-1Ra levels are chronically and markedly elevated in obese patients. In rodents, basal glycemia and insulinemia were similar in control rats and animals injected with recombinant human IL-1Ra; however, the glucose infusion rate needed to maintain stable glycemia during the euglycemic-hyperinsulinemic clamps was significantly decreased, suggesting that excess IL-1Ra reduced the sensitivity of peripheral tissues to insulin.⁴⁹

Monocyte chemoattractant protein-1 (MCP-1): The chemokine MCP-1 is produced by adipocytes and myocytes; it is one of the most important attractants of inflammatory cells to AT and, potentially, to muscle. Large adipocytes secrete immense quantities of MCP-1, attracting macrophages to AT in both mice and humans and this increased macrophage population in AT secretes more proinflammatory cytokines, as previously described. Macrophage-derived cytokines disrupt adipocyte function leading to increased lipolysis and reduced adipogenesis.⁵⁰⁻⁵² Recent studies in mice, however, suggest that additional macrophage chemoattractants are released by AT, since at least in MCP-1^{-/-} mice (MCP-1 deficient), macrophages continued to colonize the AT.⁵³

Concluding remarks and perspectives

In obesity, the interactions between multiple cells and their products mediate a state of insulin resistance and result in IGT and T2DM. The adipocytes in obesity are not only larger and more numerous, but also demonstrate a more robust metabolic profile indicative of insulin resistance, with secretion of multiple proinflammatory cytokines, leading to low-grade inflammation in AT. In turn, this attracts macrophages to AT that further secrete proinflammatory cytokines and together disrupt lipogenesis and increase lipolysis in AT. This leads to an increase in circulating FAs that deposit in muscle tissue, triggering muscle insulin resistance through diverse lipid metabolites that have an impact on insulin-derived signals. Future research should focus on further understanding the mechanistic details through which these cells interact with each other, with other tissues and organs (eg, liver, brain), and the process that leads to insulin resistance. This may also help in developing preventive and therapeutic strategies to combat the T2DM epidemic.

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