**Necroptosis**

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As early as the mid-19th century, Rudolf Virchow taught that necrosis is a recognizable form of cell death; since then, pathologists have identified necrosis as both a cause and a consequence of disease. A century later, another form of cell death, apoptosis, was defined, and we now understand that this process is driven by a set of molecular mechanisms that “programs” the cell to die. It has often been assumed that necrosis is distinct from apoptosis, in part because of the belief that necrosis is not programmed by molecular events. It is now clear, however, that in some contexts, necrotic cell death can be driven by defined molecular pathways. Here, we discuss one such process, a type of necrotic cell death called “necroptosis,” and its role in disease (see Glossary). Although some investigators have used this term to refer to any form of active necrosis, we follow recent recommendations, using it to denote necrotic cell death dependent on receptor-interacting protein kinase 3 (RIPK3) (Fig. 1). With our understanding of the molecular basis of necroptosis and other forms of regulated necrosis, along with the availability of inhibitors of some forms of necrosis (including necroptosis), a neglected therapeutic option emerges: it is possible to therapeutically interfere with necrosis.

Although necroptosis may have evolved as a line of defense against intracellular infection, recent studies implicate it in a variety of disease states. Necroptosis is of central pathophysiological relevance in myocardial infarction and stroke, atherosclerosis, ischemia–reperfusion injury, inflammatory bowel diseases, and a number of other common clinical disorders. At the molecular level, intracellular assembly of a highly regulated complex, the necrosome, can be triggered by death receptors (e.g., tumor necrosis factor [TNF] receptor 1 [TNFR1]), by cell-surface toll-like receptors, and probably by other signals.

**Induction of Necroptosis**

Apoptotic cell death involves the engagement of pathways that lead to the activation of caspase proteases, which ultimately cause the morphologic features of this type of cell death. In contrast, necroptosis was first recognized as a caspase-independent form of cell death that can be triggered by treatment with TNF only in the presence of a pan-caspase inhibitor, such as zVAD fluoromethyl ketone. Before that time, we understood that TNF causes apoptosis through the induction of protein interactions that result in the activation of caspase 8; however, necroptosis requires that the function of caspase 8 be inhibited or disrupted. Several of the upstream signaling elements of apoptosis and necroptosis are shared, and sensitivity to each death pathway is regulated (sometimes in opposing ways) by an overlapping cluster of regulatory molecules, such as FLIP, the deubiquitinases A20 and cIAP1 and cIAP2, and the cellular inhibitors of apoptosis proteins cIAP1 and cIAP2.

Other death receptors and toll-like receptors were shown to induce necro-
tosis, and intracellular triggers of necroptosis, such as DAI\textsuperscript{23} and protein kinase R,\textsuperscript{30} were subsequently identified (Fig. 2). TNFR1 ligation by TNF induces signaling through the nuclear factor κB (NF-κB) pathway that involves the polyubiquitination of receptor-interacting protein kinase 1 (RIPK1) and of NF-κB essential modulator (NEMO).\textsuperscript{31} On deubiquitination of the K63 and linear ubiquitin chains of RIPK1 by deubiquitinases,\textsuperscript{32,33} RIPK1 loses its default prosurvival function and promotes cell death. Ligated TNFR1 recruits the adapter protein TNF-receptor–associated death domain (TRADD) to associate with the adapter Fas-associated death domain (FADD),\textsuperscript{34} which then binds to procaspase 8, a protease that is autocatalytically activated on homodimer formation. Conversely, FLIP, a protein that is structurally related to caspase 8 but has no protease activity, forms a heterodimer with caspase 8, and the heterodimer prevents caspase 8–mediated apoptosis and mediates the anti-necroptotic properties of caspase 8.

Mitochondrial permeability transition: A common increase in permeability of both the inner and outer mitochondrial membrane, which may result in mitochondrial swelling, production of reactive oxygen species, nicotinamide adenine dinucleotide depletion, and subsequent necrotic cell death. Necroptosis occurs independently of mitochondrial permeability transition.

MLKL (mixed lineage kinase domain–like): A pseudokinase that is phosphorylated by RIPK3 and has a causal role in necroptosis.

Necroptosis: RIPK3-dependent regulated necrosis.

Necrosome: Supramolecular complex that consists of RIPK3 and other cell death–mediating molecules, such as RIPK1, dependent on the necroptotic trigger.

Receptor-interacting protein kinase 1 (RIPK1): One of the upstream triggers of the necrosome.

Receptor-interacting protein kinase 3 (RIPK3): The key molecule in necroptotic cell death.

RHIM (receptor-interacting protein homotypic interacting motif): A protein domain that is typically involved in necroptosis and that is found in DAI, TRIF, RIPK1, and RIPK3. The RHIM domain therefore plays a role in virus recognition and allows RIPK3 to interact with DAI, TRIF, and RIPK1, its upstream partners in the necroptotic pathway.


TUNEL (terminal deoxynucleotidyl transferase dUTP biotin nick end labeling): An assay for the detection of DNA double-strand breaks, such as those that occur during apoptosis. Although TUNEL staining is often used as an assay for apoptosis, it can also be used to detect cells that have died by other mechanisms, especially in vivo.

mice results in embryonic death on day 10.5; embryonic death is prevented if the deletion is applied to mice that are already deficient in Ripk3. Tissue-specific deletion of Fadd or caspase 8 also causes disease (depending on the type of tissue) that involves cell death, and this is also prevented by ablation of Ripk3. Therefore, it appears that a critical function of the FADD–caspase 8–FLIP complex is the prevention of RIPK3-mediated necrotic cell death (although alternative interpretations are discussed below).

It is on this basis that we have defined necroptosis as a form of regulated necrosis that follows an intracellular signaling cascade dependent on RIPK3. However, the downstream mediators in the necrotic pathway are incompletely understood, although it is tempting to speculate that plasma-membrane channels are involved in the rapid swelling of necrototic cells that results in plasma-membrane rupture.

Unlike apoptosis, in which several of the highly immunogenic intracellular proteins are sequestered in the dead cell, necroptosis is a strong trigger of innate and adaptive immune responses. But why would immunogenic cell death be preserved in higher organisms? The answer may involve the recognition of and response to microbes. RIPK3 can interact with other proteins through a RHIM domain, which is present in both RIPK1 and RIPK3. To date, only four known RHIM-containing proteins — RIPK1, RIPK3, DAI, and TRIF — have been identified in the human genome (although this may be a function of our limited ability to recognize this motif). TRIF is capable of triggering necroptosis after ligation of toll-like receptors 3 and 4, and DAI integrates viral signals into the necroptotic pathway.

Indeed, infection with vaccinia virus, which expresses a viral caspase inhibitor, was found to be lethal in Ripk3-deficient mice but not in wild-type mice. Several viruses and intracellular bacteria express proteins that interfere with the activation of caspase 8, sensitizing cells to necroptosis.

We can therefore hypothesize that necroptosis provides higher vertebrates with a defense mechanism against such intracellular invaders, and this hypothesis is further supported by the identification of viral inhibitors of necroptosis. Similarly, loss of FLIP leads to cell death by both apoptosis and necroptosis. Because FLIP undergoes rapid protein turnover and is expressed in response to NF-κB activation, anything that blocks protein synthesis or interferes with NF-κB might sensitize cells to die. Regu-
Figure 2. Activators of the Necrosome as Therapeutic Targets.

Various stimuli lead to activation of the supramolecular necroptosis-inducing complex, referred to as the necrosome. Initially, studies of necroptosis used models of death-receptor stimulation in the presence of caspase inhibition (not shown). The intracellular adapter molecules Fas-associated death domain (FADD) and TNF-receptor–associated death domain (TRADD) recruit receptor-interacting protein kinase 1 (RIPK1), which subsequently undergoes an incompletely understood series of ubiquitination, deubiquitination, and phosphorylation (P) events before exposing its RHIM domain to recruit RIPK3. RIPK1, RIPK3, and MLKL are phosphorylated during the assembly of the necrosome. Within the human genome, RIPK1, RIPK3, and two other proteins have RHIM domains. One of these is TRIF, an intracellular signal transducer that is capable of activating the necrosome downstream of toll-like receptors (TLRs), which are triggered by microbial molecules. The fourth RHIM-domain protein, DAI, integrates signals from viral RNA sensors into the necrosome. Finally, viral infection is accompanied by production of interferon (IFN), triggering new protein kinase R (PKR) synthesis that is dependent on Janus kinase (JAK) and signal transducer and activator of transcription (STAT); PKR phosphorylates FADD, which in turn directly interacts with RIPK1, inducing necrosome formation. Death-receptor–mediated necroptosis involves deubiquitination of RIPK1, the kinase domain of which is targeted by necrostatin 1. Second-generation RIPK1 inhibitors, such as necrostatin 1s, a stable version of necrostatin 1 that is more potent at lower concentrations, might have less severe side effects. Necrosulfonamide inhibits MLKL and prevents the activity of the necrosome in human cells. In addition, RIPK3 inhibitors, death-receptor antagonists, and plasma-membrane channel blockers might be attractive therapeutic targets.
lulation of the necrototic pathway by proteins such as acid sphingomyelinase\(^\text{48}\) and the mitochondrial phosphatase phosphoglycerate mutase \(^\text{540}\) may also contribute to the control of this process under a variety of conditions, but further evidence of their involvement is needed. Although the necrototic pathway in humans may be beneficial in providing a defense against some infections, this process may have harmful effects in a number of pathologic states.

### Contribution of Necroptosis to Pathophysiological Processes

The development of the RIPK1 inhibitor necrostatin 1 (a compound that was later found to be identical to a previously reported indoleamine 2,3-dioxygenase inhibitor\(^\text{49}\)) has stimulated research on necroptosis. The activity of this agent was taken as evidence supporting a role of necroptosis in neurologic disorders (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and the first disease model in which the role of necroptosis was investigated was ischemic brain injury.\(^\text{50}\)

Neuronal tissue is also associated with necrostatin 1–inhibitable cell death in clinically related models of brain damage, including controlled cortical impact\(^\text{51}\) and neonatal hypoxia–ischemia, in which necrostatin 1 was found not only to provide protection from oxidative damage but also to prevent the subsequent debilitating immune-cell infiltration.\(^\text{52,53}\) Necroptosis has been observed in microglia treated with caspase inhibitors,\(^\text{54}\) and this mechanism was interpreted as a strategy for preserving neurons; however, detailed mechanisms in vivo are not understood. Necrotic cell death is also a hallmark of retinal detachment\(^\text{55}\) and retinal ischemic cell death,\(^\text{56}\) and it has been suggested that in this specialized compartment, apoptosis and necroptosis are triggered simultaneously.\(^\text{55}\) More recently, it was proposed that cones, but not rods, undergo necroptosis in a genetic model of retinitis pigmentosa.\(^\text{57}\) These findings provided preliminary support for the concept that apoptosis and necroptosis are not mutually exclusive programs and may occur in the same organ.

Several independent studies have related the effects of necrostatin 1 to genetic ablation of Ripk3 in mouse models of ischemic organ damage and ischemia–reperfusion injury in the heart and the kidney (Table S1 in the Supplementary Appendix). Necrostatin 1 was found to have a striking protective effect in models of brain ischemia;\(^\text{50}\) its effect in the prevention of cardiac remodeling after myocardial infarction\(^\text{12}\) and the prevention of myocardial\(^\text{9}\) and renal\(^\text{11}\) ischemia–reperfusion injury was marked but not as pronounced. Administration of necrostatin 1 in mice 30 minutes after reperfusion did not provide protection from kidney ischemia–reperfusion injury,\(^\text{11}\) suggesting the presence of off-target effects of necrostatin 1, a rapid assembly of the necrosome, or another role for Ripk1 in endothelial cells of peritubular capillaries. The last of these might be of particular interest, because necroptosis has not been observed in primary kidney cells, neurons, retinal cells, or cardiomyocytes. Nevertheless, Ripk3-deficient mice are protected from ischemia–reperfusion injury, and treatment of Ripk3-deficient mice with necrostatin 1 does not provide further protection.\(^\text{58}\) Changes in parenchymal blood flow might explain the benefit of blocking necroptosis in models of ischemia–reperfusion injury, because necrostatin 1 may influence capillary diameters.\(^\text{59}\) It has been demonstrated that glomerular endothelial cells, in contrast to renal tubular cells, mesangial cells, and podocytes, express high levels of Ripk3,\(^\text{11}\) which may correlate with the likelihood that cells will undergo necroptosis on death-receptor ligation.\(^\text{2}\) It will be of interest to determine whether the involvement of the necroptotic pathway in ischemia–reperfusion injury can be confirmed in Mlkl-deficient mice.\(^\text{13}\) Ultimately, it will be important to develop tissue-specific Ripk3 or Mlkl deletion models to identify the tissues that are most relevant to the role of necroptosis in ischemia–reperfusion injury.

Necroptosis may also be associated with disorders of the skin and intestinal epithelium. A Ripk3-dependent dermal chronic inflammatory phenotype results from conditional deletion of Fadd\(^\text{60}\) or caspase 8\(^\text{61}\) from keratinocytes in mice, a phenomenon that is partially prevented when the cells are also Tnfr1 deficient.\(^\text{60}\) Although other dermatologic disorders have not yet been linked with necroptosis, it is tempting to speculate that regulated necrosis triggers skin infections, such as atopic dermatitis. Apart from atopic
dermatitis, chronic proliferative dermatitis was described in mice with a deficiency of the Ripk1 regulator Sharpin,62 a component of the linear ubiquitin chain–assembly complex, and the dermatitis was prevented when Sharpin deficiency was combined with Tnfr1 deficiency.31 However, it is not yet clear how Ripk3-dependent necroptosis is involved in this inflammatory reaction.

As with epithelial cells of the skin, specific depletion of caspase 8 or Fadd from intestinal epithelium results in spontaneous necroptosis and pathologic changes that are morphologically similar to those seen in inflammatory bowel diseases, especially Crohn’s disease14,15 (Table S1 in the Supplementary Appendix). In contrast, crossing mice that had Fadd or caspase 8 depletion in the intestinal epithelium with Ripk3-deficient mice completely prevented these pathologic changes. Similarly, ablation of the Ripk1 deubiquitinase A20 sensitizes mice to lethal colitis, and this effect is associated with TUNEL-positive Tnf-mediated death of the intestinal epithelial cells.14,15 Although this cell death has been interpreted as apoptosis, it remains possible that necroptosis is involved. Mechanistically, these inflammatory conditions may be due to the high immunogenicity of necrotic cells, the loss of barrier function that occurs on such cell death, or both.45 In contrast to Crohn’s disease, which is characterized by chronic inflammation, necrotizing pancreatitis is clinically characterized by acute inflammation. The preclinical model of pancreatitis induced by ceruleotide (formerly cerulein) was the first description of necroptosis in the gastrointestinal tract.2,4 Because necrotizing pancreatitis is a devastating disorder for which conventional treatment is limited to intensive care and the administration of fluids and anesthetics, the potential to interfere with necroptosis has raised hopes for therapy. However, whereas marked protection from ceruleotide-induced pancreatitis was seen in Ripk3−/− mice,2,4 necrostatin 1 administration increased serum lipase and amylase levels as well as histologic damage scores.63 Recently, Mlk1−/− mice were reported to be protected from ceruleotide-induced pancreatitis,13 yet another finding that sustains the debate about treatment strategies. A possible explanation for this recent finding is the short half-life of necrostatin 1, and studies of second-generation RIPK1 inhibitors or MLKL inhibitors are expected to clarify this issue.

**NECROPTOSIS IN SOLID-ORGAN TRANSPLANTATION**

One clinical situation in which interference with necroptosis is predicted to have therapeutic relevance is solid-organ transplantation. Damage-associated molecular patterns (DAMPs) are released from necrotic cells and trigger a strong immune response.45,64 It is conceivable that DAMPs, by their ability to activate both innate and adaptive immunity, promote many of the harmful immunologic responses observed in solid-organ transplantation; interference with necroptosis might be beneficial because the prevention of necrotic cell death minimizes the loss of functional parenchymal cells in the transplanted organ and minimizes the release of DAMPs, which would reduce proinflammatory responses that activate rejection pathways. In support of this concept, a recent study showed protection of Ripk3-deficient kidneys in a mouse model of allotransplantation, with a strong survival benefit.65 In that model, inhibition of caspase 8 by small interfering RNA up-regulated necroptosis and reduced renal allograft survival, whereas in comparison with kidneys from wild-type mice, Ripk3-deficient allografts had better function and longer rejection-free survival.65 These experiments might be relevant to clinical transplantation, pointing the way toward use of machine perfusion systems to saturate donor organs with necroptosis-inhibiting drugs as a potential strategy for preventing organ rejection before implantation. However, a protective effect of necrostatin 1 or its derivatives has not been analyzed thus far in a transplantation model, and blockade of necroptosis may have side effects in patients who are receiving immunosuppressive therapy after undergoing transplantation, since they are susceptible to viral infection — for example, cytomegalovirus infection46 — even without blockade of necroptosis. Nevertheless, the potential to inhibit necroptosis will probably have an effect on organ transplantation.67 Further investigations are needed before clinical trials can begin to specifically target necroptosis and to elucidate the mechanisms by which RIPK3 deficiency benefits transplanted organs. Given the protection from ischemia–reperfusion injury that is also conferred by RIPK3 deficiency, it will be important to clearly separate primary cell death from secondary organ damage mediated by infiltrating immune cells.45 Conventional clinical strategies are focused exclusively on the latter.
**BALANCE BETWEEN NECROPTOSIS AND INFLAMMATION**

TNF-shock models have suggested that Ripk1 and Ripk3 may be involved in Tnf-induced signaling in endothelial cells (Table S1 in the Supplementary Appendix). In vivo intravenous injection of Tnf causes Tnfr1-dependent apoptotic detachment of enterocytes and kills mice within 48 hours.\(^{63-68}\) Addition of the pan-caspase inhibitor zVAD-fluoromethyl ketone does not have a protective effect; in fact, it accelerates the lethal effects in this model, referred to as hyperacute Tnf shock; all mice die within 24 hours. Ripk3 deficiency provides partial protection from hyperacute Tnf shock.\(^{63-69}\) The hyperacute Tnf-shock model does not accurately mimic sepsis; the more widely used sepsis model is that of cecal ligation and puncture.\(^{70}\) However, whereas one study showed that necrostatin 1 was protective in the cecal ligation and puncture model,\(^{69}\) others showed that necrostatin 1 further accelerated the time to death in the hyperacute Tnf-shock model.\(^{63,71}\) and mice deficient in Ripk3 or Mlkl appear to have no benefit in the cecal ligation and puncture model.\(^{13,63}\) The role of necroptosis in sepsis therefore remains an open question.

The involvement of RIPK3 in pathophysiological processes is not an unequivocal demonstration of a role for necroptosis, even if our definition of the term is used. RIPK3 activation and its regulation by RIPK1 and the FADD–caspase 8–FLIP complex may have direct inflammatory effects that are independent of necroptotic cell death. It has been suggested that activation of RIPK3 directly participates in inflammation mediated by the DNA sensor retinoic acid–inducible gene 1 (RIG-I)\(^{72}\) and by the NLRP3 inflammasome.\(^{39}\) At present, it is not possible to formally separate such putative effects from those of necroptosis and the release of DAMPs, especially since in at least one case, the proinflammatory effect was observed to also depend on MLKL.\(^{39}\) Ultimately, determination of the direct contribution of RIPK3 to inflammation versus its indirect contribution through necroptosis may have to await elucidation of the final effector mechanism in necroptosis. Therefore, although we believe that the effects of RIPK1 inhibition and RIPK3 ablation in pathophysiological contexts are most likely due to effects on necroptosis, we recognize that alternative explanations are possible. Nevertheless, this distinction may ultimately be irrelevant to clinicians, because interference with RIPK3 activation, function, or both is likely to have therapeutic benefits regardless of the ultimate pathologic mechanism. It is in this context that we continue our discussion of therapeutic intervention.

**THERAPEUTIC STRATEGIES FOR THE PREVENTION OF NECROPTOTIC DISEASES**

In theory, interference with necroptosis is possible at the levels of the receptor, RIPK1, RIPK3, MLKL, the assembly of the necosome, and undefined intermediate and downstream mechanisms (Fig. 2) that may ultimately lead to cellular swelling and plasma-membrane rupture. With these targets only recently recognized, the major focus has been on necrostatin 1. Because of the outstanding specificity of necrostatin 1 to RIPK1,\(^{73}\) some authors have referred to the inhibition by necrostatin 1 as a definition of necroptosis.\(^{21}\) As the structural interaction of necrostatin 1 with the RIPK1 kinase domain has been elucidated,\(^{74}\) novel interpretations of the inhibition of necroptosis by necrostatin 1 have emerged. Ripk1-deficient mice die perinatally,\(^{75}\) and it remains formally possible that RIPK1 acts as an inhibitor of necroptosis unless its kinase activity is engaged and that necrostatin 1 might stabilize RIPK1 in its inhibitory state.

Apparently, there are effects of necrostatin 1 that are not related to cell death,\(^{59}\) and drawbacks regarding the clinical applicability of necrostatin 1 have been reported, because it appears to accelerate death in some models in which RIPK3 ablation is beneficial (discussed above). Fortunately, second-generation RIPK1 kinase inhibitors with higher affinity and specificity, such as necrostatin 1s, have been identified,\(^{74}\) and the acceleration of disease progression was not observed when necrostatin 1s was used as treatment for Tnf shock in mice.\(^{71}\) Further studies in other models are expected to clarify the mechanisms of this dichotomy.

Another attractive treatment approach emerged from studies of a direct inhibitor of human MLKL, necrosulfonamide.\(^{36}\) Although the clinical application of necrosulfonamide will depend on further analysis of its specificity and pharmacokinetic properties, its activity provides evidence that MLKL may serve as a drug target in principle. RIPK3 inhibitors may also have therapeutic poten-
Apart from necroptosis, other pathways of regulated necrosis have been identified, but only a few of these have been mechanistically separated from the necroptotic core machinery. Mitochondrial permeability transition is a process that induces necrotic cell death dependent on the mitochondrial matrix protein cyclophilin D, an intracellular target of cyclosporine. Mice deficient in cyclophilin D are partially protected from ischemia–reperfusion injury in various organs, and cyclosporine has been shown to prevent ischemic myocardial organ damage in humans.\textsuperscript{78} Although recent studies in zebra fish suggest that cyclophilin D might be a downstream target of the necrosome,\textsuperscript{48} mitochondrial permeability transition and necroptosis are now clearly understood to be separate pathways—as demonstrated, for example, by studies of ischemia–reperfusion injury in mice deficient in both cyclophilin D and Ripk3.\textsuperscript{58} Therapeutically targeting these two pathways of regulated necrosis with the use of combination therapy (Fig. 3) has resulted in strong additive protection from ischemia–reperfusion injury in initial experiments,\textsuperscript{58} and future strategies to inhibit regulated necrosis might best be based on interference with multiple pathways.

Undoubtedly, cyclosporine has revolutionized solid-organ transplantation and has been widely accepted because of its immunosuppressive properties. However, studies of isolated mitochondria clearly show that cyclosporine prevents mitochondrial permeability transition.\textsuperscript{58,79-81} The immunosuppressive capacity of cyclosporine, when administered after reperfusion, is clearly less potent than other immunosuppressive agents, such as tacrolimus, sirolimus, and mycophenolate mofetil.\textsuperscript{82} However, with the exception of tacrolimus,\textsuperscript{83} none of these compounds prevented graft loss as effectively as cyclosporine in clinical trials.\textsuperscript{84} One might therefore speculate that clinicians have already been exploiting the capacity of cyclosporine to block mitochondrial permeability transition as a means of reducing the inflammatory response and regulated necrosis and thus improving overall graft survival. Taken together, studies of cyclosporine indicate that regulated necrotic cell death—that is, necroptosis, mitochondrial permeability transi-
necroptosis

Necroptosis, or both — occurs in solid-organ transplantation, rendering this clinical field an ideal area for further investigations of the clinical potential of preventing necrosis.

Semantically, it is important to understand “regulated necrosis” as an umbrella term that encompasses mitochondrial permeability transition, necroptosis (Fig. 1), and other pathways that have been identified, such as ferroptosis, pyroptosis, PARP1-mediated regulated necrosis, NADPH-oxidase–mediated regulated necrosis, and lysosomal membrane permeabilization. However, it is not clear to what extent these pathways of necrosis are distinct, non-overlapping cell-death programs. Specific biomarkers must be identified in order to unravel them. The continuing elucidation of the molecular subroutines of various forms of regulated necrosis, including necroptosis, and the efficient design of combination therapies hold promise for our ability to control regulated necrosis in clinical settings.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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