APOPTOSIS AND DISEASE: 
Regulation and Clinical Relevance of Programmed Cell Death

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KEY WORDS: homeostasis, Bcl-2, interleukin-1β converting enzymes, tumor necrosis factor receptors, inhibitor of apoptosis

ABSTRACT
Regulation of the homeostatic balance between cell proliferation and cell death is essential for development and maintenance of multicellular organisms. Physiologic, or programmed, cell death is dependent on a genetically encoded and evolutionarily conserved pathway that induces a form of cellular suicide known as apoptosis. In the past decade, it has become clear that the regulatory mechanisms controlling programmed cell death are as fundamental, and as complex, as those regulating cell proliferation. Perturbation of the signaling cascades regulating apoptosis, whether by extracellular triggers, acquired or germline genetic mutations, or viral mimicry of signaling molecules, can result in a wide variety of human diseases. Analysis of these regulatory pathways has led to a better understanding of the etiology and pathogenesis of many human diseases, notably cancers, infectious diseases including AIDS, autoimmune diseases, and neurodegenerative/neurodevelopmental diseases. Our understanding of the regulation of programmed cell death in health and disease is far from complete, and the challenge of converting that understanding into new therapeutic modalities has only begun to be approached.

Introduction
The study of programmed cell death, or apoptosis, has emerged from relative obscurity to become a major focus of research interest in many areas of
medicine in the last decade. The driving force behind this attention has been a gradual recognition of the fundamental role played by apoptosis in normal development and tissue physiology, as well as in a surprisingly diverse collection of genetic and acquired diseases. Particularly significant advances have been made in defining the mechanisms of apoptotic control underlying the pathophysiology of viral infections, autoimmune diseases, neurodegenerative disorders, immunologic deficiencies, and cancers. Induction of apoptosis by the human immunodeficiency virus (HIV) in infected and uninfected cells appears to be integral to the pathophysiology of both the profound immunologic dysfunction and the dementia of AIDS (reviewed in 1). Conversely, inhibition of apoptosis is critical to efficient replication and establishment of latency in many pathogenic viruses, most notably the Epstein-Barr virus associated with infectious mononucleosis, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder, and Burkitt’s lymphoma. Specific mutations of genes critical for apoptosis have been found in several autoimmune strains of mice and have been associated with autoimmune diseases in humans, including systemic lupus erythematosus (reviewed in 2). Programmed cell death accounts for the necessary elimination of over 50% of neuronal cells in the developing brain, and aberrant control of apoptosis has been implicated not only in neurodegenerative disorders such as Alzheimer’s, Huntington’s, and Parkinson’s diseases, but also in various neurodevelopmental disorders including autism, Fragile X syndrome, and schizophrenia (reviewed in 3). In cancer biology, alteration in the regulation of tumor cell survival is of critical importance in the etiology and growth of tumors; it also provides clinically relevant prognostic information and will influence therapeutic decisions. The pharmacology of almost all antineoplastic agents is much more strongly tied to induction of apoptosis than had been imagined (reviewed in 4, 5). Study of these diseases has brought into sharper focus, and in some cases redefined, the molecular mechanisms by which a cell regulates its survival and the signaling pathways that activate (or inhibit) this central apoptotic pathway. This review focuses on a number of recent, exciting molecular developments in this field.

The Central Pathway of Apoptosis

Since the initial phenotypic descriptions of apoptosis, it has been suggested that there is likely to be a shared apoptotic mechanism operating in most, if not all, cells of the body (6, and references therein). The basis for this hypothesis was the morphologic similarity observed among diverse cell types in the process of nontraumatic death. Dying cells exhibit characteristic changes—including cell contraction, cytoplasmic blebbing, nuclear condensation, and genomic autodigestion into nucleosomal fragments—triggered by a heterogeneous set of inciting events; these morphologic changes are now considered
pathognomonic of apoptosis. The molecular basis of this central apoptotic pathway is beginning to be defined (Figure 1).

The first gene to be clearly associated with inhibition of apoptosis in humans was bcl-2, cloned from the breakpoint of the 14:18 translocation found in the majority of follicular lymphomas (7). A related gene, bcl-x, encodes two protein products differentiated by mRNA splicing, Bcl-xL and Bcl-xS (8). Like Bcl-2, Bcl-xL is a potent inhibitor of apoptosis and has been found to be up-regulated in many cancers. The truncated Bcl-xS protein exerts a dominant negative effect on both Bcl-2 and Bcl-xL function. Overexpression of bcl-2 or bcl-xL can confer resistance to most apoptotic stimuli, suggesting that these genes do indeed function at a central convergence of many apoptotic pathways. These genes were subsequently found to be part of a larger gene family, members of which have both positive and negative effects on apoptosis (9–15). Bcl-2 family members have been found to form both homo- and heterodimers, and the response to an apoptotic stimulus in a given cell depends on the particular complex of Bcl-2 family members expressed and their relative concentrations (16, 17). Two elements that are highly conserved between family members, the BH1 and BH2 domains, are required for family member heterodimerization and also for apoptotic inhibition by Bcl-2 and Bcl-xL (12, 18). A third conserved sequence, the BH3 domain, is required for the activity of some family members that promote apoptosis (19, 20). Evolutionary conservation of the bcl-2 gene family supports the initial hypothesis that the central pathway of apoptosis is similar in all cells. A gain-of-function mutant

![Figure 1](image_url)

*Figure 1* Schema of the central pathway of apoptosis. Initiation of apoptosis is held in check by survival signals received by cell surface receptors. Removal of the cell from its in vivo context or blockade of these survival signals allows induction of the apoptotic pathway, resulting in interleukin-1β converting enzyme (ICE)-related protease activation and the characteristic morphologic changes of apoptosis. Activation of this pathway is inhibited by Bcl-2 and Bcl-xL. This inhibition, in turn, can be overcome by interaction with pro-apoptotic Bcl-2–related molecules.
of the closely related gene in the invertebrate Caenorhabditis elegans, ced-9, rescues all 131 cells that were destined to die in the developing nematode (21), and Bcl-2 can rescue a Ced-9 loss-of-function mutant (22).

The mechanism of action of the Bcl-2 proteins in modulating the apoptotic sensitivity of the cell remains unknown. Recently, the crystal and solution structures of the Bcl-xL protein were solved by X-ray crystallography and nuclear magnetic resonance spectroscopy (23). The structure is predominantly α-helical, juxtaposing the BH1, BH2, and BH3 sequences along a hydrophobic cleft to generate a multipartite putative heterodimerization domain. An intriguing 60 amino acid loop between the first two α-helices is structurally undefined by either crystallography or spectroscopy. This domain is nonessential for anti-apoptotic effect and may, in fact, play a negative regulatory role, damping the survival signal of Bcl-xL. The arrangement of helices of Bcl-xL is very similar to the membrane insertion domain of a family of bacterial proteins responsible for inducing prokaryotic cell death, the colicins (24). The significance of this unsuspected link between death-regulatory proteins in prokaryotes and eukaryotes is currently unclear but may provide insight into the mechanism of action of the Bcl-2–related proteins.

The other component of the central apoptotic pathway that has been extensively studied is a family of cysteine proteases related to the C. elegans gene ced-3, which is essential for all apoptotic cell death in the developing worm (25). A database search revealed that Ced-3 was related to the mammalian interleukin-1β converting enzyme (ICE). Subsequent biochemical studies have shown that both proteins are produced as zymogens that, once activated, share similar ability to act as an aspartate-specific protease. The C. elegans Bcl-2 homolog Ced-9 appears to regulate the activity of Ced-3, possibly through an intermediary, Ced-4, that has no known mammalian equivalent (26). A family of ICE-related human genes has subsequently been identified, with at least seven members to date (reviewed in 27). Overexpression of many of these proteins results in apoptosis, and their central role in apoptotic regulation has been supported by studies using specific inhibitors of ICE family members (oligopeptides that bind to the active site, and the viral products crmA and p35; see below).

Several potential mechanisms for regulating ICE activity have been proposed. ICE family members are synthesized as inactive proenzymes that are stored in the cytoplasm and must undergo proteolytic processing to function (28). The protease responsible for initiating the conversion of pro-ICE to ICE is unknown. The proteolytic sites in the proenzyme are consistent with autoprocessing (29), and high local concentrations of proenzyme may permit autoactivation. Alternatively, autoprocessing may rapidly and irreversibly amplify the response to a distinct initial trigger. Other family members are not
autocatalytic but have cleavage sites that are targets for ICE, suggesting a proteolytic cascade of ICE family member activation. In analogy to the bcl-x gene, at least three ICE-related genes have the potential to encode a truncated protein that serves as a dominant negative inhibitor of the protease activity (30–32). These truncated forms may act by heterodimerization with the active proteases or by stabilizing the proenzyme forms.

Despite the wealth of data implying a central role for this gene family in apoptosis, the precise roles and relative importance of the various ICE family members have been difficult to define. Homozygous disruption of the ICE gene in mice yields only select defects in apoptotic pathways (33, 34), suggesting a functional redundancy among ICE-related proteases. There is considerable overlap in the target specificity of family members, which fall into two subsets based on cleavage site preference. CPP32, a family member with cleavage specificity distinct from ICE, was cloned on the basis of its ability to cleave poly(ADP-ribose) polymerase (PARP) (35, 36). PARP is a nuclear protein involved in genome surveillance and DNA repair that is similarly cleaved during apoptosis (37). Although CPP32 can cause nuclei to undergo characteristic changes of apoptosis, the relevance of this pathway is brought into question by the finding that PARP-deficient knockout mice appear to develop normally (38). The primacy of nuclear changes in initiating apoptosis is also in doubt; characteristic apoptotic changes can be induced by a variety of signals in anucleate cell remnants (39, 40). Teasing out the relevant pathways of apoptotic regulation involving the various mammalian ICE proteases will be a challenge.

**Signaling Pathways in Apoptosis**

The apoptotic threshold of most cells of the body is acutely sensitive to the extracellular milieu. A variety of cells, including many relatively long-lived cell types, will rapidly undergo apoptosis when removed from their in vivo context. This suggests that all cells of the body are continuously receiving signals from their local environment that determine the apoptotic threshold of the cell, and that the nature of these signals is different in different tissues. The most progress in defining the extracellular signaling mechanisms regulating apoptosis has been made in lymphocytes. B and T cells both express a wide variety of cell surface receptors that can either induce or inhibit apoptosis. The largest related group of these receptors, with at least 12 members, is the tumor necrosis factor (TNF) receptor (TNFR) family (reviewed in 41). These are characterized by cysteine-rich pseudorepeats in the N-terminal extracellular domains, through which each member binds to one or more of a family of TNF-related proteins. Under various experimental conditions, several of these receptors (including TNFR2, CD40, and CD30) inhibit apoptosis; others (including TNFR1 and Fas) induce apoptosis in lymphocytes.
The death-inducing receptors TNFR1 and Fas share a related intracellular sequence known as the death domain (Figure 2). Three cytoplasmic proteins with death domains, FADD, RIP, and TRADD, can heterodimerize with the death domains of these receptors (42–44). FADD and RIP interact directly with Fas, whereas TRADD appears to bind only TNFR1. Overexpression of any of these cytoplasmic proteins induces apoptosis. The TNFR1-TRADD complex forms only when TNFR1 has engaged extracellular TNF, and the complex was recently shown to secondarily bind FADD by heterodimerization of the C-terminal death domains of TRADD and FADD (45). Mutations in the N-terminal portion of FADD prevented TNFR1-induced apoptotic signaling. In addition, the TNFR1-TRADD complex was found to interact with TRAF2 (see below) in a pathway required for TNFR1-induced NFκB activation. These findings suggest that TRADD may serve primarily as a linker between TNFR1 and multiple downstream signaling pathways, including FADD-mediated apoptosis. Interestingly, overexpression of the death domain of TRADD or RIP alone is sufficient to induce apoptosis, whereas FADD overexpression induces apoptosis only if the N-terminal (effector?) domain is intact. FADD mutants with altered death domains unable to bind Fas are still lethal (42). Activation of FADD or similar effector proteins may be essential for both TNFR1- and Fas-mediated apoptosis. Recently, FADD has been shown to interact with a novel member of the ICE protease family known as MACH or FLICE (46, 47). FADD can recruit this protease to the ligand-engaged Fas receptor and promotes the cleavage of the FLICE prodomain, presumably activating the protease. Although such activation may be sufficient to induce apoptosis, Fas may also activate other signaling molecules that contribute to programmed cell death.

Ceramide generation by sphingomyelinase activity in the plasma membrane appears to be a necessary step in Fas ligand- and TNFα-triggered apoptosis. Ceramide production leads to c-Jun activation by the stress-activated protein kinase (SAPK) cascade pathway and to Ras activation. Dominant negative Ras mutants and anti-Ras antibodies (48), as well as SAPK pathway inhibitors and a dominant negative c-Jun mutant (49), block ceramide-mediated apoptosis. This pathway is evolutionarily conserved: Reaper, a Drosophila protein consisting of a 65 amino acid minimal death domain, similarly induces ceramide production and apoptosis in an insect cell line (50). Reaper- or ceramide-induced apoptosis in these cells, like Fas ligand- and TNFα-induced apoptosis in mammalian cells, is blocked by inhibitors specific for ICE-like proteases.

Ligand binding by several of the TNFR family members inhibits apoptosis. A shared feature of many of these receptors, despite their seemingly unrelated intracytoplasmic domains, is the interaction with a common set of intracellular signaling molecules, the TRAF proteins. The first members of this family to be
described, TRAF1 and 2, were cloned by virtue of their interaction with TNFR2 (51). TRAF2 binds directly to TNFR2 and TRAF1 heterodimerizes with TRAF2 through their sequence-related C-terminal TRAF domains. TRAF3 (CRAF1, CD40bp, CAP-1, LAP-1) was independently cloned shortly

Figure 2  Apoptotic signaling complexes associated with the Fas and TNFR1 receptors. Receptor engagement by extracellular ligand promotes receptor multimerization and initiates formation of the depicted complexes, recruiting FADD either by direct interaction or through the intermediary TRADD. An interleukin-1β converting enzyme—related protease (FLICE) associates with the Fas receptor complex, but no similar protease has yet been found to associate with the TNFR1 receptor complex. In addition to binding FADD, TRADD is able to recruit TRAF2 to the TNFR1 complex and, via TRAF2, activates NFκB. Although ceramide generation has been implicated in apoptotic signaling from both Fas and TNFR1, the mechanism leading from receptor engagement to ceramide generation has not been determined.
thereafter by four groups (52–55), three groups cloning it as a CD40-associated
protein, and one group cloning it as an Epstein-Barr virus (EBV) latent
membrane protein LMP-1–associated protein. In addition to the C-terminal
TRAF domain, TRAF2 and TRAF3 have in common an N-terminal RING
finger, a cysteine-rich, zinc-binding motif implicated in protein-protein inter-
action. The most recently described family member, CART1, which was
cloned in a screen for genes overexpressed in metastatic breast cancer, like-
wise contains both an N-terminal RING finger and a C-terminal TRAF domain
(56). The binding properties of CART1 have not been defined.

The associations between cytoplasmic TRAF proteins and transmembrane
TNFR family members are complex, with potential for both homo- and het-
erodimerization between TRAF family members. TNFR2 binds TRAF2 and,
via TRAF2, forms an indirect complex with TRAF1. CD40 interacts directly
with both TRAF2 and TRAF3. CD30 directly binds TRAF1, TRAF2, and
TRAF3 through two distinct binding sites (57), and EBV LMP-1 also appears
to associate with all three of these proteins.

Despite the interaction networks that have been mapped between the TRAF
proteins and TNFR family members involved in inhibition of apoptosis, the
functional role of the TRAF proteins in apoptotic signaling remains to be
defined. There is strong evidence that TRAF2-mediated signaling may be
responsible, at least in part, for regulation of NFκB activation by TNFR2,
CD40, CD30, and LMP-1 (45, 58; CS Duckett, RW Gedrich, CB Thompson,
unpublished data). The association between TRAF binding and apoptotic inhibi-
tion is currently only correlative and is made more tenuous by the recently
described indirect association of TRAF2 with the TNFR1 receptor involved in
apoptotic initiation. A dominant negative N-terminal deletion mutant of
TRAF2 inhibits NFκB induction from TNFR1 but had no evident effect on
apoptotic signaling. It is likely that the signaling properties of these receptors,
initiating multiple signaling cascades, are dependent on the particular complex
of TRAF family members and the additional second messengers with which
they interact.

Viral Modification of Apoptosis

Regulation of apoptotic pathways is exploited by a wide variety of viruses,
either to permit the maintenance of latent viral infection or to maintain the
viability of the host cell, thus enhancing the efficiency of viral replication. The
mechanisms by which viruses have co-opted control of the apoptotic machin-
ery in the host cell have provided insight into important regulatory steps in
mammalian cell apoptosis. The adenovirus E1B 19-kDa protein inhibits host
cell apoptosis and was used as a probe to identify three novel cellular proteins
that were subsequently found to interact with Bcl-2 (59). These proteins are
likely to play a role in Bcl-2 signaling. Both EBV and African swine fever virus encode homologs of mammalian Bcl-2 (60, 61). In addition, EBV LMP-1 interacts with members of the TRAF family, inhibits apoptosis of infected B cells, and up-regulates endogenous bcl-2 expression (52, 62). This membrane protein, evidently mimicking a ligand-bound TNFR family member, plays a critical role in maintenance of latent infection and in the development and survival of EBV-positive Burkitt’s lymphoma. Other viruses inhibit apoptosis at other points in the central apoptotic pathway. The cowpox virus crmA gene encodes a specific inhibitor of ICE-like proteases, down-regulating both host cell apoptosis and the inflammatory response from interleukin-1β generation (63). Baculovirus p35 protein inhibits apoptosis in insect cells by a similar mechanism (64).

Recently, a search for mammalian homologs of a baculoviral inhibitor of apoptosis (IAP) has led to the discovery of a new class of apoptotic regulatory proteins. Overexpression of baculovirus IAP in mammalian as well as insect cells leads to inhibition of apoptosis, suggesting that cellular homologs of the viral proteins might exist. Four human IAP-related genes that are able to confer apoptotic resistance in mammalian cells have been identified (65–69). Mutation of one of these genes, naip, is associated with spinal muscular atrophy, a common neurodegenerative disorder characterized by inappropriate cell death of lower motor neurons. Intriguingly, two IAP-related proteins, cIAP-1 and cIAP-2, were cloned as proteins binding to the TRAF1-TRAF2 heterodimeric complex associated with TNFR2. Thus, IAP-related proteins may represent another integral link in the chain between TNFR family member ligand binding and anti-apoptotic effect.

**Cell Cycle Regulation and Apoptosis**

Mutation or deletion of genes that regulate progression through the cell cycle is a central theme in cancer biology. Oncogenic mutations that increase the proliferative rate of the cell are increasingly being found to alter the apoptotic threshold. This crosstalk between cell-cycle regulation and the apoptotic pathway serves as a screen for the inappropriate proliferation that typifies malignancy. A central factor in the functioning of this screen is the tumor suppressor gene p53. The p53 gene product has been reported to participate in both G1-S and G2-M checkpoints regulating cell-cycle progression and induces cell-cycle arrest in response to DNA damage, allowing repair enzymes to function. However, in a cell being driven through the cell cycle by expression of cellular or viral oncogenes (e.g. c-myc, Ras/E1A, or simian virus 40 T antigen), a p53-dependent apoptotic response may result (70–72). Thus, p53 appears to play a key role in preventing propagation of potentially oncogenic variants, deleting cells that demonstrate deregulated replication by triggering apoptosis.
The central nature of this mechanism in preventing outgrowth of putative transformants may explain the remarkably high frequency of inactivating p53 mutations in hematopoietic and solid tumors, and the predisposition toward malignancy in patients heterozygous for p53 (Li-Fraumeni syndrome): The loss of p53 would permit replication of these malignant cells and, by failing to enforce cell-cycle checkpoints, may contribute to a higher mutation frequency in the resulting tumor.

The retinoblastoma gene Rb, like p53, is integrally linked to cell-cycle regulation and, likewise, is frequently inactivated in human malignancies, including tumors of the retina, lung, breast, bladder, prostate, and bone (reviewed in 73). The Rb gene product functions by binding to members of the E2F family, which are critical regulators of cell-cycle progression. Homozygous deletion of Rb leads to inappropriate cell-cycle progression in cell lines and is embryonically lethal in mice; these mouse embryos demonstrate increased apoptosis of neurons, liver, and possibly hematopoietic precursors (74–76). Homozygous deletion of one of the five E2F family members, E2F-1, is markedly tumorigenic in mice, and this tumorigenicity has been attributed to a failure to properly initiate apoptosis in response to aberrant cell-cycle progression in the absence of E2F-1 (77, 78). Rb and E2F-1 may function coordinately as tumor suppressor genes by regulating entry into S phase of the cell cycle, triggering apoptosis in cells that initiate DNA replication inappropriately. These studies and others have begun to outline the molecular determinants of the delicate balance between cellular quiescence, proliferation, and death.

**Chemotherapeutic Resistance and Apoptosis**

In addition to the role of apoptotic inhibition in oncogenesis, it is becoming clear that the same process is responsible for the chemotherapeutic resistance of many cancers. Inactivation of p53 correlates with poorer prognosis in most human malignancies (79). In a controlled experiment using genetically defined tumors in immunocompromised mice, p53 mutation is associated with treatment resistance to both chemotherapy and gamma radiation, and with tumor relapse (80). Bcl-2 and Bcl-xL can both confer high-level resistance to chemotherapeutic agents of several drug classes, and to radiation (81–87). Bcl-2 expression correlates with poor response to chemotherapy in acute myeloid leukemia, and Bcl-xL expression correlates with negative prognostic features in breast cancer (88, 89). Inhibition of apoptosis confers resistance to a wide array of toxins, including DNA-damaging agents, metabolic inhibitors, microtubule assembly inhibitors, topoisomerase inhibitors, and others, leading to a reinterpretation of the way chemotherapy agents and ionizing radiation work in killing tumor cells. Antineoplastic therapy appears to kill cells not by direct and irreversible damage to cell structures (i.e. necrotic cell death) but rather by...
the indirect triggering of the inherent autolysis pathway (i.e. apoptotic cell
death). The mechanical damage to the cell, such as DNA strand breaks intro-
duced by ionizing radiation, are not inherently fatal and can be repaired (albeit
imperfectly) if apoptosis is prevented.

Conclusions

A number of disparate signals are capable of modulating apoptosis in different
cells and in different contexts, and these signals appear to focus in on a central
regulatory pathway–determining cell fate. Many of these signaling pathways,
including components of the central apoptotic pathway, are evolutionarily
conserved. The pathways that have been outlined have yielded important in-
sights into organism development, tissue homeostasis, and the pathophysiol-
ogy of whole categories of disease. Major gaps in our understanding of the
regulation of apoptosis include the chain of events connecting ligand binding
to cell surface receptors with the central apoptotic pathway, the mechanisms of
action of the Bcl-2– and ICE-related proteins, the communication between
Bcl-2 and ICE family members, and the mechanisms directly responsible for
the characteristic cytoplasmic and nuclear changes of apoptosis. Clearly,
greater definition of the essential connections among these various pathways is
required.

The ultimate challenge may be to translate the knowledge gained into
therapeutic strategies to improve clinical outcome in the many diseases linked
to deregulation of apoptosis. In cancer research, the surprising finding that the
cytotoxic effects of chemotherapeutic agents operate primarily through induc-
tion of tumor cell apoptosis has prompted an investigation of anti-neoplastic
therapies that more directly target the aberrant control of apoptosis in tumors.
A pilot study of antisense bcl-2 oligonucleotides in the treatment of B cell
lymphomas is currently being conducted (90). Direct antitumor therapy target-
ing apoptotic modulation may prove to be much less systemically toxic than
standard chemotherapy and could also be used in an adjuvant manner, to
increase the apoptotic susceptibility of tumors at the time they are exposed to
chemotherapy. In the treatment of autoimmune disease, targeted induction of
apoptosis in autoimmune subsets of lymphocytes may be possible using the
specific autoantigen in the absence of costimulatory survival signals. The
potential utility of this strategy was demonstrated in mice treated for experi-
mental autoimmune encephalitis (91). Targeted modulation of EBV LMP-
1–derived signaling may be an ideal way to specifically treat post-transplant
lymphoproliferative disorder without risking transplant rejection and may play
an important role in the management of EBV-positive lymphomas. Finally,
mofication of the apoptotic induction in uninfected lymphocytes in HIV
infection, which has been linked to effects of free extracellular gp120 and Tat
protein (92–94), may have a major impact on the progression of AIDS. The era of widespread clinical implementation of apoptotic modulation in the treatment of disease has not yet arrived, but it has the potential for tremendous impact on the prognosis of many important and challenging diseases.

ACKNOWLEDGMENTS

We would like to thank Colin Duckett for his many helpful suggestions. CMR is supported in part by the Daniel N. Epstein fellowship fund.

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