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EDITORIAL

Deciphering the mammalian stress response – a stressful task

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Almost any change in cellular homeostasis that results from exogenous or endogenous imbalance is expected to cause stress, which, in turn, will initiate a complex cascade of stress-inducible enzymes and related transcription factors in an attempt to return the cell to its original equilibrium. It is, however, the type and dose of stress that dictates the nature of this cellular response. Cellular rescue from stress is not achieved when damage is too great, or when one or more components of the stress-activated cascade is impaired.

It has been a most exciting decade with regard to our understanding of the cellular stress response. Our ability to decipher the components involved in mammalian cells' ability to cope with stress has led to remarkable new developments in our basic understanding of this process, as well as in our ability to design means to alter its regulation. This review issue brings together articles from leading scientists in the field of stress response, which together provide an updated picture of our current knowledge and point to questions yet to be addressed.

One of the key questions to understanding the stress response is how does the cell sense stress? Damage to cell surface receptors results in a different set of stress-activated kinases than does cytoplasmic or nuclear damage, suggesting that a sensitive array of cellular sensors distinguishes the source and nature of stress. Indeed, the possible existence of stress sensors in different cellular compartments has been the target of extensive investigation. Current data allow us to distinguish among three types of stress-related sensors on the basis of their primary cellular localization: nuclear, cytoplasmic and membrane/cell surface receptors.

Co-ordinated activation of the stress response could occur in response to activation of one or multiple sensors, depending on the type and magnitude of treatment (Figure 1).

Cell surface/membrane-anchored sensors of stress include receptors (e.g., EFGR, PDGFR, IGFR) that dimerize as well as complex arrays of membrane-associated proteins that mediate much of the extracellular signal through interaction with such molecules as upstream components of stress kinases, exemplified by ASK1/TRAFs and PI3K. In this issue, Ichijo provides an updated summary of molecular links between inflammatory cytokine receptors and stress-activated kinases and illustrates the complex interplay among upstream stress-regulatory components.

Regulation of stress kinases is mediated by several upstream signaling components. These include TRAF2/5, which has been implicated in the regulation of MEKK1, IκB, MEK, and ASK1. It is not clear how a single upstream denominator elicits activation of downstream effectors, which is often seen. These are among the questions for intensive investigation that addresses the co-ordinated regulation of multiple stress kinases as well as the regulation of cross-talk ('wiring') between alternate cascades.

Among membrane related stress sensors is phosphoinositol 3 kinase (PI3K), which has been implicated in the regulation of nearly all stress signaling pathways. The 3′ phosphorylated lipid products of this enzyme promote activation of PKB, a key player in PI3K's ability to confer cell survival. Further insight into this enzyme's key role comes from mutations (often found in human tumors of lipid phosphatase PTEN), which antagonizes PI3K function. The current understanding of PI3K-dependent regulation of cell survival and death is summarized in the review by Stambolic *et al.*

Many stress stimuli, both endogenous and exogenous, do not involve the membrane. Among the cytoplasmic sensors implicated in the regulation of stress kinases are cysteine-rich molecules that are modulated in response to ROS and altered redox potential. These molecules play key roles in regulating stress kinases, exemplified by GSTp and thioredoxin, which make essential contributions to the regulation of JNK and ASK1, respectively. In this issue, Adler *et al.* review current understanding of ROS-related regulation of stress kinases, an area that has been subject to exponential growth over the past few years. Our better understanding of ROS-mediated regulation of stress kinases is expected to provide fundamental information for understanding the selectivity of a given stress response. For example, it is the regulation of stress kinases by ROS-regulated molecules that is expected to play an important role in determining the nature of the stress kinase to be activated in the cellular response to a particular form of stress.

A new aspect of the stress response is pointed out in Williams' review, which summarizes our current understanding of PKR, a protein kinase, which upon activation by cytokines, growth factors and stress signals binds to double-stranded RNA. PKR binding results in inhibition of RNA synthesis via the phosphorylation of eIF2a. PKR also induces the transcription of inflammatory genes by PKR-depen-

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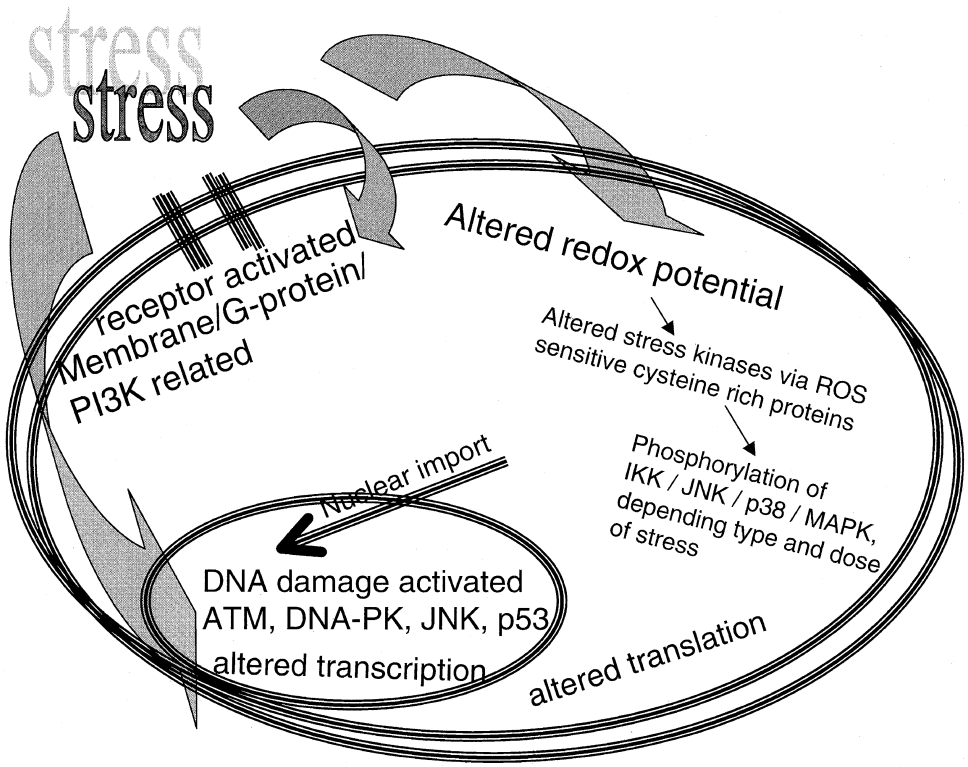

Figure 1

dent activation of NIK/NFκB, p38/ATF2, and ERK/STAT signaling with activation of the transcription factors concerned. Importantly, PKR inhibition by viral transcripts has been implicated as a mechanism that aids viruses in evading the immune system. Sheikh and Fornace further discuss translational regulation in response to stress in this issue. Phosphorylation of eukaryotic translation initiation factor-2alpha (eIF-2alpha) is one of the key steps by which protein synthesis is regulated in response to changes in environmental conditions. The phosphorylation is carried out in part by three distinct eIF-2alpha kinases, including mammalian double-stranded RNA-dependent eIF-2alpha kinase (PKR), heme-regulated inhibitor kinase (HRI), and yeast GCN2.

An important part of the mammalian stress response relates to the translocation of active components from the cytoplasm to the nucleus. Whereas the importance of nuclear localization for stress-responsive transcription factors is key for their ability to elicit their activities, the mechanisms underlying import and export of transcription factors to and from the nucleus are better understood, thanks to a set of pivotal studies published in recent years. In this issue Ferrigno and Silver summarize regulated nuclear localization of stress-responsive factors and their implications for cell survival. Current knowledge of HOG-, AKT-, NFAT-, NFκB- and p53-regulated nuclear localization points to the role of phosphorylation by stress kinases as a common mechanism for controlling interaction with specific nuclear import and export factors.

The nuclear stress sensors are likely to include several proteins, some of which have been well characterized over the past few years, including DNA-PK and ATM. ATM has been implicated in damage detection and as a key regulator of the cellular response to double-strand breaks. Through its ability to activate key components of multiple signal transduction pathways, ATM mediates the efficient induction of signaling control of cellular recovery and survival. Rotman and Shiloh provide an up to date summary of our current understanding of ATM function in the mammalian stress response.

One of ATM's substrates is the protein product of the tumor suppressor protein p53, which plays a central role in regulating the cell's fate in response to stress. In this issue Sionov and Haupt summarize current knowledge of mechanisms underlying p53's ability to elicit death or survival signals. Among the mechanisms underlying p53's ability to elicit opposing regulatory signals are the changes that p53 undergoes in response to various external stimuli. For example, the nature of p53 phosphorylation and its effects may be attributed to the magnitude of stress. Low-dose damage to p53 has been implicated in growth arrest and DNA repair, whereas high-dose damage has been associated with p53's ability to elicit apoptosis. Further, the availability of cellular factors such as functional Rb and the ability to activate p21 (which inhibits activation of the apoptosis-regulating kinase, ASK1 and of the stress-activated kinase, JNK) identify one scenario in which apoptosis could be prevented via p53-dependent p21 trans-activation. In the same vein, our better understanding of regulatory proteins that control the apoptosis cascade identifies the ratio between other p53 effectors, anti- and pro-apoptotic proteins (i.e. Bax and Bcl-2), as a critical component in determining whether p53's activities promote or protect against, cell death.

The transcription factor c-Jun, which has been a paradigm of signal-responsive factors, represents one of the important components of the cellular stress

response. In this issue, Leppa and Bohmann discuss the role of c-Jun/JNK in cellular proliferation, as in mediating pro- and anti-apoptotic responses to stress. Our current understanding of JNK/Jun's contribution to the cellular stress response further illustrates the importance of the cell type and the context formed by other regulatory influences in the environment.

Among the primary regulators of the mammalian stress response is NFκB, whose role in cell growth and differentiation, apoptosis and adaptive responses to changes in cellular redox balance is critical. The importance of NFκB in the cellular stress response is best illustrated in the pathogenesis of several diseases that exhibit aberrant regulation of NFκB. In this issue, Mercurio and Manning summarize our current knowledge of the regulation and function of NFκB in response to various stress stimuli.

A common denominator in the discovery of stress kinases is our underestimation of their complexity. Much of our understanding of the organization and function of stress signaling relies on studies from *Drosophila*, as summarized in the review by Stronbach and Perrimon. In addition to identification of JNK and its upstream kinase homologs, studies in *Drosophila* provided important lessons on the role of DJNK in cytoskeletal remodeling during embryogenesis, as shown for the morphogenetic process of dorsal closure. Further studies in *Drosophila*, have pointed to the role of specific GTPases, including DN-Cdc-42, DN-Rac and DN-Rho as well as TRAF1 and its downstream effector Msn, in the regulation of JNK activity. Direct evidence for the role of cell junction proteins in regulation of JNK was provided through the analysis of *Drosophila cno* mutants.

Summarized in Figure 1 is the outline of major changes in the mammalian stress response, as detailed in each of the contributions made in this special issue. The next few years are expected to be just as exciting as the earlier period, as some of the key open questions are addressed – the nature of wiring and cross talk among different stress kinases, the co-ordinated regulation of multiple stress kinases in response to diverse stimuli, and the factors involved in regulating the magnitude and duration of the stress response.