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Editorial

Inducible gene expression in apoptosis

L Fésüs*,[1]

[1] Department of Biochemistry and Molecular Biology, University Medical School, Debrecen, Hungary
Tel/Fax: 36 52 416-432; E-mail: fesus@indi,dote.hu
* Corresponding author: László Fésüs

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In the early years of programmed cell death as well as apoptosis research there was a general agreement that both phenomena require the induction of death-related genes and macromolecular synthesis.[1–3] Later studies demonstrated that in some cells inhibitors of transcription and translation can initiate apoptosis[4] and there are compounds like staurosporin which can induce apoptosis in all examined cell types in the presence of such inhibitors.[5] These observations, cell free studies[6] and genetic experiments in both *C. elegans* and *Drosophila* lead to the conclusion that protein components of the intracellular death program (caspases, DNA degrading enzymes and others which act in the so called effector/execution or degradation phase of apoptosis) are constitutively expressed in all nucleated animal cells.[7] The fact that in many systems death is prevented by inhibitors of macromolecular synthesis has been explained by suggesting that *de novo* transcription and translation are needed only to provide the 'activators' (regulators) of the death program. Do all recent data support this conclusion? Four reviews in this issue of Cell Death and Differentiation[8–11] focus on inducible gene expression in apoptosis showing a picture which has elements challenging the presently dominant views.

Pinkoski and Green argue[8] that Fas ligand (FasL) qualifies as a bona fide death gene which is often transcriptionally inactive but become activated in many forms of transcription/translation dependent apoptosis. A number of transcriptional activators acting on well defined response elements of the FasL gene also have been identified including *NFAT* (Nuclear Factor in Activated T cells), *NF*κB, the transcriptional factor *Egr* (Early Growth Response), *JNK* forming AP-1 with c-Fos and c-*myc*. Clearly, the induction of the FasL gene leading to the appearance of an intercellular death signal in either lymphoid or non-lymphoid tissues is a typical example of activating the death system which is presumed to be constitutively expressed. Another related example may be apoptosis resulting from the action of transcriptionally active p53 in various stress conditions. Most of the known genes activated in response to p53 induction, such as BAX,[12] IGFBP3,[13] PAG608,[14] KILLER/DR5[15] and several redox-related PIG genes[16] are thought to code death activators – though the action of BAX and oxygen radicals are often considered as part of the execution phase of apoptosis. Furthermore, there are examples of transcriptional regulation of death effector proteins – such as cathepsin D[17] and transglutaminase[18] – in p53 mediated death programs.

Riccardi and colleagues have reviewed[9] the modulation of gene expression by glucocorticoids in T cell death, one of the classical apoptosis systems requiring newly induced genes. Several of these genes seem to operate rather in the execution phase of apoptosis than in its activation. There are data pointing to the possibility that caspases themselves can participate in the regulation of apoptosis genes. The regulation of GITR and GILZ, two new dexamethasone-induced inhibitors of apoptosis is also transcriptional suggesting that the dual effect, death *versus* survival, of glucocorticoids on T cells is manifested at the level of gene expression.

Fu has summarized results of several laboratories pointing out that the availability of the 'machine' for execution of apoptosis, such as caspase family proteases, can be regulated by specific transcriptional factors which could be further modulated by cytokine-triggered signaling pathways.[10] STAT1 (Signal Transducer and Activator of Transcription) and possibly other STATs activated through protein tyrosine kinase signalling pathways can induce expression of caspases and perhaps several other target genes and this way mediate apoptosis induced by cytokines and growth factors (e.g. IFN-γ and EGF). It is not clear whether the apoptosis-linked induction of caspase genes is direct or indirect; identification of promoter elements responsible for their regulation is in progress. Several additional examples of the induction of caspase genes parallel to apoptosis have been reported including cell death initiated by etoposide,[19] hypoxia[20] and thyroid hormone.[21]

It is often stated that the built-in death machinery of eukaryotic cells is kept under control by various surviving factors and one of the most general initiator of apoptosis in living tissues is the limiting amount of such factors. Are expression of proteins of the death machinery induced by withdrawal of survival factors? The answer seems to be yes at least in hormone-dependent tissues as suggested in the review of Marti *et al*.[11] They show that activation of caspases is a general feature of apoptosis also in the mammary gland, prostate and ovary following the withdrawal of the appropriate hormones. However, it looks that a number of extracellular, cytoplasmic and nuclear proteins are often induced in the early phase of apoptosis. Some of these proteins may be considered as activators of the death program (e.g. IGFBP-5, PKA, AP-1) but others like caspases, SGP-2 and transglutaminase clearly belong to the category of death effectors.

Differentiation of various cell types often involves a definite expression pattern of death genes including

downregulation of apoptosis inhibitors (such as bcl-2) and upregulation of death-related genes and this way setting up the fully differentiated cells for elimination. Several of the upregulated gene products are apoptosis executioners such as caspases.[22,23] One of the execution enzymes often induced during differentiation is a transglutaminase. The Ca^{2+}-dependent, protein cross-linker transglutaminases are usually not present in cells but induced at sites of programmed cell death and apoptosis.[24–26] Several promoter elements of the tissue transglutaminase gene responding to apoptosis signalling pathways have been identified including retinoid[27] and AP-1 sites (L Fésüs unpublished results).

Based on the presented reviews and some recent data one may conclude that the effectors of the death machinery are not necessarily and always expressed constitutively in all nucleated cells but require transcriptional regulation involving distinct signalling pathways which often coincide with the death signal. The lack of death executioners may represent a safety mechanism of survival for certain cell types of the organism such as precursor and stem cells. It is also likely that there is a threshold concentration of effector/killer proteins which must be reached for cell death to occur – similarly to the drop of apoptosis inhibitors to a critical level – providing a regulatory paradigm of apoptosis at the transcriptional level. It should be also considered that in a given cell a number of alternative mechanisms – some are caspase-dependent while others are not[28] – may be used for the execution of programmed cell death. Elements of one maybe constantly expressed and easily activated (e.g. by drastic treatments like staurosporin resulting in death and the appearance of part of the typical apoptosis morphology) without the expression of new genes and complete utilization even one of the alternative death programs. Dissecting the molecular details of the complex transcriptional regulation of apoptosis genes – both of the regulator (activators/inhibitors) and the executioner proteins – is very much in progress in several laboratories and will help to understand the full significance and depth of transcriptional regulation in apoptosis. This area of apoptosis research also has promising clues for finding new pharmaceutical approaches either to kill (and sensitize for the killing of) unwanted cells or to prevent the loss of indispensable ones.

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