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# Lipocalin-2: pro- or anti-apoptotic?

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**Abstract** Survival and apoptosis signaling pathways are altered concomitantly in response to numerous endogenous and exogenous stressors. The lipocalin family of small soluble proteins has been implicated in modulating apoptosis. However, the overall effect of these proteins has been variable, showing both pro- and anti-apoptotic activities. The goal of this minireview is to summarize the studies on lipocalins and apoptosis and consider what roles lipocalin-2 may play in cell death and survival.

**Keywords** Apoptosis · Signaling · Lipocalin-2 · 24p3 · Neutrophil gelatinase-associated lipocalin (NGAL)

## Introduction

The fine tuning of biological functions often requires a dynamic balance between opposing activities. This is most obvious in the nervous and immune systems, but a similar balance between death and survival signals appears to exist and to be essential for normal tissue development and homeostasis. Disrupting the balance of cellular decisions regarding life and death is a critical factor in the progression and in the treatment of cancer (Danial and Korsmeyer 2004; Waxman and Schwartz 2003) and is likely involved in many other disease states. A number of pathways controlling apoptosis signaling have been defined (Danial and Korsmeyer, 2004; Melet et al. 2008), and additional components continue to be identified. However, the full range of pathways involved, including those activated and/or inhibited by different xenobiotics that induce apoptosis, are incompletely understood.

Lipocalins are a diverse family of over 20 small soluble and, often secreted, proteins. These proteins have a large degree of diversity at the sequence level (only 20% identity), although most share three conserved motifs. These proteins are defined as lipocalins based on their three-dimensional structure, which is comprised of a single eight-stranded, continuously hydrogen-bonded anti-parallel β-barrel.

The functions of the lipocalins are not well-understood. The cavity in the β-barrel is thought to bind and transport a variety of lipophilic substances (Flower 1996). In addition, lipocalins can bind to specific cell-surface receptors and may deliver ligands, including iron, growth, or survival factors, to the cell by receptor-mediated endocytosis (Elangovan et al. 2004; Flower 2000). Iron binding has also been suggested as a mechanism by which lipocalins exert antimicrobial activity (Ratledge 2007). However, physiological ligands have not been identified for most lipocalins, and little is known about receptors that may, or may not, mediate their cellular uptake,

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although some work has indicated that megalin acts as a receptor for NGAL (Hvidberg et al. 2005).

Lipocalins appear to have roles in cell regulation, both in terms of proliferation and differentiation (Flower 1994). This has suggested a number of functions related to cancer where elevated expression of lipocalins is often observed (Bratt 2000). Several lipocalins such as $\alpha_1$-microglobulin, $\alpha_2\mu$-globulin, and orsomucoid are expressed in different forms of cancer, and it has been proposed that lipocalins mediate cell signaling either by delivering lipophilic ligands, such as retinoids and fatty acids, or by inhibiting proteases (Bratt 2000). This latter effect may be particularly important in cancer progression. Neutrophil gelatinase-associated lipocalin (NGAL) has been found complexed with matrix metalloproteinase (MMP)-9 and protects MMP-9 from autodegradation (Yan et al. 2001) in vitro and may play a similar role in vivo for breast cancer resulting in enhanced MMP-9 activity and increased angiogenesis and tumor growth (Fernández et al. 2005). In addition, the presence of the NGAL/MMP-9 complex in urine from breast (Fernández et al. 2005) and brain (Smith et al. 2008) cancer patients has suggested this protein as a potential cancer biomarker.

Signals for apoptosis, which are the default signal for many cells, are normally suppressed by survival signals that are generated both internally and through molecules derived from neighboring cells. Apoptosis can be initiated by removing or blocking essential survival signals or in response to the more direct activation of the extrinsic (death receptor) or intrinsic (mitochondrial) death pathways (Adams 2003). At the same time, pro-survival pathways may be activated. For example, serum starvation, etoposide, and BMD188 (a mitochondrial toxin) cause apoptosis in LNCaP prostate cancer cells, SV40-transformed GM701 fibroblast cells, and MDA-MB231 breast cancer cells but paradoxically induce pro-survival molecules, including bcl-2/bcl-$X_L$ and the superoxide dismutases (Liu et al. 2005). In addition, FOXO3a, a transcription factor involved in both pro-survival and pro-apoptotic signaling (Burgering and Medema 2003), is activated in this system (Liu et al. 2005). Similarly, in Jurkat T cells, the induction of apoptosis by TRAIL is accompanied by the activation of anti-apoptotic pathways, particularly those associated with phosphoinositide 3-kinase and Akt (Zauli et al. 2005), while in lung carcinoma cells, the induction of apoptosis with quercetin is accompanied by increased levels of survivin and p53 that appear to limit the extent of apoptosis (Kuo et al. 2004). Thus, in response to many stressors, there is a balance between effects on pro-survival and pro-apoptosis pathways (Fig. 1). Several publications have reported on research that explored the role of the lipocalins in apoptosis. Because of the disparate results seen with these studies, the goal of this review is to summarize the findings and consider what role lipocalin-2 may play in cell death.

## Lipocalin-2 and apoptosis

Lipocalin-2 (24p3) was first identified as an overexpressed gene in SV40-infected primary kidney cells from mice (Hraba-Renevey et al. 1989). This gene is part of a family of small secreted proteins that bind and transport lipophilic materials. NGAL, the human analog of 24p3 [NGAL and 24p3 are 85% homologous in amino acid sequence (Kjeldsen et al. 2000) and about 70% similar in nucleotide sequence], was first purified from human neutrophils because of its

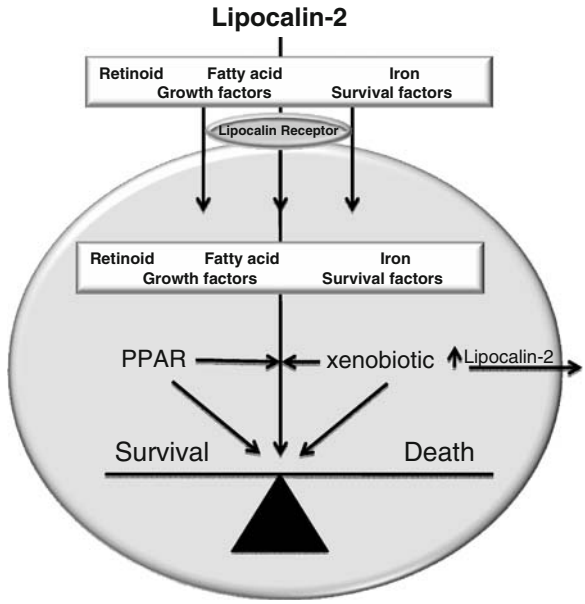


**Fig. 1** Schematic diagram illustrating the hypothesized role of lipocalin-2 in modulating cell survival and death pathways. The lipocalin-2 protein is synthesized in the cell at basal levels, which can increase in response to certain toxic xenobiotics. The protein is secreted and can bind to different factors extracellularly, potentially affecting their uptake into the cell. The availability of factors involved in regulating apoptosis helps to determine whether survival or death pathways prevail

association with gelatinase (Kjeldsen et al. 1993). Although this association suggests the potential to modulate neutrophil gelatinase, NGAL does not directly affect this enzyme activity, rodent forms of this lipocalin are not associated with gelatinase, and most NGAL is exocytosed from neutrophils in a form that is not complexed with gelatinase (Kjeldsen et al. 1993).

Several functions of 24p3/NGAL have been identified, but precisely which, if any, are important under normal circumstances is unknown. Functions related to cancer have been suggested (Bratt 2000), but overall, the role of 24p3/NGAL in cell signaling, proliferation, and apoptosis is unclear. Some data suggest a role in inflammation, while other data indicate that NGAL has an important role in iron metabolism (Yang et al. 2002). A number of inducers of this gene have been found, including serum, lipopolysaccharide, various growth factors, retinoic acid, glucocorticoids, and phorbol esters (Bratt 2000; Kjeldsen et al. 2000). In addition, we have demonstrated that MK886, nordihydroguaiaretic acid, and several compounds related to cyclooxygenase-2 inhibitors that induce apoptosis are potent inducers of 24p3/NGAL (Tong et al. 2003, 2005).

24p3 is expressed at high levels in the mammary gland and uterus where it is proposed to induce neutrophil apoptosis, thereby allowing selected cells to survive involution (Ryon et al. 2002). Although previous publications suggested that lipocalin-2, in particular, the murine 24p3, has pro-apoptotic functions (Devireddy et al. 2001, 2005; Lin et al. 2005; Leng et al. 2008; Tong et al. 2003), some data are more suggestive of the opposite effect. For example, we have reported that NGAL appears to have survival activity (Tong et al. 2005). Data supporting this conclusion include the following. First, although celecoxib-derived compounds that are devoid of cyclooxygenase-2 inhibitory activity but potently induce apoptosis cause a dose- and time-dependent increase of NGAL and 24p3 messenger RNA (mRNA) and protein levels (Tong et al. 2003), the addition of up to 150 μg recombinant NGAL/$10^6$ cells (both A549 and Jurkat cells were tested with both iron loaded and native NGAL) did not affect proliferation or viability, showing that this protein is not directly toxic (Tong et al. 2005). Second, A549 cells transfected to overexpress NGAL proliferated normally (Tong et al. 2005). Third, a rabbit polyclonal antibody against the full-length NGAL protein induced substantial apoptosis in A549 cells by 24 h (Tong et al. 2005), a finding consistent with work with antibodies to a related chicken lipocalin that kills chondrocytes (Gentili et al. 2005). Interestingly, the commercially available monoclonal NGAL antibody was non-toxic. The reason for this discrepancy is unclear, although it may be because it is monoclonal and was developed using only a peptide fragment of the NGAL protein. Such an antibody may not affect the "active" portion of NGAL, while the polyclonal against the whole protein would be more likely to block a major portion of NGAL, thereby inhibiting its survival activities. Finally, small-interfering RNA (siRNA) against either 24p3 or NGAL enhanced the pro-apoptotic activity of celecoxib-related compounds (Tong et al. 2005).

Work from other researchers also supports protective rather than pro-apoptotic activities for lipocalin-2. The expression of 24p3/NGAL in all tissues examined (Kjeldsen et al. 2000) and the high levels of expression of 24p3/NGAL by various cancers (Bratt 2000) as well as in normal mammary gland, uterus (Ryon et al. 2002), and testes (Tanaka et al. 2002) are consistent with a survival function. Furthermore, NGAL is upregulated in the kidney following transient ischemia, and protection against kidney damage (including apoptosis) is seen with exogenously administered NGAL in mice (Mishra et al. 2004; Mori et al. 2005) in vivo. Although this protection involves a bound cofactor (siderophore) originating with the bacteria in which it was cloned, the authors suggest some similar factor exists in mammals and that NGAL is a "siderophore delivery protein." Survival activity has been also identified with *ExFABP*, a secreted avian lipocalin that binds fatty acids and induces apoptosis when downregulated (Di Marco et al. 2003). These authors showed that antibodies to ExFABP damaged myoblast cells in culture (Gentili et al. 1998) and induced apoptosis in vivo in developing chick embryos. The authors hypothesized that this lipocalin, which is induced in response to stress, acts as a survival protein (Gentili et al. 2005). Other work has shown that *N*-(4-hydroxyphenyl)retinamide induces apoptosis and the expression of lipocalin-2. However, preventing the induction of lipocalin-2 by siRNA does not alter the response to *N*-(4-hydroxyphenyl)retinamide, suggesting that this lipocalin is not responsible for the observed apoptosis

(Caramuta et al. 2006). Finally, a report has confirmed our finding (Tong et al. 2005) that NGAL protein does not induce apoptosis in cultured cells (Klausen et al. 2005). These authors conclude that there may be major differences between the mouse 24p3 and the human NGAL.

In contrast to data indicating that lipocalin-2 is protective, the work of other researchers suggests that it is a pro-apoptotic protein. Devireddy et al. (2001) have shown that extracellular 24p3 has biologic activity in terms of stimulating apoptosis in mouse pro-B FL5.12 cells. These workers have subsequently shown that this pro-apoptotic effect may be mediated by modulating iron uptake (Devireddy et al. 2005). Other researchers have provided experimental evidence indicating that lipocalin-2 inhibits the growth of erythroid and monocyte cells but not immature hematopoietic progenitor cells or other primary cells in vitro (Miharada et al. 2008). The authors suggested that lipocalin-2 plays a role in regulating human hematopoiesis, similar to the effects seen in murine hematopoietic cells. In the study of Miharada et al. (2005), the authors propose that lipocalin-2 may suppress survival and differentiation of erythroid progenitor cells under normal conditions by enhancing apoptosis but that these cells become resistant to lipocalin-2-mediated apoptosis under conditions requiring more such cells (e.g., anemia) by the upregulation of intracellular survival factors. This concept is consistent with the proposal shown in Fig. 1, whereby there is a balance between pro- and anti-apoptotic factors.

Related studies in murine hematopoietic cell lines transformed by the BCR-ABL oncogene that causes chronic myeloid leukemia found an increase in the expression of 24p3 (Lin et al. 2005). Interestingly, these transformed cells were resistant to 24p3-induced apoptosis relative to untransformed cells. In addition, only BCR-ABL-transformed cells that express 24p3 were able to cause leukemia (Arlinghaus and Leng 2008). A human chronic myeloid leukemia cell line K562 that expressed *bcr-abl* secreted high levels of NGAL and suppressed hematopoiesis in mice while inducing more apoptosis (Leng et al. 2008). Furthermore, chronic myeloid leukemia patients exhibit high lipocalin-2 levels. Overall, these authors concluded that lipocalin-2 has at least two functions related to tumorigenesis. One involves the induction of apoptosis in normal hematopoietic cells, and the other involves facilitating tissue invasion by the leukemic cells. In many of these studies, a differential response of normal and tumorigenic cells to lipocalin-2 exists and, along with species differences, could potentially explain some of the differences in apoptotic responses that have been observed.

Additional data supporting pro-apoptotic effects of lipocalin-2 comes from work in microglia, showing that stable expression of lipocalin-2 or the addition of lipocalin-2 protein in vitro sensitizes these cells to apoptosis, while the knockdown of lipocalin-2 expression has the opposite effect (Lee et al. 2007). Work with a murine endometrial carcinoma cell line (RL95-2) has shown that 24p3 protein secretion correlates with stress and that adding this protein to the medium reduces cell viability (Lin et al. 2007). These authors also provided evidence of oxidative stress and suggested that 24p3 creates an intracellular oxidative environment that induces apoptosis. It must be noted, however, that the cause–effect relationship between oxidative stress and apoptosis is relatively weak in this and other systems where it has been studied.

One recent study has reported that treatment with 13-cis retinoic acid induces NGAL and apoptosis in sebaceous glands, and siRNA to NGAL inhibited this apoptosis (Nelson et al. 2008). This work is almost in direct opposition to the findings described above with *N*-(4-hydroxyphenyl)retinamide. Somewhat less conclusive is the report that renal tubular cells produce large amounts of NGAL in patients with autosomal-dominant polycystic kidney disease (Bolignano et al. 2007). These authors hypothesized that this production was a consequence of increased apoptosis or perhaps a compensatory stress response. In any event, lipocalins have been proposed as disease markers (Xu and Venge 2000) and lipocalin-2 is a promising biomarker of both acute and chronic kidney disease (Devarajan 2008).

## Peroxisome proliferator activated receptor

Peroxisome proliferator activated receptor (PPAR) agonists, particularly for PPARγ, are well-established inducers of apoptosis (Elrod and Sun 2008). Interestingly, the induction of NGAL by xenobiotics that induce apoptosis in cell culture systems can be modified by PPAR agonists. For example, the upregulation of 24p3 mRNA expression by MK886 was

enhanced a further threefold by WY14643, an activator of PPAR$\alpha$, whereas ciglitazone, an activator of PPAR$\gamma$, attenuated the MK886-induced 24p3 expression by more than 50%. Neither WY14643 nor ciglitazone alone had any effect on the expression of 24p3 (Tong et al. 2003). A potential connection between PPAR and lipocalins has not been extensively studied, and more research into this area might yield new insights into the role of lipocalins in apoptosis.

### Survival vs. apoptosis

With the available data, it is not possible to ascertain precisely what role lipocalin-2 plays in apoptosis. The preponderance of evidence suggests that it is not directly pro-apoptotic but that, under some conditions, it may augment cell death by modulating the availability of signaling factors (Fig. 1). Overall, the correlation of lipocalin-2 levels with the induction of apoptosis by various stressors may represent an attempt by cells to compensate for apoptotic stress rather than being a cause of apoptosis, although in some systems, it is clear that lipocalin-2 more directly initiates this form of cell death.

There are now substantial data showing that lipocalin-2 plays an important role in iron transport (Schmidt-Ott et al. 2007). Whether or not this activity affects apoptosis or is the sole function of lipocalin-2 remains unclear. It is notable that 24p3 knockout mice produce normal litters with no phenotype (Flo et al. 2004), suggesting that this lipocalin is a facilitator of cellular processes but not an essential survival factor.

Lipocalin-2 is a secreted protein and is present within cells at only very low levels. Thus, lipocalin-2 is unlikely to be acting through direct effects on intracellular signaling pathways. Rather, its activities may be indirect through facilitating the uptake of iron or other growth factors from the medium—a proposal also made for the lipocalin ExFABP (Gentili et al. 2005). Because NGAL is presumed not to act directly on apoptotic pathways, this would explain why its overexpression modulates but does not control apoptosis. However, its effects on growth factor transport and uptake are likely variable based on cell type and species. For example, human A549 cells are quite resistant to serum withdrawal, and thus, down-regulating NGAL has only minimal effects. In contrast, murine FL5.12 cells are IL3-dependent, and thus changing levels of the murine 24p3 may have quite different effects—possibly even pro-apoptotic if too much growth factor is bound and not enough is available for uptake. The possibility of such an effect is supported by work showing 24p3/NGAL binds hepatocyte growth factor decreasing normal signaling and that optimal effects on cell migration occurred at 20–40 ng/ml, with no effect at lower doses and an inhibitory effect at higher doses (Gwira et al. 2005). It is also possible that membrane binding sites can become occupied by 24p3/NGAL that does not contain growth factors, thereby preventing normal uptake of such factors.

## Conclusions

Apoptosis is a complex and highly regulated process. Numerous cellular factors and pathways are involved in regulating survival and death. Lipocalins appear to be part of this regulatory apparatus but seem not to be directly acting mediators. The potential therapeutic benefits of manipulating lipocalins is highlighted by work investigating “anticalins” as antagonists against signaling molecules or toxic compounds, carriers for drug delivery, membrane receptor antagonists or agonists, as well as other possibilities (Skerra 2008). Thus, the clinical significance of lipocalins is rapidly increasing despite the incomplete knowledge of their functions.

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