Targeting the death machinery in mammary epithelial cells: Implications for breast cancer from transgenic and tissue culture experiments

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Abstract

Apoptosis plays important roles in the development of the mammary gland, and its impairment has been speculated to promote breast cancer. In mammary epithelial cells apoptosis is triggered via the intrinsic pathway which is controlled by interactions between pro- and anti-apoptotic members of the Bcl-2 protein family. The impact of impairing this pathway on the development of breast cancer has been addressed experimentally using transgenic mouse models. Neither overexpression of anti-apoptotic Bcl-2 nor a deficiency of pro-apoptotic Bax were tumorigenic on their own in mammary glands of transgenic mice. Both ways of impairing apoptosis, however, promoted mammary tumorigenesis elicited by c-myc or SV40 T antigen. Likewise, inhibition of the intrinsic pathway in a three-dimensional mammary tissue culture model was insufficient to generate solid aggregates resembling early breast cancer stages but required the concomitant activity of proliferation-stimulating oncogenes. These two experimental approaches have thus substantiated the concept of apoptosis acting as a tumor suppressor mechanism, however point towards a complex picture in which alternative routes to cell death may be involved.

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Apoptotic cell death plays multiple roles during embryonic and organ development (reviewed in [1]). It is involved in sculpturing tissues; it serves to delete structures that are no longer required; it ensures tissue homeostasis by counteracting the proliferative processes involved in tissue renewal; finally, it is involved in the destruction of harmed or potentially harmful cells. Conceivably impairment of any of these functions may lead to neoplasia and cancer.

This review will first demonstrate how the first three of these functions of apoptosis are implemented in the development of the mouse mammary gland. Then the molecular machinery initiating or blocking apoptosis will be described with reference to mammary development. Finally, the consequences of disrupting this machinery in mammary epithelial cells will be discussed based on experiments using transgenic mouse or three-dimensional tissue culture models, respectively. These experiments have substantiated the concept expressed by the fourth of the aforementioned functions of apoptosis in the mammary gland: to counteract malignancy by destroying neoplastically transformed cells.

1. Contributions of apoptosis to mammary gland development

Most development in the murine mammary gland occurs postnatally (Fig. 1A; reviewed in [2]). At birth, the mammary epithelium consists of a small tree-like rudiment which, starting from the nipple, protrudes into an adipose stroma, the mammary fat pad. Already at this stage, the principal tubular organisation of the epithelium is achieved: the ductal lumen is formed by a layer of epithelial cells which is covered by contractile myoepithelial cells. Both cell types are separated by a basal lamina.

During puberty, under the influence of ovarian and pituitary hormones, the tips of the ducts form bulb-shaped structures, the terminal end buds (TEBs). These highly proliferative structures represent the growth zones of the mammary epithelium and serve to elongate the ducts and to add novel branches by bifurcation, thus finally generating an arborized ductal network extending throughout the fat pad [3]. TEBs consist of two cell types: an outermost layer of cap cells which subsequently will differentiate into myoepithelial cells; and the body cells which generate the ductal epithelium. As TEBs are solid structures, lumen formation occurs secondary to growth. It has been shown, that centrally located body cells next to the already existing lumen undergo extensive apoptosis during ductal elongation (Fig. 1B) [4]. Thus, apoptosis helps to shape the luminal space.

With attainment of sexual maturity, pituitary and ovarian hormone levels undergo cycling changes to prepare the organism for a possible pregnancy. The resulting estrous cycle affects the mammary gland which responds to these systemic hormonal changes by a regional proliferation and a limited differentiation of responsive epithelial cells as assessed by thymidine incorporation or milk-protein gene expression, respectively [5,6]. At the end of each cycle, a high proportion

![Fig. 1. Schematic representation of mammary development. (A) Schematic representation of the ductal tree (solid lines), the terminal endbuds (bulbous structures at the ductal tips at puberty; arrows denote direction of duct extension) and the formation and disappearance of differentiated structures during the estrous cycle (small circles) or during pregnancy/involution (clustered circles represent secretory alveoli). See main text for details. (B) Schematic drawing of a longitudinal section through a terminal endbud (TEB). The location of apoptotic cells is indicated. (C) Schematic drawing of a mammary alveolus during involution (cross section). Grey: epithelial cells. Black: cells undergoing apoptosis. Asterisk: alveolar lumen. For the sake of simplicity myoepithelial cells are not shown.](image-url)
of these epithelial cells undergoes apoptosis, thus assuring tissue homeostasis [6,7].

During pregnancy extensive proliferation and cellular differentiation takes place within the mammary epithelium at the expense of the adipose stroma to generate the secretory alveoli [2]. The alveoli represent the secretory units of the mammary gland: they are spherical structures which consist of a single layer of differentiated epithelial cells secreting milk into a hollow lumen and are surrounded by myoepithelial cells serving to squeeze out the milk into the connected duct upon suckling stimulus. After cessation of lactation, this secretory epithelium regresses in a process termed involution [8,9] which can be subdivided into two phases: a first phase characterized by the massive apoptosis of secretory epithelial cells; and a second phase characterized by structural remodeling (Fig. 1C) [10]. By this means, apoptosis is involved in the deletion of structures that are no longer required and thus returns the mammary gland to the pre-pregnant state.

Taken together, apoptotic cell death decisively participates in several aspects of the development of the mammary gland. Because this development predominantly takes place after birth and the murine mammary gland is especially amenable to analysis and experimental manipulation, it represents an attractive system to study fundamental roles of apoptosis during normal differentiation and tumorigenesis.

2. Molecular control of apoptosis in the mammary gland

Apoptosis is an active, cell-autonomous mode of death associated with the extensive proteolysis of cellular proteins (see [11] for review). Cleavage of a subset of these substrate proteins is thought to cause the stereotypic morphological and biochemical pattern associated with apoptosis, such as chromatin condensation, interchromosomal DNA degradation, nuclear shrinkage and fragmentation, cell membrane blebbing and finally fragmentation of the cells into so-called apoptotic bodies that are subsequently phagocytosed by neighbouring cells or macrophages [12].

The key proteases involved in this process belong to a family of cystein-dependent proteases termed caspases that cleave proteins adjacent to aspartate residues within their respective target sequences (see [13] for a recent review). Caspases are present inside the cell as inactive molecules that become activated following extrinsic or intrinsic cues. The caspase family can be subdivided into two classes, effector caspases and initiator caspases. Effector caspases, such as caspase-3, -4 and -7, majorily account for the proteolysis of cellular substrate molecules and exist as dimeric inactive zymogens called pro-caspases [14]. Cleavage by other caspases results in the formation of the active heterotetrameric caspases. By this means, activation of only a few caspase molecules will result in an activation cascade, irres Gibbsely culminating in apoptosis. Therefore, caspase activation is tightly controlled at several levels the most important of which is activation of the initiator caspases which represent the caspases most apical within the activation cascade. Different initiator caspases classify two major molecular pathways controlling apoptosis, the extrinsic and the intrinsic pathway (see Fig. 2) [15].

The initiator caspases of the extrinsic pathway, caspase-8 and -10, become activated by induced close proximity upon binding to adaptor molecules which are recruited to the intracellular portions of activated “death receptors” of the Fas/Tumor Necrosis Factor (TNF) receptor family [15]. To what extent this pathway that is so important for the lymphoid system [16] is involved in the apoptosis of mammmary epithelial cells is not entirely clear. Microarray analyses of gene expression showed increased transcript levels of genes belonging to this pathway at the initiation of involution, suggestive of a causal involvement [17]. However, experiments using mice that are mutated in Fas receptor or Fas ligand led to conflicting conclusions [18,19], with only one study showing impairment of apoptosis within the first day of involution [19]. Recently, two other ligands of the death receptor family, TNF and TWEAK, became implicated in controlling apoptosis early at involution [20]. However, the peak in number of apoptotic cells is normally observed at a time when death receptor ligand expression has already ceased and Bcl-2-related proteins belonging to the intrinsic pathway become expressed [17]. Mechanistically, the first phase of involution can therefore be subdivided into an initiation stage which possibly is triggered by death receptor signalling and a later stage that is rather controlled by the intrinsic pathway.

The activation of the initiator caspase of the intrinsic pathway, caspase-9, is controlled by proteins of the Bcl-2 family which are located at the endoplasmic reticulum, the nuclear envelope and at the outer mitochondrial membrane [21]. Whereas their function at the first two locations is only poorly understood, it is well established that mitochondrial localized Bcl-2 family members control the release of cytochrome c from mitochondria into the cytoplasm. There, cytochrome c binds to an adaptor molecule termed APAF-1 which subsequently multimerizes and recruits pro-caspase-9 molecules [22]. The resulting large multiprotein complex has been termed apoptosome and contains the active caspase-9 initiating the apoptotic cascade [23].

Several studies [10,18,24,25] have demonstrated the activation of effector and initiator caspases during mammary involution, which likely proceeds via the intrinsic pathway and is controlled by Bcl-2-related proteins (reviewed in [26]). These are characterized by the presence of conserved short alpha-helical stretches of amino-acids, the Bcl-2 homology (BH) domains, which mediate protein–protein interaction between family members and structurally as well as functionally classify them as multidomain family members (containing three or four BH domains) or the less well conserved BH3-only proteins (characterized by a single BH3 domain). Multidomain proteins contain a hydrophobic carboxyterminal tail serving for their insertion into intracellular
membranes. The pro-apoptotic multidomain family members Bax and Bak promote the release of cytochrome c at the mitochondria upon activation and are counteracted by anti-apoptotic multidomain proteins such as Bcl-2 or Bcl-xL residing at the same location [21]. BH3-only proteins, like Bad or Bim, can physically interact with multidomain Bcl-2 family members to either activate the pro-apoptotic proteins or to block the anti-apoptotic ones [27]. BH3-only proteins can be controlled at the level of transcription, i.e. by p53 or E2F transcription factors, or post-translationally (reviewed in [28]). The latter comprises mechanisms such as phosphorylation by Akt kinase [29,30] or mitogen-activated kinase (MAPK) [31], sequestration by other proteins [32] and confinement to specific subcellular locations [33]. Activation of the BH3-only protein Bid by caspase-8-mediated proteolysis connects intrinsic and extrinsic pathway [34]. By these means, BH3-only proteins transduce death or survival stimuli to the multidomain family members, thus connecting cellular signalling with the cell death machinery.

The control of apoptosis in the mammary gland by Bcl-2 family members has so far not been precisely elucidated. Whereas changing expression patterns of several multidomain proteins and their differential interactions during the different developmental stages have been documented, the crucial BH3-only proteins triggering apoptosis remain to be identified in most instances [4,35–37]. During post-lactational involution as well as at the metestrous stage of the estrous cycle, increasing levels of Bak have been demonstrated [35]. In addition, upregulation of Bax and of Bcl-xS, a pro-apoptotic splice variant of Bcl-xL, has been observed at the initiation of involution [38]. Bak-deficient transgenic mice verified a partial involvement of Bax in involution [36]. Deletion of the bcl-x gene from the mammary glands of conditional transgenic mice resulted in an accelerated involution.
indicating that Bcl-xS is not of significance for apoptosis induction whereas Bcl-xL is preventing apoptosis at the initial stages of involution [39]. Three-dimensional tissue culture of the human mammary epithelial cell line MCF-10A has suggested a role of the BH3-only protein Bim in lumen formation by apoptosis [40] which was later on substantiated when studying pubertal mammary development of Bim-mutant transgenic mice [41]. Mammary ducts of such mice displayed a disturbed clearing of the lumina adjacent to the TEBs with death of centrally located cells occurring delayed and not by apoptosis.

Caspases can be kept in check by a family of related cellular proteins, the IAPs (reviewed in [42]). One member, XIAP, has been demonstrated to stochiometrically bind and directly inhibit executioner and initiator caspases and their non-activated pro-forms [43]. Other IAPs have been suggested to target caspases for proteasomal degradation [43]. IAPs furthermore interact with two proteins released from mitochondria, Omi/HtrA2 or Smac/DIABLO, respectively, which can trigger apoptosis (reviewed in [44,45]). In the mammary gland, XIAP protein levels increase during secretory differentiation, and the mammary glands of XIAP-deficient transgenic mice showed as the only phenotype a delayed secretory differentiation [46]. Therefore, XIAP appears to fulfill functions different from preventing apoptosis in the mammary gland.

3. Impact of disrupting apoptosis on mammary tumorigenesis

3.1. Impairing the intrinsic pathway in the mammary epithelium of transgenic mice

Transgenic mice which either overexpress foreign genes in their mammary epithelium or carry mutated alleles of endogenous genes offer the possibility to rigorously test putative oncogenic insults in vivo [47]. Many genes leading to breast cancer in transgenic mice also influence apoptosis. TGF-alpha overexpression for instance is impairing for Bax-independent mechanisms of cell deletion during the first phase of involution [36] thus confirming functional significance of the observed upregulation of Bax [38] and furthermore verifying the involvement of the intrinsic pathway in involution. However, reduction was not complete and lower than in WAP-bcl-2-transgenic mice suggesting the existence of a partially redundant molecular mechanism, possibly provided by the pro-apoptotic multidomain Bcl-2 family member Bak. Strikingly, the reduction in apoptosis did not lead to the accumulation of cells or hyperplasia [36], arguing for Bax-independent mechanisms of cell deletion during the second phase of involution. Loss of Bax was per se not tumorigenic [36].

3.2. Impairing apoptosis in transgenic breast cancer models

To address whether impairment of the apoptotic machinery would cooperate with breast tumorigenesis, WAP-bcl-2-transgenic [51] or Bax −/− [54] mice were crossed with transgenic mice which either express SV40 large T antigen (SV40-Tag) or c-myc in their mammary epithelium (see Table 1 for a summary of results).

3.2.1. SV40 T antigen-induced breast cancer

C3(1)/SV40-Tag transgenic mice express the SV40 large T antigen in mammary epithelial cells which functionally impairs Rb family proteins and p53 and thus leads to cancer [53]. Mammary cancer development in these animals progresses in a highly predictable fashion reflecting progressive stages of human breast cancer. Preneoplastic tumors
Bcl-2 overexpression results in a block of cell cycle progression stages where the anti-apoptotic effect dominated the increased proliferation. This anti-proliferative effect was prominent in the sequence of Bcl-2 overexpression, namely a block of the cell cycle. Therefore, the outcome of blocking the intrinsic pathway of apoptosis in preneoplastic or in tumor cells will depend on the relative impact of Bcl-2 family members on apoptosis and proliferation in the particular cell type.

### 3.2.2. c-Myc-induced breast cancer

The c-myc gene encodes a nuclear transcription factor which regulates the expression of target genes associated with cell growth and proliferation (reviewed in [65]). It, in addition, renders cells susceptible to apoptosis [66, 67]. Apoptosis may thus represent an inherent safe-guard mechanism of c-Myc to prevent cellular transformation. Deregulated c-Myc expression induces apoptosis via the intrinsic pathway [68]. Bax and the BH3-only protein Bim have been shown to be transcriptional targets of c-Myc [69, 70]. Amplification of the c-myc gene is commonly found in human breast cancer and thought to contribute to the disease [71]. When overexpressed in the mammary glands of transgenic mice, c-Myc leads to tumor formation only after a latency period which is indicative of the requirement of additional oncogenic events [72]. The mammary epithelium of such MMTV-c-myc transgenic mice displays a high rate of apoptosis at parturition [51], and extensive cell death (which may not be typically apoptotic [73]) has been detected within tumors [74]. Two studies have thus far examined whether an impairment of the intrinsic pathway would act synergistically with c-Myc in inducing mammary tumors.

Overexpression of Bcl-2 was achieved by crossing MMTV-c-myc transgenic mice with W AP-bcl-2 transgenic mice [51]. Expression of Bcl-2 inhibited the c-Myc-induced apoptosis in the mammary epithelium at parturition although not completely. A possible influence of Bcl-2 on proliferation was not assessed. Importantly, overexpressed Bcl-2 shortened the latency period of tumor development [51]. Cell death within tumors appeared not to be influenced by Bcl-2 (R.J., unpublished observations). This experiment therefore suggests that impairing the intrinsic pathway of apoptosis cooperates with c-Myc in initiating mammary tumors.

By crossing with Bax-/- mice, MMTV-c-myc transgenic mice were generated which lack one or both bax wildtype alleles [75]. No information was given whether loss of Bax would result in reduced rates of c-Myc-induced apoptosis in the normal epithelium. However, apoptosis in...
tumors was reported to be impaired when already one bax gene copy was missing whereas proliferation remained unaltered. Neither multiplicity nor latency of tumors were affected by complete loss of Bax. Surprisingly, haploid loss of bax resulted in a higher tumor multiplicity and a trend towards earlier tumor appearance, suggesting that some amount of Bax is indeed contributing to c-Myc-induced mammary tumorigenesis by a thus far unknown mechanism.

In summary, deregulated expression of c-myc is leading to mammary tumors but is counteracted by the concomitantly activated intrinsic pathway of apoptosis. Apoptosis in the epithelium prior to tumor development can be blocked by Bcl-2. As loss of Bax, in contrast to Bcl-2 overexpression, did not accelerate tumorigenesis, Bcl-2 overexpression and Bax loss are not equivalent in this tumor model. A Bax-independent activation of the intrinsic pathway may be used by c-Myc to prevent cellular transformation.

### 3.3. Impairing the intrinsic pathway in a 3D-cell culture model

When cultivated on a reconstituted basement membrane, the mammary epithelial cell line MCF-10A forms spherical aggregates consisting of a layer of polarized epithelial cells which is surrounding a hollow central lumen [76]. These aggregates thus resemble mammary acini. When in such preformed MCF-10A acini ErbB-2, an oncoprotein involved in breast cancer, was activated, proliferation was reinitiated and multi-acinar structures developed which notably were characterized by a filled lumen [76]. This solid, proliferative growth pattern is characteristic of early stage breast tumors. Therefore, the three-dimensional (3D) culture of MCF-10A cells is providing a well-suited model to study basic mechanisms of mammary tumor development in vitro.

#### 3.3.1. Lumen formation

The 3D-growth pattern of MCF-10A cells recapitulates the morphogenetic potential of mammary epithelial cells in vivo. Starting as solid aggregates of proliferating cells, lumen formation (and maintenance) occurs secondary by death of the inner cells [77]. Two distinct modes of cell death of inner cells can be distinguished based on morphology, apoptosis and autophagy, respectively [77]. Autophagy represents an alternative mode of cell death which is characterized by the lysosomal degradation of cellular constituents and organelles [78].

To understand whether inhibition of apoptosis would result in lumen filling, Bcl-2 or Bcl-xL were overexpressed in MCF-10A cells grown in 3D-culture [77]. Overexpression of these molecules prevented caspase-3 activation and apoptosis of inner cells. Lumen formation was, however, only delayed and inner cells were finally cleared by autophagy. This experiment therefore reflects the effect of Bcl-2 overexpression in vivo which despite of impairing apoptosis in the TEB could not prevent lumen formation [4]. In the 3D-culture model, lumen filling required both, inhibition of the intrinsic cell death pathway and of death receptor-mediated autophagy [79]. Thus, it is possible that autophagy plays a role in the lumen formation in vivo as well.

#### 3.3.2. A filled lumen as cancer model

Solid 3D-aggregates of MCF-10A cells bearing a filled lumen have been interpreted to reflect early stages of tumorigenesis, because (i) they can be generated by activating the oncogenic ErbB-2 tyrosine kinase, and (ii) they resemble the solid growth pattern characteristic of carcinoma in situ [76]. Strikingly, expression of oncogenes that primarily induce cellular proliferation was insufficient to prevent lumen formation as exemplified by overexpression of either Cyclin D1 or HPV E7 in MCF-10A cultures (see Table 2) [77]. The enhanced proliferation induced by these oncoproteins provoked an increased number of intraluminal apoptotic cells. Coexpression of Bcl-xL or Bcl-2, however, blocked apoptosis and resulted in lumen filling [77]. These experiments elegantly demonstrated that enhanced proliferative activity requires a concomitantly blocked apoptosis to cause neoplasia. Likewise, the disruption of the intrinsic apoptotic pathway per se is not oncogenic and requires the synergistic activity of a proliferation-promoting oncogene to cause cancer.

Oncoproteins which can induce lumen filling, such as ErbB-2 or v-Src, do so by simultaneously inducing proliferation and preventing apoptosis [77]. Apoptosis of inner cells is triggered by the pro-apoptotic BH3-only protein Bim which is subject to regulation by the mitogen-activated protein kinase (MAPK) pathway [31]. ErbB-2 and v-Src have

### Table 2: Effect of impairing apoptosis on lumen formation in MCF10A 3D-cell culture

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Bcl-2 gene</th>
<th>Proliferation</th>
<th>Apoptosis</th>
<th>Lumen&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>bcl-2</td>
<td>—</td>
<td>Blocked</td>
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<td>[77]</td>
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<td>—</td>
<td>bcl-xL</td>
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<td>Blocked</td>
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<td>[77]</td>
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<tr>
<td>cyclinD1</td>
<td>—</td>
<td>Enhanced</td>
<td>Enhanced</td>
<td>+</td>
<td>[77]</td>
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<td>cyclinD1</td>
<td>bcl-xL</td>
<td>Enhanced</td>
<td>Blocked</td>
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</tr>
<tr>
<td>HPV E7</td>
<td>—</td>
<td>Enhanced</td>
<td>Enhanced</td>
<td>+</td>
<td>[77]</td>
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<tr>
<td>HPV E7</td>
<td>bcl-2</td>
<td>Enhanced</td>
<td>Blocked</td>
<td>Filled</td>
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</tr>
<tr>
<td>erbB-2</td>
<td>—</td>
<td>Enhanced</td>
<td>Impaired</td>
<td>Filled</td>
<td>[40,77]</td>
</tr>
<tr>
<td>v-src</td>
<td>—</td>
<td>Enhanced</td>
<td>Impaired</td>
<td>Filled</td>
<td>[40]</td>
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</tbody>
</table>

<sup>a</sup> “−” denotes: proliferation is unaffected.

<sup>b</sup> “+” denotes: normal clearing of lumen occurs.
been shown to interfere with Bim expression in MCF-10A cells using the MAPK pathway and by this means impair the intrinsic pathway [40].

Obviously, proliferative oncogenes spare the necessity to simultaneously impair apoptosis and autophagy in order to fill the lumen (see above). It is possible that such oncogenes disrupt the signalling pathways involved in autophagy. On the other hand it remains unclear whether the solid MCF-10A aggregates resulting from impairment of both autophagic and apoptotic death do reflect early tumor stages. Such an interpretation, however, would explain why neither in cell culture nor in the transgenic models the disruption of solely the mitochondrial cell death machinery resulted in tumorigenesis. Upon commitment to death the prevention of apoptosis would result in choosing the alternative route of autophagic cell destruction.

4. Conclusions

Expression of Bcl-2 family members has been documented in human breast cancer, although the actual contribution to disease progression and outcome is in many instances unclear [80]. Oncogenic insults such as amplification of the c-myc gene or perturbation of Rb or p53 tumor suppressor function are frequently detected in human breast cancer and thought to contribute to disease [71,81]. It may seem paradoxical that these insults should provoke a high rate of apoptosis in preneoplastic lesions as is the case in the transgenic breast cancer models. Apparently, however, a tumor exhibiting a high rate of apoptosis will have undergone more cell divisions before reaching a certain volume, and thus the likelihood of acquiring additional oncogenic alterations will be increased. By this means apoptosis may in fact contribute to tumor progression [82]. Then, however, the relationship between expression of Bcl-2 family members and breast cancer development may be rather complex. In light of these considerations it may become understandable why the cooperation between impairment of the intrinsic apoptotic pathway and proliferative oncogenes in vivo was not as pronounced as in the 3D-cell culture model.

In combination, however, these two experimental approaches revealed as a common theme that disruption of the apoptotic machinery in mammary epithelial cells is insufficient to cause tumors but does contribute to mammary tumorigenesis in conjunction with proliferative oncogenes. Therefore, as a general notion, the elimination of neoplastically transformed cells is an important function of apoptosis in the mammary gland to counteract malignancy. However, the impairment of the intrinsic cell death machinery at the level of Bcl-2 family proteins did neither in the transgenic models nor in the 3D-cell culture experiments result in a complete abolishment of cell death. Therefore, the actual contribution of apoptosis to tumor suppression in the mammary epithelium cannot be estimated, and alternative routes to cell death may play a role, too.

For a deeper understanding of the role of apoptosis in the tumorigenesis of the breast, it is imperative to more accurately decipher the molecular mechanisms involved in mammary cell death. Thereby it has to be taken into account that Bcl-2 family members can influence cell cycle progression [64] and furthermore interact with the machinery controlling autophagy [83]. Transgenic and 3D-cell culture approaches will then be well suited to rigorously test the predictions resulting from such analyses.

Reviewers

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Biography

Richard Jäger obtained his Ph.D. in 1997 working on the role of Bcl-2 in breast cancer in a transgenic model. As a researcher at the Department of Developmental Pathology, Institute for Pathology, Bonn Medical School, Germany, his current work is aimed at understanding roles of AP-2 transcription factors and of apoptosis in mammary development and breast cancer using transgenic technology.