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The hallmarks of ovarian cancer: proliferation and cell growth

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ABSTRACT

Epithelial ovarian cancer (EOC) is a heterogeneous group of diseases with distinct biological and clinical behaviour. Despite the differences between them, the capability of tumour cells to continuously proliferate and avoid death is maintained among histotypes. This ability is the result of alterations at different levels, causing the deregulation of cell cycle and proliferative-related pathways. Even if the leading role is played by RB and TP53, changes in other molecular pathways are involved in the development of EOC. This ability can be exploited to generate *in vitro* and *in vivo* models resembling the conditions of tumour development in a patient. *In vivo* models, such as patient-derived xenografts (PDX) or genetically engineered mouse models (GEMM), represent a fundamental tool in the study of the molecular mechanisms implicated in each EOC biotype for testing new therapeutic approaches. Herein we describe the major proliferation-related pathways and its disruption found in EOC and how these features can be used to establish *in vivo* models for translational research.

1. Introduction

Epithelial ovarian cancer (EOC) comprises different tumour types, primarily classified by histology into serous, mucinous, endometrioid, clear cell and Brenner (transitional) tumours. This heterogeneity is originated by the presence of a wide variety of alterations affecting oncogenes and tumour suppressor genes, leading to the deregulation of main molecular pathways with divergent cellular function. Based on these molecular changes, ovarian cancer has been stratified into two major classes [1]. Type I tumours are defined by low-grade serous and endometrioid neoplasms that arise in a stepwise manner from borderline, mucinous, clear cell carcinomas and malignant Brenner neoplasms; whereas type II tumours include high-grade carcinomas, carcinosarcomas and undifferentiated carcinomas which precursor lesions have not been identified. Molecularly, type I tumours are associated with distinct genomic defects affecting *BRAF*, *KRAS*, *NRAS*, *ARID1A1*, *CTNNB1* and *PTEN* genes. Besides, a fraction of endometrioid tumours are characterised by defects in the DNA miss-match repair (MMR) machinery leading to microsatellite instability. The aforementioned alterations are rarely found in the other type. On the contrary, type II tumours are characterised by *TP53* mutations and high genomic instability as a consequence of defects in the DNA homologous recombination repair (HR) system [2,3].

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This review highlights the major proliferation-related pathways and its disruption found in EOC and how these features can be used to establish *in vivo* models for translational research.

2. Proliferation and cell growth

The ability to sustain chronic proliferation is shared by all tumour types. Cancer arises from the accumulation of genetic changes that confer to the incipient neoplastic cells the properties of unlimited, autonomous growth and resistance to normal homeostatic regulatory mechanisms. These capabilities can be achieved by different mechanisms, and their understanding will accelerate the development of new molecular targeted therapies that promise to change medical oncology practice.

2.1. *Tumour suppressors: Key regulators*

During cell-cycle progression, tumour-suppressor proteins play a crucial role through the integration of intrinsic and extrinsic signals to decide whether the cell should remain in a quiescent state or enter into the cycle of active growth and division. Two main proteins regulate these processes: RB (retinoblastoma-associated) and TP53. They operate as central control nodes within two key complementary cellular regulatory circuits that govern the decisions of cells to proliferate or, alternatively, activate senescence and apoptotic programmes (Fig. 1) [4]. Most cancer cells harbour defects in these pathways, inactivating them and promoting advantageous mutations, oncogenic growth and uncontrolled cell proliferation [5].

2.1.1. *RB pathway*

The key role of RB protein is the regulation of G1/S checkpoints, acting as the gatekeeper of cell-cycle progression. When RB is working well, it originates the transduction of growth-inhibitory signals that repress E2F (family of transcription factors), modulating the expression of genes involved in cell-cycle progression. Besides RB, other proteins play a crucial function as regulators. This is the case of cyclin-D/cyclin-dependent kinase (CDK) 4/6 and cyclin-E/CDK2 complexes, which regulate RB activity by phosphorylation, leading to the release of E2Fs. The existence of defects in RB signalling pathway causes persistent cell proliferation and cell-cycle deregulation. The loss of RB protein is a common event in some cancer types; however, alterations in other cell-cycle proteins that regulate RB have also been described [6,7].

Alterations in the RB pathway are very common in EOC, being the main defects mutations in *RB* and amplification in *cyclin D*. Particularly, Inactivation of RB in 60% and LOH in 70% of EOC patients has been reported [8–11]. In the most common subtype, high-grade serous ovarian carcinoma (HGSOC), 67% of patients harbour defects in the RB pathway [12].

2.1.2. *TP53 network*

TP53, as a transcription factor, executes each response by directly binding regulatory regions of target genes involved in response to DNA damage and other cellular stresses, DNA repair and cell growth [13]. When the degree of genomic damage is excessive or the levels of nucleotide pools, growth-

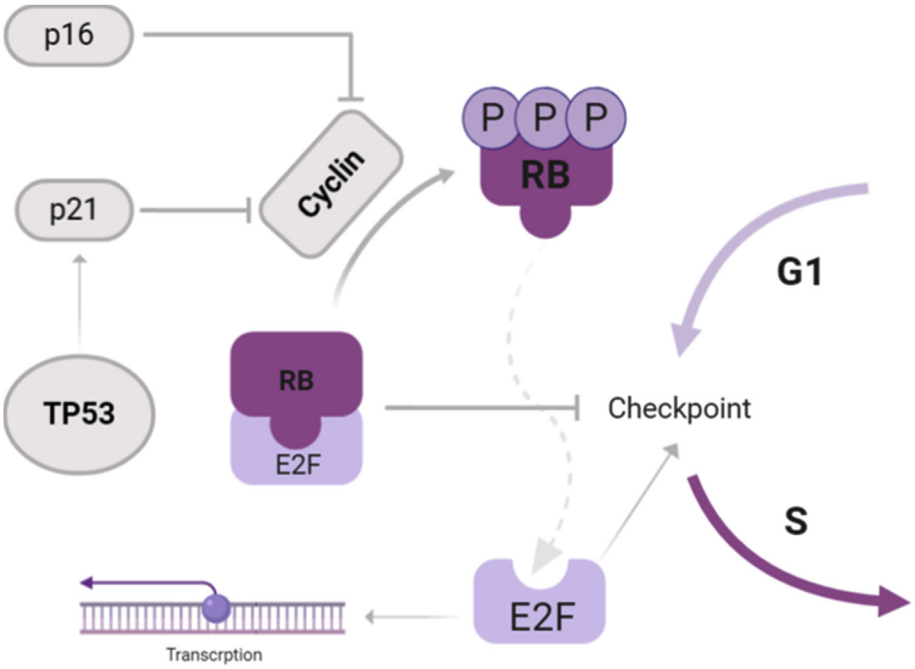

Fig. 1 – The main role of major components implicated in TP53 and RB pathways: Activation of TP53 occurs in response to genotoxic stresses, inducing growth arrest or apoptosis depending on the signal. This TP53 anti-proliferative activity is mediated by its own transcriptional target, p21. RB, however, is inactivated by phosphorylation due to the action of cyclin-dependent kinases CDK4 and CDK6 (inhibited by p16 and p21). This hypophosphorylated form of Rb binds E2F repressing proliferation.

promoting signals, glucose or oxygenation are suboptimal, TP53 can arrest cell-cycle progression until these conditions have been normalised or it can activate apoptosis. Numerous stimuli have been demonstrated to activate TP53, including UV irradiation-induced DNA damage, inappropriate proto-oncogene activation, mitogenic signalling and hypoxia. Depending upon the cellular context, one of several responses is implemented. Deficiency in TP53 protein, loss, gain or inappropriate activation abolishes the G1 checkpoint, compromising the capacity to control cellular proliferation and growth [8].

Although *TP53* mutations have been detected in all histological types of EOC, they have higher frequencies of such mutations in serous carcinomas. According to the TCGA, alterations in the TP53 network represent up to 96% of HGSOC patients [12]. It has been described that the most common altered locus in EOC is 17p13, being the majority of the alterations missense mutations, largely occurring in the DNA binding domain [14].

Even if both key pathways act individually, extensive interaction exists between them. Over 50% of EOC patients have mutations in both the TP53 and RB pathways, including 40% of serous carcinomas [8,15,16].

2.2. *Beyond cell-cycle regulation: Other molecular pathways implicated in proliferation*

Survival and cell growth processes are also controlled by additional pathways that implicate signalling stimuli by growth factors and hormones. In cancer conditions, it is common to find disruption of these pathways by genetic and epigenetic changes leading to constitutively activate proliferation programmes [6]. These signalling pathways often begin with the activation of tyrosine kinase receptors (TKR) by growth factors. However, activation of some G-protein-coupled receptors (GPCRs) can also activate certain branches of this signalling pathway. Depending on the proteins that are subsequently recruited by the receptor, several downstream signalling pathways might be activated, promoting uncontrolled proliferation in addition to overcoming cell death programmes. Some of the major pathways that impact on cell proliferation are explained in the following sections.

2.2.1. *Epidermal growth factor pathway (EGF, IGF, TGF-β)*

EGF receptors are implicated in gonad development, growth and differentiation of the ovarian follicle and post-ovulatory repair. These receptors are also known as the ErbB or type I TKRs and include four ErbB proteins; ErbB-1 (EGF receptor), ErbB2, ErbB3 and ErbB4 [17].

The normal ovarian surface epithelium (OSE) responds to signals generated by the EGF receptor displaying phenotypic plasticity. This is characterised by the transition between epithelial and fibroblastic phenotypes. This situation, usually limited to immature, regenerating or neoplastic epithelia, if it is presented in adult OSE, suggests that this tissue is 'primed' to respond to EGF receptor during tumour development and progression [18].

Activation of the EGF receptor is also implicated in the stimulation of numerous signal transduction pathways related to cell growth and survival, including the ERK/MAPK, PI(3)K/Akt, STAT, PLCγ, STAT, among others. In malignant cells, EGFR is associated with metastasis, angiogenesis, pro-apoptotic and pro-survival signalling cascades. There is evidence that increased EGF receptor expression is an early event in EOC development and some studies provide data about how early changes in EGF receptor expression may promote ovarian cancer [19].

Defects on this receptor are common among cancer types, particularly, in approximately 48% of EOC expressed (between 10 and 20% due to *EGF receptor* amplification), with higher incidence in mucinous and low-grade serous subtypes [20,21]. In a significant proportion of HGSOC, hyperactive PI3K/Akt/mTOR pathway may be attributable to upstream deregulations in TKRs. In fact, amplifications or mutations in TKRs such as *ERBB3*, *ERBB2*, *EGFR* or *IGF1R* have been described with frequencies of 1–9% [22].

Another mechanism involved in the expression of EGF is the dysregulation in TGF-β signalling. TGF-β is a potent inhibitor of cellular growth, and loss of function in the TGF-β pathway can result in uncontrolled proliferation leading to tumour development [23]. Although mutations in this pathway are rare in this tumour, there are other mechanisms by which TGF, directly or indirectly, is associated with the promotion of ovarian cancer cell proliferation [24].

2.2.2. *Cytoplasmic tyrosine kinases and phosphates-AKT/mTOR pathway (PI3K/Akt/mTOR)*

The PI3K-Akt-mTOR signalling pathway is a central regulator of many crucial functions in normal conditions such as cell survival, growth, proliferation, angiogenesis, transcription, translation and metabolism. Phosphatidylinositol 3-kinase (PI3K), Akt (a serine/threonine kinase) and mammalian target of rapamycin (mTOR) are the three main junctions in the pathway and are typically activated by upstream signalling of tyrosine kinases and other receptor molecules such as hormones or mitogenic factors [25]. The primary role of PI3K proteins is to convert phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) [26,27]. These molecules activate downstream signalling components, being the most notable one of the protein kinase Akt. Acting both upstream and downstream Akt is found mTOR, a key Ser/Thr kinase. mTOR is presented in two different multiprotein complexes, target of rapamycin complex (TORC) 1 and 2 (Fig. 2) [28]. Defects in this pathway are very common in most human cancers. Dysregulation of major components will cause activation of other downstream signalling pathways linked with oncogenesis, survival and tumour cells proliferation [29–33].

In EOC, PI3K/Akt/mTOR has been identified as the most frequently altered pathway. Mutations in PIK3CA, mainly in exons 9 and 20, were prevalent in ovarian clear cell (35%) and endometrioid carcinoma (20%) compared to serous carcinoma (2.3%) [34,35]. On the other hand, HGSOC presents amplifications of the p110 subunit of PI3K (PIK3CA) presented in 20% of cases while amplification of one of the *AKT* isoforms (*AKT1*, *AKT2* or *AKT3*) occurs in 15–20% [29,36,37].

Besides the major components, other participants appear to be implicated in the regulation and modulation of the pathway: firstly, PTEN protein, which can act as a negative

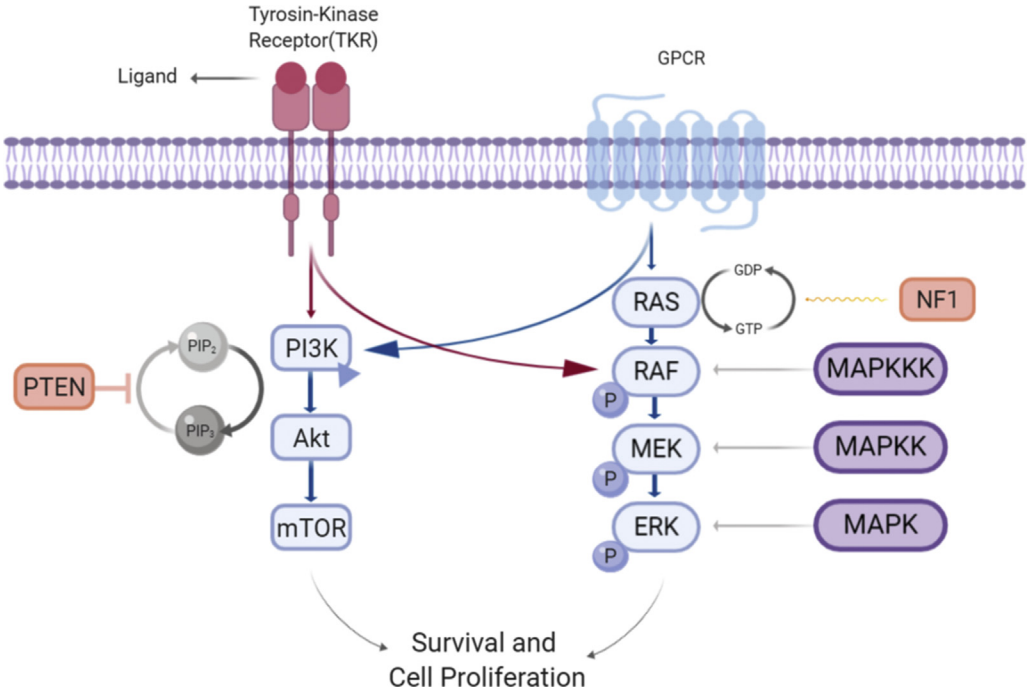

Fig. 2 – Principal signalling pathways implicated in survival and cell proliferation: activation by ligands triggers autophosphorylation of the receptors (GPCRs or TKRs), leading to the generation of binding sites that consequently will recruit pathway-initiation proteins (RAS and PI3K), thus provoking the beginning of the signalling cascade.

regulator while functioning as a tumour-suppressor gene. In normal conditions, PTEN counteracts PI3K by degrading its product, PIP_3. Loss of function of PTEN due to homozygous deletions, inactivating mutations, loss of heterozygosity (LOH) or epigenetic modifications amplifies PI3K signalling and promotes tumourigenesis. Between alterations found in EOC, LOH was described to be common in endometrioid (up to 40%) and serous ovarian carcinoma (up to 28%) [37,38]. Somatic mutations in *PTEN* (21%) have also been detected in the majority of grade 1 or stage 1 endometrioid tumours. Like PTEN, INPP4B also functions as a negative regulator of this pathway. LOH at the *INPP4B* locus (4q31.1–3) in 39.8% OC patients has been detected [29,36,39].

2.2.3. *Ras/Raf/MEK pathway*

The mitogen-activated protein kinases (MAPKs) cascade (the Ras/Raf/MEK/ERK pathway) is a TKR-mediated signalling pathway that regulates several physiological processes, such as cell growth, differentiation and apoptotic cell death. Due to the crucial importance of this signalling pathway, the deregulation of the MAPK signalling cascades is involved in the pathogenesis of various human cancer types [40]. One of the classical alterations in this pathway involves RAS oncoprotein. Mutations compromise Ras–GTPase activity (intrinsic negative-feedback mechanism), triggering a cascade of serine/threonine kinases (such as RAF and MEK) that culminates in the activation of a mitogen-activated protein kinase (usually an extracellular signal-regulated kinase/ERK). Finally, MAPKs are translocated to the nucleus where they will modulate the expression of a wide range of genes involved in cell growth and survival (Fig. 2) [41].

Punctual mutations are more prevalent in early-stage associated histologies of EOC such as low-grade serous, mucinous, endometrioid or clear-cell ovarian cancer [42,43]. On the contrary, HGSOC often presents alterations related to copy number changes such as amplifications in *KRAS* (11%), *MAPK* (20%), loss of *NF1 gene* (8%) or less frequently, mutations in *KRAS*, *NRAS* or *BRAF* [12].

2.2.4. *Notch signalling*

Notch is a family of mammalian transmembrane receptors (Notch 1–4) for membrane-bound ligands (JAG1, JAG2, delta-like1-4). Upon binding, Notch receptors undergo cleavage, releasing a Notch intracellular domain. This domain migrates to the nucleus, where different target genes such as *cyclin D, p21CIP1, NF-β* and *c-MYC* are found (Fig. 3). Aberrant activation of the Notch signalling pathway has been implicated in numerous human malignancies, including EOC [44–47]. Particularly, the amplification of the chr19p13.12 region (*Notch3*) and its up-regulation at mRNA and protein levels have been detected in a large percentage of OC [48,49]. Another example of alteration in this pathway is the CXCR4/SDF1α chemokine system, which plays a key role in EOC cell biology [50]. CXCR4 and its ligand, chemokine SDF1α, are widely expressed in EOC cells and are associated with an unfavourable prognosis, promotion of tumour cell proliferation, survival and government of the migration of malignant cells [51].

2.2.5. *WNT pathway*

The WNT signalling pathway is an ancient and evolutionarily conserved pathway that regulates crucial aspects of cell fate

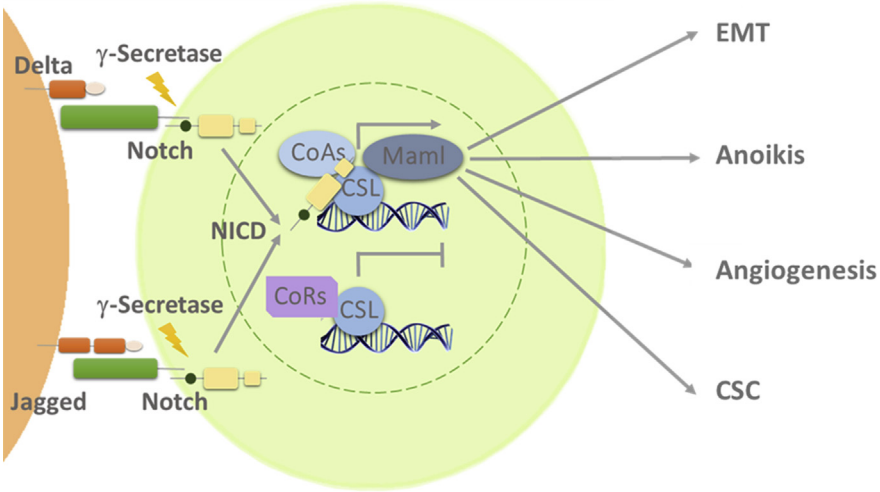

Fig. 3 – The Notch signalling pathway: Activation of Notch by its ligand leads to the cleavage of the intracellular domain and its following translocation to the nucleus. Once in the nucleus, this domain will activate CSL (transcription factor). The CSL co-repressor complex (CoR) is replaced by the co-activator complex (CoA), initiating transcription of Notch target gene.

determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development. Two major signalling branches have been identified including a canonical or Wnt/β-catenin dependent pathway and non-canonical or β-catenin-independent pathway which can be further divided into the planar cell polarity and the Wnt/Ca2+ pathways [52].

The functional relevance of the WNT pathway is reflected by the high number of cancers that present its deregulation [53]. Specifically, in EOC, alterations at different levels have been found across the different components of the pathway. Endometrioid subtype often presents constitutive activation via missense mutation of *β-catenin* (*CTNNB1*) [54]. This tumour also shows nuclear accumulation of β-catenin [55]. However, nuclear localisation of CTNNB1 in other subtypes lacking mutations in this gene suggests that the WNT/β-catenin pathway could be activated by other molecular mechanisms [56].

Endometrioid tumours represent a notable exception as mutations in Wnt-related genes are in general extremely rare in the other ovarian cancer histotypes. *CTNNB1* mutations are found in 16–54% of endometrioid ovarian cancer cases. Besides endometrioid subtype, mutations in *CTNNB1* are also found in rare cases of mucinous ovarian cancer. Likewise, genetic alterations in other members of the Wnt cascade, such as *APC*, *AXIN1* and *AXIN2*, have also been detected in this specific ovarian cancer histotype [57–61]. Additional alternative epigenetic mechanisms leading to autocrine overexpression of Wnt components or the inhibition of antagonists have also been reported in the EOC [53].

2.3. *Resistance to cell death*

Most, if not all, cancer cells acquire resistance to the various mechanisms limiting tumour growth. This has been associated with two distinct barriers to proliferation: senescence, a typically irreversible entrance into a non-proliferative but viable state; and apoptosis, which involves cell death. Tumour cells develop a variety of mechanisms to limit or circumvent proliferation barriers [4].

The most common way of blocking apoptosis is by inactivating the TP53 tumour-suppressor pathway, which eliminates a critical damage sensor from the apoptosis-inducing circuitry [62]. As already mentioned, *TP53* is altered in almost all HGSOC, suggesting that, in this tumour, cancer cells escape the control mechanisms that regulate apoptosis [4,63]. Another strategy to avoid apoptosis is up-regulating anti-apoptotic pathways, increasing expression of anti-apoptotic regulators (BCL-2, BCL-XL) or survival signals (IGF1/2) and down-regulating pro-apoptotic factors (BAX, BIM, PUMA) (Fig. 4).

Additionally, it has also been demonstrated that necrotic cells can release bioactive regulatory factors, such as IL-1a, directly stimulating the proliferation of adjacent cells and facilitating neoplastic progression. These tactics to evade cell death programmes through modulation of apoptotic regulatory factors are used by tumour cells in EOC [64,65].

2.4. *Replicative immortality*

Telomere maintenance works as a generational clock that counts cell divisions and regulates cell lifespan [66]. The eventual immortalisation of cells with rare variants has been attributed to their ability to maintain telomeric DNA length long enough to avoid cell death programmes.

The most common mechanism involves TERT, the protein component of telomerase (a ribonucleoprotein enzyme that synthesises telomeres and maintains telomeric ends). It has been seen to be active in 85–90% of human cancer cells. *TERT* variants together with other telomere-maintenance genes have been associated with ovarian cancer risk and outcome [67,68].

2.5. *Increased metabolism in cancer cells*

Cell proliferation constitutes the essence of neoplastic disease and involves not only the deregulation of cell cycle and other

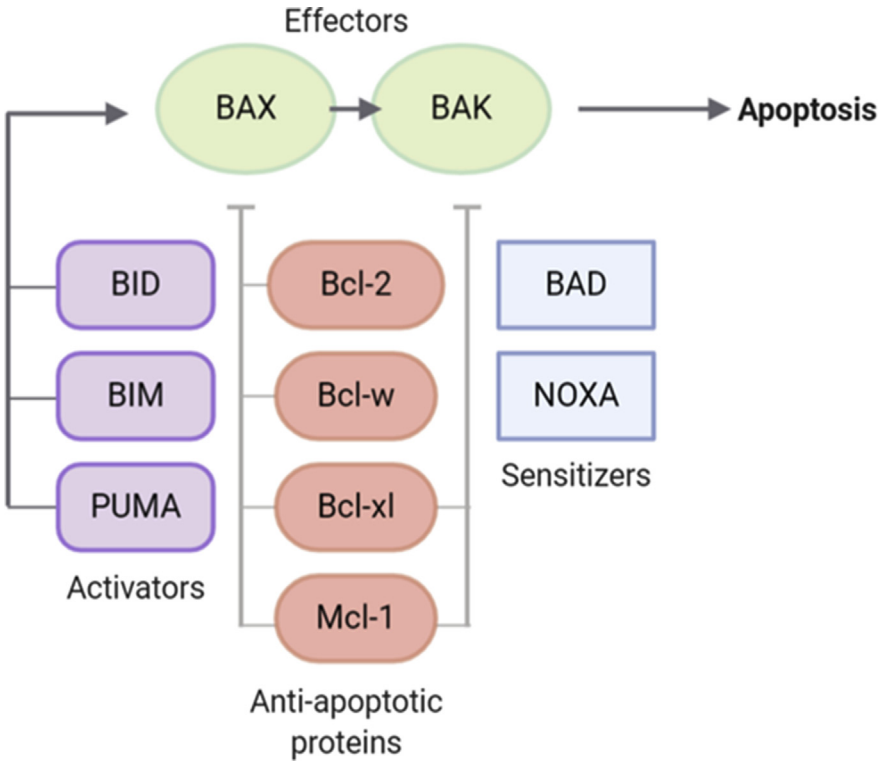

Fig. 4 – The BCL-2 family members and their role in the apoptotic pathway. While anti-apoptotic proteins or gatekeepers will promote cell survival, the combinational effect of pro-apoptotic proteins (effector, sensitisers and activators) will induce cell death cascade.

proliferation-related pathways but also adjustments in energy metabolism in order to fuel the main functions of cells [4]. In this way, metabolic reprogramming and the ability of cancer cells to switch between energy substrates and metabolic pathways (termed bioenergetics flexibility) enable cancer cells to fulfil their high proliferative and survival potentials [69–72].

Cancer cells employ both conventional oxidative metabolism and glycolytic anaerobic metabolism. However, their proliferation is marked by a shift towards increasing glycolytic metabolism even in the presence of O2 (Warburg effect) [73]. This effect has been shown to be associated with activated oncogenes (e.g. *RAS*, *MYC*) and mutant tumour-suppressor genes (e.g. *TP53*). These alterations in tumour cells have been primarily selected for their benefits in conferring the capability of cell proliferation, avoidance of cytostatic controls and attenuation of apoptosis [74].

3. Animal models

Advances on understanding the molecular biology of tumours, especially the defects in proliferative pathways, have allowed the generation of *in vitro* and *in vivo* models that reflect this reality. However, the existence of appropriate

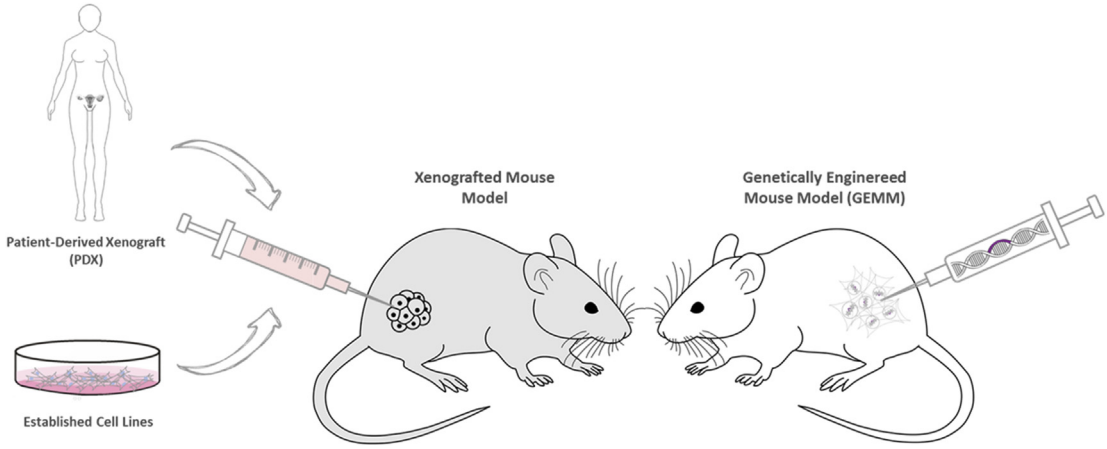

Fig. 5 – Principal strategies to generate adequate animal models: Tumour xenografts and GEMMs.

Table 1 – Available animal model for the study of proliferation and cell growth of EOC

Tumour Type	GENOTYPE	Main findings	Reference
High-grade serous carcinoma (HGSC)	DICER−/−; PTEN −/−	Establishment of the fallopian tube cell as the origin of the tumour. Presents envelop to the ovaries and aggressive metastasis through the abdominal cavity	Kim et al. (2012) [89]
High-grade serous carcinoma (HGSC)	TP53mut; DICER-; PTEN-	Suggests that the ovary can also be a potential site of origin of HGSOC. Develops HGSOC tumour in the peritoneal cavity, including primary tumour and metastasis (ascites)	Kim et al. (2015) [90]
Serous carcinoma	BRCA1−/−; TP53−/−; CMYC+	Describes higher sensitivity in BRCA1-associated ovarian cancer to platinum and DNA-damage response	Xing and Orsulic (2006) [91]
Serous carcinoma	BRCA1−/−; TP53 −/−; PRB−/− BRCA2−/−; TP53−/−; PRB−/−	Contribution of different molecular pathways, Rb, Tp53 and BRCA proteins in the development of the stage IV of the disease (presenting peritoneal carcinomatosis, ascites and distant metastasis)	Szabova et al. (2012) [92]
Low-grade serous carcinoma/ granulosa cells tumour (LGSC)	KRAS−/−; PTEN-	Contribution of different molecular pathways to the development of the disease (particularly Kras mutation and pten depletion) and remark the OSE cell as origin.	Fan et al. (2009) [93]
Endometrioid carcinoma	KRAS+; PTEN−/−	Describes the specific tumour histomorphology and metastatic potential of the disease. Model of endometriosis and endometrioid ovarian carcinoma.	Dinulescu et al. (2005) [86]
Endometrioid carcinoma	APC−/−; PTEN −/−	Cooperative role of PI3K/PTEN and Wnt/b-catenin pathways in pathogenesis.	Wu et al. (2007) [94]
Endometrioid carcinoma	KRAS+; PTEN−/− MUC1+; KRAS+; PTEN−/−	Concomitant activation of kras and depletion of pten trigger Muc1-positive epithelial tumours with endometrioid histology	Tirodkar et al. (2014) [95]
Endometrioid carcinoma	ARIDA−/−; PTEN−/−	Demonstration of the insufficient role of inactivation of Arid1a for tumour initiation, showing the requirement of additional genetic alteration such as pten depletion to produce tumourogenesis	Guan et al. (2014) [87]
Mucinous ovarian (MOC)	TP53+/+; PTEN−/−; KRAS+ TP53+/−; PTEN−/−; KRAS+ TP53−/−; PTEN−/−; KRAS+	Presents the first mouse model of mucinous tumour formation from ovarian cancer cells.	Ren et al. (2016) [96]
Leiomyosarcoma	BRCA1−/−; TP53−/−	Demonstrates the cooperative role of BRCA1 and tp53 to ovarian tumourigenesis.	Quinn et al. (2009) [97]
Leiomyosarcoma	TP53−/− BRCA1−/−;T P53−/− RB−/−; TP53−/− RB−/−; TP53−/−; BRCA1−/−	Examines tumour formation with conditionally expressed alleles of BRCA, TP53 and Rb alone or in collaboration.	Clark-Knowles et al. (2009) [98]
Serous tubal intraepithelial carcinoma (STIC)	BRCA1−/−;TP53mut; PTEN−/− BRCA1+/−; TP53 mut; PTEN−/− BRCA2−/−; TP53 mut; PTEN−/− BRCA2+/−; TP53 mut; PTEN−/−	Establishment of serous tubal intraepithelial carcinoma as a precursor lesion in HGSOC and demonstrates the origin in fallopian tube secretory epithelial cells.	Perets et al. (2013) [85]
Poorly differentiated carcinoma	TP53−/−; RB−/−	This model serves for a better understanding of the neoplasm and as a useful tool for the evaluation of emerging detection and treatment strategies.	Connolly et al. (2003) [99]
Poorly differentiated carcinomas and serous carcinomas	TP53−/−; CMYC+; KRAS+ TP53−/−; KRAS+; AKT+ TP53−/−; AKT+; CMYC+ TP53−/−; AKT+; CMYC+; KRAS+	The model resembles human ovarian carcinomas in their rapid progression and intraperitoneal metastasis spread.	Orsulic et al. (2002) [100]
Poorly differentiated carcinomas (OSE)/ well-differentiated tumours (FTE)	APC−/−; PTEN−/−	Demonstrate the importance of cell of origin in mouse cancer GEM.	Wu et al. (2016) [101]

models that accurately predict clinical efficacy and perfectly mimic the evolution of the disease is not yet a fact, delaying the progress in oncology research. In this sense, EOC is not an exception. EOC histotypes (serous, endometrioid, mucinous and clear cell) are characterised by distinct histopathological and molecular features that pose unique therapeutic challenges. These particular attributes and challenges can be addressed through the use of laboratory models.

In cancer research, cell culture systems should be the starting point of any study. However, the use of a more reliable and disease-mirroring system such as animal models is essential for the advancement in the field. Whereas tumour-derived cell lines play a critical role in facilitating cancer biology in *in vitro* studies, representing a powerful tool, *in vivo* animal models can more accurately recapitulate molecular characteristics of primary tumours and their micro-environment, being a more pertinent pre-clinical testing platform [75]. Focusing on *in vivo* system, murine models are the most commonly used in experimental studies, due to their similarity with human physiology and molecular signalling pathways. Among these models, human tumour xenografts and genetically modified mouse models (GEMM) are the ones that better simulate the human progression of the disease, representing adequate *in vivo* platforms for investigating tumourigenic mechanisms and testing novel therapies (Fig. 5) [76,77].

In view of each model having its own advantages and limitations, it is advisable to carefully consider them when choosing the most suitable one for every type of study. Human tumour xenografts, on their behalf, are appropriate for fast-growing tumours, being usually applied for the study of tumourigenesis, tumour histology and tumour response to novel therapies. Xenografts are typically generated by isolating tumour cells from patients (surgical samples, ascites or established cell lines) and transplanting into immunocompromised mice that do not reject human, either under the skin or into the organ type in which the tumour originated. These models display a suppressed immune system such as thymus-deficient 'nude' or severe combined immunodeficient mice (SCID) [78]. The implementation of xenografts from established cell lines has disadvantages due to discrepancies concerning the origin of several ovarian cancer cell lines, typically resulting in tumours with histology distinct from what is expected [79]. However, PDX models are considerably interesting when going with well-characterised clinical and molecular data. PDXs have unique attributes that make them particularly adequate for drug discovery and pre-clinical studies on new therapies, including concurrent human and murine clinical trials, since they closely resemble human cancers in terms of drug response [75,80–82].

On the other hand, GEMMs are especially useful to study the role of certain oncogenes and suppressor genes in the initiation and progression of many cancers, allowing the analysis of specific roles and interactions during disease progression [83]. Additionally, advances in GEMMs technology have enabled the management and control of previously introduced transgenes or gene mutations through conditional expression tools, mimic disease progression and physiologic states in a more accurate way.

Due to the existing variability among EOC histotypes, a wide number of GEMMs models with different molecular features are available. The largest offer appears within the most prevalent histology, serous ovarian cancer. In these studies, models have been used to display progression from untransformed tubal epithelium to invasive ovarian HGSC [84]. Similar models have been used to mimic different stages of the HGSOC disease by specifically inactivating key regulator genes such as *BRCA1/2*, *TP53*, *PTEN and Dicer1*, also leading to the formation of ascites and metastatic HGSOC lesions (Table 1) [85].

GEMMs have also been successfully used to study the oncogenesis of endometrioid EOC. To achieve a reliable model for this disease, different combinations of depletions and mutations of different genes such as *KRAS, PTEN, ARID1A* or *APC* were used. These models accomplished the generation of endometriosis and endometrioid ovarian adenocarcinoma with widespread metastases among others (Table 1) [86,87].

However, the availability of an animal model for mucinous EOC is particularly scarce as it is difficult to establish a cell of origin and also because it harbours unique clinical features when compared to other EOCs. Some avatar models have been generated for this tumour entity in which patient tumour histology was recapitulated with a high degree of similarity with the corresponding PDX xenograft, indicating the clinical utility of this *in vivo* platform [88]. Similar to mucinous EOC, clear-cell carcinoma GEMMs have not yet been engineered. Other GEMMs have been generated with the objective of imitating different EOC histotypes or describing the progression and development of the disease under variable conditions (Table 1).

In conclusion, EOC cells present multiple alterations in molecular pathways that lead them to proliferate and survive. Thanks to novel technologies, many sophisticated models have been generated, allowing the study of ovarian cancer. Comprehension of the main mechanisms involved in proliferation pathways is crucial to understand the pathogenesis and overcome the disease through the establishment of adequate *in vivo* models that can be used as pre-clinical testing platforms.

Declaration of competing interest

None declared.

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