When flies and mice develop cancer

Meeting on Development and Cancer

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The Spanish National Cancer Institute (CNIO) Meeting on Development and Cancer took place between 4 and 6 February 2008 in Madrid, Spain, and was organized by K. Basler, G. Morata, E. Moreno and M. Torres.

Keywords: cancer development; cancer progenitors; cell competition; stem cells

EMBO reports (2008) 9, 730–734. doi:10.1038/embo.2008.137

Introduction

Developmental biologists rightly argue that genes regulating developmental pathways are reiterated in cancer development. At the recent Spanish National Cancer Institute (CNIO) Meeting on Development and Cancer, novel concepts and processes that are considered to

be common to both embryonic and cancer development were discussed. It is worth pointing out that tumour formation should be considered to be a form of aberrant organ development, in which many developmental pathways that control proliferation, differentiation and growth or morphogenesis are affected.

This report is structured in three parts, describing the work presented at the meeting according to the stages of tumour development to which it pertains. First, the normal behaviour of cell populations that are the targets of transformation, in particular adult stem cells and the pathways that regulate their behaviour. Second, processes that occur at the early stages of cancer development before morphological malformations are detectable, in particular the process that is best known from studies in flies as ‘cell competition’. Third, developmental processes and pathways that are active in the growing tumour—which we consider to be an extrinsic organ—for example, the recruitment of blood vessels or the role of morphogens in controlling the size and shape of tumours, and the progression from hyperplasia to invasive tumours (Fig 1).

The stem cells of cancer

One of the unsolved mysteries of most cancers is the identity of the tumour-initiating cell that precedes pre-cancerous mutations. One of the prevailing theories is that cancer originates from adult stem cells. The reasoning behind this theory is that mutations in adult stem cells are more likely to have tumorigenic consequences than if the same mutations occur in cells that are destined to die or to terminally differentiate. I. Sánchez-García (Salamanca, Spain) addressed the contribution of cancer stem-cells to tumour biology by limiting oncogene expression only to stem cells. He showed that the phenotype and biology of B-cell lymphoma (BCL) can be established in mice by restricting BCL6 expression to stem cell antigen 1 (SCA1)⁺ cells; this implies that oncogene expression in a stem cell is all that is required to reprogramme it fully, giving rise to a full-blown oncogene-specific tumour with all its mature cellular diversity.

Several researchers reported on studies regarding normal stem-cell biology in *Drosophila* and mouse tissues, given the evidence that stem cells might be the target population of cancerous mutations. R. Lehmann (New York, NY, USA) described new targets of the translational regulators Nanos and Pumilio that affect germline stem-cell proliferation in the *Drosophila* ovary. She highlighted

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Submitted 6 March 2008; accepted 16 June 2008; published online 18 July 2008

the importance of 14 RNAs that localize to the germplasm and are translationally regulated, among which are some transcriptional repressors that might provide an exciting link between translational and transcriptional control of stem-cell self-renewal. It is not fully understood how stem cells regulate their proliferation rate or how they control the balance between self-renewal and differentiation. J. Knoblich (Vienna, Austria) showed that in the absence of the *Drosophila* tumour suppressor Brat, stem cells in the fly brain overproliferate because all daughter cells continue to self-renew (Betschinger *et al*, 2006). He also showed that the Brat-related protein Mei-P26 regulates self-renewal in germline stem cells by repressing cellular growth in daughter cells that no longer contact the stem-cell niche, thereby establishing a link between lack of stem-cell differentiation and cancer formation. Interestingly, Mei-P26 binds to the Argonaute (Ago) 1 protein and controls stem-cell lineages by inhibiting the microRNA pathway (Neumueller *et al*, 2008). H. Lin (Yale, CT, USA) discussed the Piwi/Ago gene family—which is essential for stem-cell division in diverse organisms—and the exciting recent discovery of a new class of Piwi-interacting small RNAs, which have crucial roles in self-renewing divisions of germline stem cells in *Drosophila* and mice (Lin, 2007).

The relevance of findings in *Drosophila* pertaining to the subject of stem cells and cancer development was questioned by M. Manzanera (Madrid, Spain). Manzanera talked about embryonic pluripotency in various vertebrates, highlighting the fact that mammalian development is remarkably different from that of other vertebrates, and that embryonic stem cells use different gene networks to maintain pluripotency. M. Torres (Madrid, Spain) described new methods to mark embryonic lineages and reported recent findings on the role of the transcription factor MEIS1 in haematopoietic stem-cell development. An interesting connection between stem-cell behaviour and telomere biology was pointed out by M. Blasco (Madrid, Spain). Blasco described how long telomeres can act as a general marker of adult stem cells in several tissues. Moreover, she used telomerase mutant mice to reveal effects on epidermal stem-cell behaviour, and consequent premature aging and cancer formation. She also provided evidence that telomeric RNAs might regulate telomerase activity at chromosome ends. Overall, it became clear that the study of stem-cell biology is essential for understanding of early tumour formation.

During the various talks, a lively discussion emerged on the concept of the 'cancer stem-cell' and whether this is too loose a definition that should be replaced by, for example, the 'tumour-initiating cell'—the cell that starts to accumulate pretumoral mutations—or the 'tumour-propagating cell'—the cell that is required for the growth and propagation of a tumour in transplantation experiments.

Cancer growth before morphological changes

One of the reasons behind the poor (or absent) detection of pre-tumoural lesions is their size—they are often too small to be noticed, for example, when the number of tumour cells present in a given tissue is only in the order of hundreds or thousands. Recent research in *Drosophila* indicates that reduced cell numbers might not be the only reason as to why a group of proliferating cells grows unnoticed. What if a transformed cell proliferates without producing morphological changes because the increase in cell number is balanced by the apoptotic elimination of surrounding cells and, therefore, the total cell number does not change? An intriguing phenomenon in which this occurs is known as 'cell competition' and has been described in

Fig 1 | Tumour development and genes involved in the different stages.

Schematic representation of how stem cells (A), by acquiring a mutation through cell competition (B) and by the selection of additional mutations, can give rise to the 'tumour organ' (C). The genes involved in these processes are listed on the right-hand side, and most of them have been described to have a functional role only in studies in *Drosophila*. Bcl6, B-cell lymphoma 6; dMyc, *Drosophila* Myc; Dpp, decapentaplegic; Jak, Janus kinase; JNK, C-Jun amino-terminal kinase; Lgl, lethal-giant-larvae; Mwd, Maxwell's Demon; Prep1, Pbx-regulating protein 1; STAT, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor; Wg, Wingless.

Drosophila. During this process, cells proliferate while killing surrounding wild-type cells through the induction of apoptosis, so that the total cell number does not change. As a consequence, clonal expansion does not generate morphological aberrations and the growth of these cells goes unnoticed. Stormy debates and discussions centred on the extent to which this process is relevant to human cancers, in which the surrounding cells are often not killed, but rather act as 'nurse' cells supporting tumour-cell proliferation and growth.

N. Baker (New York, NY, USA) discussed the active role of corpse-engulfment pathways in cell competition, and vividly described the cellular behaviour of winner and loser cells at the interaction boundary. He showed that the probability of a loser cell dying at the boundary is 10-times higher than that of the same cell dying if it is not in contact with the winning cells. Moreover, this probability increases if the losing cell is surrounded by more than one winning cell. As a consequence, clones of outcompeted cells break into increasingly smaller patches before their disappearance from the growing disc. This implies that engulfment and/or the amount of winning cells in

contact with the losing cell are important determinants in the triggering of apoptosis (Li & Baker, 2007). Interestingly, Baker also showed that, at the interaction boundary, winning cells orientate their division towards the dying cell through an unknown mechanism that might involve planar polarity genes such as *atrophin*. In an attempt to identify components that are crucial for cell competition, the E. Moreno (Madrid, Spain) laboratory analysed a cell-competition response. By using a combination of RNA-interference screening and microarray analysis, his group has identified four new genes that are upregulated specifically in loser cells at early stages of cell competition and that are required for their apoptotic elimination. The expression of one of these novel genes, termed *Maxwell's Demon*, distinguishes winner cells from loser cells. Finally, Moreno also reported a non-apoptotic form of cell competition induced by *Drosophila* Myc (dMyc) in the *Drosophila* germline stem-cell niche that appears to regulate stem-cell fitness and accelerates the differentiation of the daughter cells. A similar form of non-apoptotic cell competition in somatic stem-cell niches of the *Drosophila* ovary was discussed by A. Spradling (Baltimore, MD, USA). He gave an inspiring talk speculating on the possible role of cell competition in maintaining stem-cell fitness and on its requirement for the accumulation of pre-cancerous mutations. Moreover, by using the somatic stem cells of the *Drosophila* ovary as an example, he showed how the migration of stem cells from one niche to another could aid stem-cell competition. T. Adachi-Yamada (Kobe, Japan) described cell competition in a stem-cell-based tissue such as the *Drosophila* midgut. By manipulating the Notch pathway, undifferentiated overproliferating tumours are formed that trigger non-autonomous activation of C-Jun amino-terminal kinase (JNK) around the mutant cell population, which is reminiscent of the phenomena of cell competition and morphogenetic apoptosis. It is unclear whether JNK activation has a role in the absence of tumours; however, Adachi-Yamada proposed that the differentiated cells (enterocytes) might use the JNK pathway to suppress the overproliferation of stem cells (enteroblasts). In addition, he showed that clones mutant for *discs overgrown* generated in imaginal discs overproliferate and trigger JNK activation at the borders between wild-type and mutant cells, indicating that various abnormalities, including overproliferation, trigger non-autonomous apoptosis.

O. Gerlitz (Jerusalem, Israel) described a novel mechanism that regulates cell competition spatially, in which Decapentaplegic (Dpp) regulates the responsiveness to its own survival signal across the developing wing by inversely controlling the expression of the Brinker (Brk) repressor and a new co-repressor. In the centre of the wing disc, Dpp represses Brk and induces the expression of the co-repressor so that, in competitive situations where Dpp signalling activity is abnormally reduced, the resulting increase in the levels of Brk, which complexes with this co-repressor, activates the JNK-mediated apoptotic pathway. This new mechanism provides a solution to the longstanding puzzle of why cell competition induced by weakened Dpp signalling is stronger in regions where the levels of Dpp are higher and, therefore, less limiting. T. Igaki (Kobe, Japan) described the role of Eiger in cell competition induced by lack of Scribble (Scrib). Scrib-mutant clones are eliminated from wild-type tissues by JNK-induced apoptosis. Igaki showed that Eiger is required to trigger JNK-mediated apoptosis in Scrib-mutant cells. Interestingly, endocytosis through Rab5 appears to be crucial for correct Eiger signalling. He proposed a model wherein the presence of normal surrounding cells would stimulate endocytosis in the Scrib-mutant cells through an unknown mechanism. This increase in endocytosis leads to

activation of Eiger signalling, resulting in JNK activation and cell death. Igaki proposed that this could act as an intrinsic tumour-suppression mechanism to prevent the appearance of Scrib-mutant tissues.

Cell competition has so far been described only in *Drosophila* and it is unclear whether it exists in vertebrates. D. Shafritz (New York, NY, USA) described a cell competition-like process in the rat liver on transplantation of fetal liver stem/progenitor cells (Oertel & Shafritz, 2008). Transplanted progenitor cells are able to expand while killing normal surrounding hepatocytes. Intriguingly, the process is observed only after a partial hepatectomy, implying that some regenerative signals are required to activate the transplanted progenitor cells and to trigger this cell competition-like process. Multipotent cells could also be involved in the regeneration of damaged tissues. I. Hariharan (Berkley, CA, USA) introduced an elegant mutagenesis scheme designed to identify enhancers of the regenerating potential of developing tissues and, as an example, showed that dMyc enhanced regeneration.

In conclusion, it was apparent that the genetic network and the mechanisms underlying cell competition are slowly being deciphered, and evidence is accumulating for the relevance of this process in vertebrates.

Developmental pathways involved in cancer growth

Several speakers provided good examples that developmental and growth-control pathways are frequently mutated in cancer development in flies and mice. Starting with flies and continuing with cell competition, G. Morata (Madrid, Spain) gave an overview of how cell competition was originally discovered (Morata & Ripoll, 1975), and went on to present recent results that link cell competition to tumour progression in the *Drosophila* wing imaginal disc. Cell competition is an ongoing process that invasive and highly aggressive tumours use continuously for expansion. Mutant larvae lacking the tumour suppressor Lethal-giant-larvae (Lgl) develop extensive tumours affecting the central nervous system and imaginal discs. However, gl-mutant clones generated in wild-type imaginal discs are apoptotically eliminated by surrounding non-tumour cells through a process akin to cell competition. The Morata group identified a mutation in a so far unknown gene—termed 'factor X'—which transformed lgl-mutant cells into super-competitors that eliminate surrounding normal cells and give rise to invasive neoplastic tumours.

Several speakers described novel components of growth-control pathways in *Drosophila*. K. Basler (Zurich, Switzerland) identified new nuclear coactivators of the Wingless (Wg)/Wnt and Hedgehog pathways that execute their transcriptional outputs. In particular, his laboratory has described Coop as a cofactor of Pangolin (Pan) in the Wg pathway. When Pan binds to Armadillo, it recruits Legless, Pygopus, Hyrax and cAMP response element-binding protein, and this complex can act as a transcriptional activator of Wg target genes, such as *Dll* and *senseless* (Mosimann *et al*, 2006). By contrast, when Pan binds Coop, they recruit the co-repressor Groucho and thereby repress Wg targets like *Dll* and *senseless*. Basler also showed a surprising role for Hyrax/Parafibromin in the Hedgehog pathway, where it acts as a dimer with Cubitus interruptus (Ci)/Glioma-associated oncogene homologue 3 to enhance Ci transcriptional outputs.

D. Pan (Baltimore, MD, USA) spoke about the Hippo (Hpo) kinase cascade, which is a growth-suppressive pathway that represses target genes by phosphorylating, and thereby inactivating, the transcriptional coactivator Yorkie (Yki; Dong *et al*, 2007). He showed spectacular results regarding the conserved role of the Hpo pathway in growth control in both *Drosophila* and mammals. In

addition, he described a Hpo-responsive enhancer element in the locus of the cell-death inhibitor, *Drosophila* inhibitor of apoptosis 1, which contains a binding site for the transcription factor Scalloped (Sd). Sd binds to Yki directly and is required for Yki-induced target-gene expression and tissue overgrowth *in vivo* (Wu *et al*, 2008). Continuing with the Hpo pathway, G. Halder (Houston, TX, USA) showed that the atypical cadherin Dachshous regulates growth through the Hpo pathway and has a role in organ-size regulation. He proposed that a gradient of Dachshous drives organ growth, suggesting that differences in the levels of Dachshous are more important for organ growth than its absolute levels. According to the Halder model, differences in Dachshous levels in the developing wing primordium induce proliferation until the gradient becomes too shallow. N. Tapon (London, UK) described how imaginal disc cells that contain mutations in components of the *Drosophila* carboxy-terminal Src kinase, Src, *Drosophila* ankyrin-repeat, SH3-domain, and proline-rich-region containing protein network can have increased motility and detach from the epithelia, but when doing so activate JNK and undergo apoptosis (Langton *et al*, 2007). This system might act as a tumour-suppression mechanism. Finally, M. Dominguez (Alicante, Spain) described the roles of the Notch and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways in tumour growth and development. She showed that JAK/STAT signalling is instrumental for *Drosophila* eye development and acts upstream of Notch to induce organ growth. When both pathways are forced to act together, they promote a notable tumour phenotype in both epithelial and blood systems.

The mammalian experimental systems then took to the stage. F. Blasi (Milano, Italy) described the role of the Pbx-regulating protein 1 (PREP1) homeobox gene in normal mouse development and cancer. This gene is essential for mouse development, as knockout mice die at the pre-gastrulation stage. A hypomorphic strain exhibits several phenotypes, for example, on adult haematopoietic stem cells, and these mutant mice also develop tumours, which are mostly lymphomas. Consistent with PREP1 having a role in tumour suppression, a large portion of human tumours lose expression of PREP1. N. Ferrara (San Francisco, CA, USA) described the recruitment of blood vessels by growing tumours through the cross-talk between tumour cells and stromal cells (Shojaei & Ferrara, 2007). He also reported on the successful use of anti-angiogenic therapies in the clinic, in particular the use of Avastin—a humanized murine antibody—in solid tumours. L. Parada (Dallas, TX, USA) elegantly described studies in mice that model brain cancers, in particular glioma formation. Only recently has it become apparent—from studies *in vivo* and *in vitro*—that the glioma tumour-initiating cell might be an ‘adult’ neural stem cell (Kwon *et al*, 2008). By using conditional alleles of phosphatase and tensin homologue deleted on chromosome 10, p53 and neurofibromatosis 1 in mice, Parada attempted to identify the tumour-initiating cell in glioblastoma (Zhu *et al*, 2005); his findings indicated that it is an early progenitor cell. He vividly defended the mouse as the preferable genetic model for the study of cancer development, and emphasized his opinion on the caution needed before relating conclusions from studies of cell competition in flies to human cancers. E. Wagner (Madrid, Spain) showed that epidermal deletion of c-Fos caused cessation of papilloma growth in a Son of sevenless-transgenic skin-tumour model. Inhibition of tumour growth is due to increased epithelial differentiation caused by induction of tumour necrosis factor- α -converting enzyme and premature induction of the Notch pathway. Finally, G. van den Brink

(Leiden, The Netherlands) described the morphogenetic pathways that mediate colon cancer development. He proposed the existence of a morphogenetic code in colon crypts, determined by a series of morphogens that maintain the correct architectural complexity of the adult tissue. Consistent with a ‘French flag model’ of positional information, several morphogens were found to dictate cell identity. From bottom to top, the Wnt morphogen stimulates the proliferation of the precursor cells, whereas from top to bottom, an Indian Hedgehog gradient inhibits their proliferation by inducing bone morphogenetic protein signals that counteract Wnt function. Disruptions of the morphogenetic code can lead to cancer, for example, mutations in adenomatous polyposis coli that disrupt the dependency of the stem/precursor cells on the extrinsic Wnt gradient (van den Brink & Offerhaus, 2007). Interestingly, these ideas are already prompting the design of clinical trials (see below).

Conclusions and future perspectives

What new concepts relevant to human cancers have emerged from this meeting, and what are the unanswered questions in the field of development and cancer from which cancer patients will benefit in the future?

Tumours can be viewed as an aberrant organ in which developmental signals and processes have been disrupted, resulting in the unregulated growth of self-renewing cells. A crucial question is to what extent this process diverges from normal developmental pathways. Greater differences between the ‘tumour organ’ and the normal tissues result in better chances of detection and the implementation of targeted therapies that do not affect the function and homeostasis of other organs. One opportunity for intervention originates from the fact that the tumour might be using embryonic developmental pathways that are no longer active in the adult. Therefore, targeting such embryonic pathways should be safe for the adult and should only be deleterious during pregnancy. This potential is already being exploited in the case of anti-angiogenic therapies. Angiogenesis is essential during embryonic development, but is less important during adult life. However, tumours of certain size are often crucially dependent on angiogenesis for their growth, and the recruitment of vasculature by the tumour is being successfully targeted by drugs with manageable side effects. The knowledge of how adult tissues are maintained by positional information could also be of use for therapeutic purposes. The roles of morphogens and the morphogenetic code in maintaining normal tissue homeostasis in adult tissues are already being used to design clinical trials for the treatment of colon-cancer patients. By using Hedgehog proteins to repress colon stem-cell proliferation, patients might finally benefit from the growing knowledge of morphogenetic signalling.

Evidence is accumulating that tumorigenic ‘cancer stem cells’—capable of infinite self-renewing divisions—exist in a range of tumours. What is the cellular origin of these cells? One possibility is that they might derive from normal stem cells, which are long lived and share the ability for self-renewing. An alternative nonexclusive possibility is that fully or partly committed progenitors dedifferentiate through genetic alterations and acquire stem-cell characteristics. A pivotal issue in this regard is the extent to which cancer stem cells differ from normal stem cells. If cancer stem cells—like the best-studied stem cells in *Drosophila*—depend on external signals and have to reside in specialized stem-cell niches, the interaction between the niche and the cancer stem cells might provide another target for therapeutic intervention. Conversely, if cancer stem cells

are substantially different from their normal counterparts, they could be targeted without affecting normal homeostasis and tissue renewal, which would also provide a therapeutic opportunity. Induction of differentiation in cancer stem cells at the expense of proliferation is already being successfully applied in the treatment of promyelocytic leukaemias (Wang & Chen, 2008).

Many of the current cancer-detection methods are based on the morphological changes that the disease causes in the affected tissue. Unfortunately, detectable aberrations tend to appear only at late stages, when tumours have crossed a certain size threshold, and are generally more aggressive and refractory to clinical treatment. Is it possible to detect earlier lesions? One possible mechanism through which tumour cells might proliferate without creating apparent aberrant morphology is through a cell competition-like process, in which tumour-cell proliferation is coupled with apoptotic elimination of neighbouring normal cells (Moreno, 2008). If the mechanisms used by cancer cells are similar to those underlying cell competition in flies, our knowledge of this phenomenon might make it possible to recognize cancer at early stages by using 'cell-competition markers'. Protecting wild-type cells by preventing cell competition at early stages might provide a new means to impair tumour growth, and could be combined with classical therapies that directly attack the cells of the tumour. However, the possible role of cell competition in cancer development requires further research, and must be validated by studies in mice and humans.

ACKNOWLEDGEMENTS

We thank all of the speakers for sharing their results and apologize to those whose work could not be reported owing to space constraints.

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