The albino deletion complex and early postimplantation survival in the mouse

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Summary

The albino deletion complex in the mouse represents 37 overlapping chromosomal deficiencies that have been arranged into at least twelve complementation groups. Many of the deletions cover regions of chromosome 7 that contain genes necessary for early embryonic development. The work reported here concentrates on two of these deletions (c6H, c" DSD), both of which were known to be lethal around the time of gastrulation when homozygous. A detailed embryological analysis has revealed distinct differences in the lethal phenotype associated with the c 6H and c" DSD deletions. c6H homozygous embryos are grossly abnormal at day 7-5 of gestation, whereas C "DSD homozygous embryos appear abnormal at day 8-5 of gestation. There is no development of the extraembryonic ectoderm in c6H homozygotes, whereas extensive development of this tissue type occurs in c" DSD homozygotes. The visceral endoderm is abnormally shaped and the parietal endoderm appears to be overproduced in c6H homozygotes; these structures are not affected in c" DSD homozygotes. The embryonic ectoderm is runted in both types of embryo and it is not possible to obtain homozygous embryo-derived stem-cell lines for either deletion. Mesoderm formation occurs in the c" DSD but not in the c6H homozygotes. The c" DSD deletion chromosome complements the c6H chromosome in that the lethal phenotype of the compound heterozygote is similar to that of the c6H homozygote. These results suggest that a gene(s) necessary for normal development of the extraembryonic ectoderm is present in the c" DSD but deficient in the c6H deletion chromosome.

Key words: mouse development, chromosomal deletions, homozygous lethals, early postimplantation survival, genetic complementation.

Introduction

The genetic system in the mouse known as the albino deletion complex represents an extremely promising model for studies dealing with genes that are known to be involved in mammalian development. These deletions represent a series of 37 overlapping chromosomal deficiencies that cover the albino (c) locus on mouse chromosome 7 (Russell, 1979; Russell & Raymer, 1979; Russell, Russell, & Kelly, 1979; Russell et al. 1982). Complementation analyses have resulted in the classification of these deletion chromosomes into 12 groups (see Fig. 1 for map) (Russell et al. 1982). Three of the deletions, c1H, c6H and c25H (Gluecksohn-Waelsch, 1979), while not part of this complementation study, were assigned, on the basis of published information, to 3 of the 12 groups, namely E, Bi and Dp (or Dq), respectively (Russell et al. 1982). The complementation analysis showed that
Fig. 1. Complementation map of the albino deletions. This map is modified from that published by Russell et al. (1982). Deleted regions are represented by dark lines. The exact positions of the chromosomal breakpoints are not known. Postulated functional areas of the chromosome are indicated below the genetic map and no correlation with physical distance is implied. Marker loci include \( tp \) (taupe), \( c \) (albino), \( Mod-2 \) (mitochondrial form of malic enzyme), and \( sh-1 \) (shaker-1). \( \text{cM} = \) centimorgan. Symbols on the right represent the name of each complementation group and the number in parentheses represents the number of individual deletion chromosomes assigned to each group. The number for complementation groups \( E \), \( Bi \) and \( Dp \) includes deletions \( c^{25} \), \( c^{M} \) and \( c^{25H} \) (Gluecksohn-Waelsch, 1979), respectively, which were not part of the complementation analysis involving the other 34 deletions but were tentatively assigned to these groups on the basis of published information (Russell et al. 1982); \( c^{25H} \) is assignable to \( Dp \) or \( Dq \), as denoted by the ?. 'V' indicates viable albino mutants; the number of V mutants listed represents mutations derived from radiation (or control) mutagenesis experiments. There is yet no direct genetic or molecular evidence that \( V \) mutations are deletions.

There are at least three regions surrounding the albino locus that are needed for normal embryonic development during the preimplantation or early postimplantation stages. Homozygous deletion of one of these regions, located proximal to the albino locus, results in embryonic death around the time of implantation. A second region, located distal to the albino locus, is needed for normal development during the preimplantation stages. A third region, which is located distal to the albino locus but proximal to the preimplantation lethal region, is needed for normal development around the time of gastrulation.

Although several of the albino deletion chromosomes affect the embryo during early development, only two of them have been studied in any detail (reviewed by Gluecksohn-Waelsch, 1979). One of these is the \( c^{25H} \) deletion, which is presumed to belong to either the \( Dp \) or \( Dq \) complementation group. This deletion represents about 7% (approximately 5cM) of chromosome 7 (Miller et al. 1974) and, when homozygous, causes cessation of cell division beginning at the 2- to 6-cell stage, with death occurring 1-2 days later (Lewis, 1978; Nadijcka, Hillman & Gluecksohn-Waelsch, 1979). The only obvious ultrastructural abnormality that has been found for this deletion is aberrant shapes of the nuclei. This phenotype is quite distinct from that observed for other preimplantation lethals and is the earliest acting of all known genetic abnormalities that affect the mouse embryo (reviewed by Magnuson, 1986).

Embryos homozygous for the other deletion that has been studied, the \( c^{M} \) deletion (approximately 2cM in length and presumed to belong to the \( Bi \) complementation group), are morphologically abnormal by 6-5 to 7-0 days of gestation (Lewis et al. 1976). At this time, cells of the extraembryonic ectoderm are abnormally organized and begin to show signs of degeneration. In addition, the parietal yolk-sac endoderm extends markedly into the decidual tissue. The
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embryonic ectoderm, however, is structurally normal. By 7-5 days of gestation, the extraembryonic ectoderm is extremely disorganized and pyknotic in appearance. The embryonic ectoderm is reduced in size but still remains organized normally. Death of the embryo occurs by day 8.0, and resorption moles are still detectable at day 12-14. Lewis and associates (1976) have proposed that the c6H deletion, when homozygous, interferes with normal differentiation of the parietal endoderm and extraembryonic ectoderm, and that reduction in the embryonic ectoderm and failure of primitive-streak formation are secondary abnormalities attributed to a dying embryo.

The c6H deletion affects the embryo at a time when the three primary germ layers are being formed and the anterior-posterior axis is being established. There are four other deletions (c11DSD, c6FRO40Hd, c4FRO40Hd, c2YPS) that also affect the embryo around this time. Although they map to the same general area of mouse chromosome 7 as c6H and have been included in the same complementation group (Bi) as c6H (Russell et al., 1982), the exact chromosomal breakpoints are not known. A detailed embryological analysis has not been done for these latter four deletions, and it is not known whether they produce a homozygous phenotype similar to the c6H deletion.

In the work described here, we confirm the phenotypic observations reported by Lewis et al. (1976) for the c6H deletion. In addition, we have extended their observations by attempting to establish embryo-derived stem-cell lines from c6H-homozygous embryos. Our results indicate that the deleted genes are needed not only for normal development of the extraembryonic structures but also for development of the embryonic ectoderm. In addition to the work on the c6H embryo, we describe for the first time the homozygous phenotype associated with the c11DSD deletion. Our results show that this homozygous phenotype is not the same as that described for the c6H deletion, and a complementation analysis indicates that the c11DSD deletion partially complements the c6H deletion, thereby defining a new functional unit and complementation group in this region of chromosome 7.

Materials and methods

(A) Mice

The c6H and c11H albino deletion mice used in these experiments originated at the MRC Radiobiology Unit, Harwell, UK, and were obtained from Dr Salome G. Waelsch (Albert Einstein College of Medicine, Bronx, New York). The c11DSD mice originated at the Oak Ridge National Laboratory. The mice are maintained as closed-colony, but not strictly inbred, homozygous stocks (c6H/c6H, c11H/c11H, c11DSD/c11DSD), and all three stocks, when present in the heterozygous state with chinchilla (ch), produce a dilute chinchilla coat colour. For experimental purposes, the stocks were expanded by crossing deletion heterozygotes with CF-1 mice (c/c) to produce c6H/c (albino) and c11H/c (chinchilla) offspring (c6H, c11H or c11DSD). The albino progeny were then crossed to appropriate males (described in the Results section) to produce experimental embryos.

(B) Histology

Embryos were dissected from uterine horns of naturally mated females at days 7.5, 8.5 or 9.5 of development (the day of the vaginal plug is considered to be day 0). The dissected embryos were fixed in 2.5% glutaraldehyde in phosphate-buffered saline (PBS) for 2-3 h at room temperature. They were then washed extensively with PBS, dehydrated and embedded in plastic. Sections of 3 μm thickness were cut and stained with Schiff’s reagent and counterstained with 0.05% toluidine blue.

(C) Production of embryo-derived stem-cell lines

Embryo-derived stem-cell lines were established from inner-cell masses according to the in vitro culture procedures outlined by Martin (1981). Day-3-5 blastocysts were obtained by flushing the uterine horns of pregnant females. These embryos were cultured overnight and the inner-cell masses were isolated the following day by immunosurgery (Solter & Knowles, 1975). The inner-cell masses were then plated onto a feeder layer of irradiated STO fibroblast cells, cultured for 3-5 days, trypsinized and passaged to a new feeder layer. Stem-cell lines were established by progressive passage of these inner-cell-mass-derived colonies. The only change from the original procedure of Martin (1981) was that medium containing 10% fetal calf serum and 10% calf serum was substituted for teratocarcinoma-conditioned medium.

Because the embryo-derived stem-cell lines were established from embryos obtained from heterozygous crosses, they could either be homozygous or heterozygous for the deletion chromosome, or homozygous for the wild-type, non-deleted chromosome. For genotyping, DNA was purified from stem cells that had been separated from STO-feeder cells by a double preplating technique (Martin, 1981). The purified DNA was then cut with EcoRI, run on an 0.8% agarose gel and transferred to nitrocellulose. The blotted DNA was then hybridized (0.1% sodium pyrophosphate, 1% sodium dodecyl sulphate (NaDodSO4), 0.2% bovine serum albumin, 0.1% Ficoll, 0.2% polyvinylpyrrolidone, 5 mM-EDTA, 10% dextran sulphate, 1m-NaCl, 0.1 mg ml⁻¹ denatured, sonicated salmon testis DNA, 50 mM-Tris-HCl, pH 7.5, 65°C for 18 h) with an α-32P dCTP nick-translated clone 12A probe (specific activity of 2×10⁶ cts min⁻¹ μg⁻¹). Clone 12A contains a 5.2 kb EcoRI fragment which maps to mouse chromosome 7 somewhere between the albino locus and the Mod-2 locus (Disteche & Adler, 1984; clone 12A was kindly provided by Dr Christine Disteche of the University of Washington).

Thus, homozygous stem cells would not contain this fragment, whereas heterozygous stem cells would contain one copy and wild-type stem cells would contain two copies. In those cases where a faint hybridization signal was detected,
possibly due to STO contamination, the stem cells were then double preplated and cultured for an additional 8–10 days in the absence of feeders. This procedure induces embryoid body formation and completely removes any possible STO contamination (Martin et al. 1977). When a homozygous-deletion stem-cell line was identified by the absence of hybridization with clone 12A, the blot was stripped in 1·5 mm-NaCl, 0·01 mm-EDTA, 0·02% NaDodSO4, 0·02 mm-Tris–HCl, pH 7·8, by adding the filter to the boiling solution and incubating for an additional 15 min at 70°C. These blots were then rehybridized with a nick-translated mouse α-actin cDNA clone obtained from Dr G. Schultz, University of Calgary. Using this clone, the DNAs from all stem-cell lines hybridized with equal intensity irrespective of c-region genotype.

Results

(A) The c^6H deletion

Histology

74 embryos were dissected at 7·5 days of gestation from uterine horns of c/c^6H females that had been mated to c/c^6H males. Of these, 15 (20%) embryos were small and similar in appearance to what has been described by Lewis et al. (1976) as the c^6H phenotype. Histological sections of normal embryos (Fig. 2A) were examined and compared to sections of the putative homozygous embryos (Fig. 2B,C). The extraembryonic ectoderm of homozygous embryos was completely disorganized and small in appearance when compared to normal littermates. The visceral endoderm consisted of a layer of cuboidal cells that thickened into a small clump at the antimesometrial pole. This appearance is in contrast to the single layer of squamous-shaped cells observed in normal littermates. The parietal endoderm was organized into a long extension that protruded from the antimesometrial tip of the homozygous embryo. Upon dissection, this overgrowth could be seen to extend into the surrounding decidual material. This organization was abnormal when compared to the single layer of parietal endoderm that surrounded the visceral endoderm of normal littermates. The embryonic ectoderm of homozygous embryos was organized into a small egg cylinder with the beginning of proamniotic cavity formation. Neither primitive-streak formation nor mesoderm production had occurred in the homozygous embryos. Both events, however, had taken place in normal littermates. By day 8·5 of gestation, only resorption moles remained.

Embryoid-derived teratocarcinoma stem-cell lines

Embryoid-derived stem-cell lines were established from 40 inner-cell masses isolated from blastocysts obtained from c/c^6H females that had been mated with c/c^6H males. When these lines were genotyped by Southern blot analysis, all of them gave a hybridization signal with clone 12A. Since this fragment is missing from c^6H DNA (Disteche & Adler, 1984), these results indicate that all of the lines are either heterozygous for the deletion or homozygous wild-type. The expected number of homozygous c^6H lines, based on a 25% frequency, is 10, which is significantly different (χ² = 11·428, P < 0·0005) from the observed frequency of 0.

To serve as a positive control for the c^6H results, embryo-derived stem-cell lines were also established from eight inner-cell masses isolated from blastocysts obtained from a cross of c/c^6H females mated with c/c^6H males. The c^6H deletion (E complementation group) partially complements the c^6H deletion (Bi group) producing runted and sterile adult mice (Gluecksohn-Waelsch et al. 1974; Lewis et al. 1978). Of the 8 c^6H embryo-derived stem-cell lines, six showed hybridization signal with clone 12A and two did not. When hybridized with the α-actin cDNA clone, all lanes showed hybridization (Fig. 3). These results indicate that the two negative lines are homozygous for the c^6H deletion whereas the remaining six positive lines are heterozygous or wild type.

(B) The c^11DSD deletion

Histology

37 embryos were dissected at day 7·5 of gestation from uterine horns of c/c^11DSD females that had been mated to c^6H/c^11DSD males. It was not possible to distinguish a mutant class of embryos based on gross phenotypic differences at this time. None of the embryos showed a c^6H/c^6H phenotype. Although there was a variation in size amongst the embryos, the range was not noticeably different from that observed for the 47 control embryos (c/c female × c^6H/c^11DSD male) also dissected at day 7·5 of gestation.

At day 8·5 of development, 91 embryos were dissected from c/c^11DSD females mated to c^6H/c^11DSD males. Of these, 21 (23%) were grossly abnormal when compared to their littermate embryos. None of the 51 control embryos (c/c female × c^6H/c^11DSD male) showed this same phenotype. Examination of histological sections of 14 of the abnormal embryos revealed a consistent morphology (Fig. 2D,E). Both the parietal and visceral endoderm were normal in appearance and the extraembryonic structures were well developed. The embryonic ectoderm had progressed to the stage where primitive streak formation and mesoderm production had occurred. The amniotic cavity, amnion, exocoelom, chorion and eutocoplacental cavity were present. In many cases, the mesodermal layer of the amnion appeared thicker than expected. A striking feature associated with most of the abnormal embryos was the extensive development of the allantois. When dissected at day
Fig. 2. Thick-section light micrographs of (A) day-7.5 normal embryo, (B) day-7.5 $\epsilon^H / \epsilon^H$ embryo, (C) higher magnification of the embryo in B to show the parietal endoderm extension, (D) day-8.5 normal embryo, (E) day-8.5 $\epsilon^{HSD} / \epsilon^{HSD}$ embryo, (F) day-8.5 $\epsilon^{HSD} / \epsilon^H$ embryo, (G) day-8.5 $\epsilon^H / \epsilon^{HSD}$ embryo. a, amniotic cavity; al, allantois; am, amnion; c, chorion; ec, ectoplacental cavity; eo, exocoelom; ep, ectoplacental cone; ee, embryonic ectoderm; ex, extraembryonic ectoderm; h, heart; m, mesoderm; nt, neural tube; pe, parietal endoderm; ps, primitive streak; s, somite; tb, trophoblast cells; ve, visceral endoderm; ys, yolk sac. Magnification: A,B,D,E,F,G, x40; C, x80.
occurred in either embryo. Littermates and mesoderm formation had not yet been established. This is significantly different from uterine horns of \( c^+/c^11DSD \) females mated to \( c^+/c^6H \) males. Of these, six (18%) were grossly abnormal when compared to their littermates. All six showed a phenotype similar to that described above for the \( c^{11DSD}/c^{11DSD} \) homozygous embryos. Examination of histological sections of four of the abnormal embryos (Fig. 2F) revealed that the parietal and visceral endoderm were normal in appearance. Primitive-streak formation and mesoderm production had occurred, and the extraembryonic structures were well developed. The amniotic cavity, amnion, exocoelom, chorion and ectoplacental cavity were present. The mesodermal layer of the amnion was often thick and development of the allantois was extensive.

A cross of \( c^+/c^6H \) females mated with \( c^{ch}/c^{11DSD} \) males was also made and 49 embryos were dissected at day 8-5 of gestation. Of these, 15 (30%) were grossly abnormal when compared to littermates. 12 of these embryos (24% of the total) were phenotypically similar to the \( c^{11DSD}/c^{11DSD} \) and the \( c^{11DSD}/c^H \) embryos described above, whereas three of the embryos (6% of the total) were extremely small and retarded in development. Eight of the former and two of the latter abnormal embryos were prepared for histological analysis. Of the eight, all showed a histological phenotype similar to that described for the \( c^{11DSD}/c^{11DSD} \) and the \( c^{11DSD}/c^H \) embryos (Fig. 2G). The extraembryonic structures were well developed, mesoderm had been established and the visceral and parietal endoderm were normal in appearance. In addition, the development of the amnion and allantois was extensive. The two severely retarded embryos had very small egg cylinders in which the embryonic ectoderm showed normal organization but the extraembryonic ectoderm was extremely disorganized. No signs of mesoderm production were detected and the parietal endoderm was not overgrown. This phenotype is not consistent with what has been observed for \( c^{H} \), or \( c^{11DSD} \)-homozygous embryos. It is possible that these severely retarded embryos were dying for reasons unrelated to the c-region genotype.

**Discussion**

The \( c^H \) phenotype was described 11 years ago by Lewis et al. (1976), and we have repeated and confirmed their original observations in this report. The most striking feature of the homozygous phenotype is the lack of any differentiation of the extraembryonic ectoderm. By day 7-5 of gestation, this structure clearly remained as a mass of disorganized, dying cells. The apparent overgrowth of the parietal endoderm is also interesting. However, it is not clear whether this phenotype represents an overproduction
of cells or a normal proliferation of parietal endoderm coupled to the absence of growth in the rest of the embryo.

Lewis and coworkers postulated that the deleted genes affect directly the development of the extraembryonic structures and that the runted appearance and eventual death of the embryonic ectoderm are secondary effects. We tested this hypothesis by attempting to make embryo-derived teratocarcinoma stem-cell lines from c^H-homozygous embryos and found that this was not possible. These results suggest that a gene(s) which affects viability of inner-cell-mass cells has been deleted. Because the inner-cell-mass cells represent a pool of stem cells that give rise to the embryonic ectoderm (Gardner, 1978), one can conclude that the deleted gene(s) are affecting directly the development of this cell type.

Four other mutations (c^11DSD, c^4FR60Hd, c^5FR60Hg and c^2YPSj) are known to delete the same general area of chromosome 7 as c^H, and are also known to cause homozygous lethality around the time of implantation (Russell & Raymer, 1979; Russell et al. 1982). We report here for the first time a detailed embryological analysis of c^11DSD-homozygous embryos and find that their lethal phenotype is quite distinct from that observed for c^H/c^H embryos. The extraembryonic ectoderm is extensively developed in c^DSD/c^DSD embryos; whereas small and disorganized in c^H/c^H embryos. The amnion, chorion, allantois, exocoelom and ectoplacental cavity were all present in these embryos, which is in marked contrast to the complete lack of development of these structures in c^H/c^H embryos. Both the parietal and visceral endoderm also appear to develop normally in c^11DSD/c^11DSD embryos whereas in c^H/c^H embryos the visceral endoderm is abnormal in appearance and the parietal endoderm appears to be overproduced.

The embryonic ectoderm of c^11DSD homozygotes, while severely runted when compared to that of normal littermates, progressed further in development than the corresponding tissue of c^H/c^H embryos. Primitive-streak formation and mesoderm production occur in c^11DSD/c^11DSD but not in c^H/c^H embryos. The reason for this difference may be due to the fact that the extraembryonic structures develop extensively in c^11DSD/c^11DSD embryos but not in c^H/c^H embryos. Alternatively, there may be a gene(s) affecting the development of the embryonic ectoderm that is removed by the c^H deletion but not by the c^11DSD deletion. Surprisingly, we found that it was not possible to establish embryo-derived teratocarcinoma stem-cell lines from c^11DSD-homozygous embryos. These results indicate that both the c^H deletion and the c^11DSD deletion have removed another gene(s) that affects the viability of the inner-cell-mass cells and their descendants. This result

![Fig. 4. Complementation map of the gastrulation survival region. The c^11DSD, c^4FR60Hd, c^5FR60Hg and c^2YPSj deletion chromosomes originated from the Oak Ridge Laboratory and were originally assigned to the Bi complementation group (see Fig. 1; Russell et al. 1982). The c^H and c^H deletion chromosomes originated from the Harwell MRC Radiobiology unit and were tentatively assigned to the Bi and E complementation groups, respectively (see legend to Fig. 1). The E group deletions complement the Bi group for prenatal lethality, indicating that it is the distal of the two areas of chromosomal non-overlap between the two groups that is needed for normal development of the early postimplantation embryo. This complementation map is modified from Fig. 1 to show the distal breakpoint of the c^11DSD deletion lying more proximal than the distal breakpoint of the c^H deletion. The proposed new functional units governing the development of the embryonic and extraembryonic ectoderm are also indicated. The dotted lines and question marks for the c^4FR60Hd, c^5FR60Hg and c^2YPSj deletions indicate that nothing can be said about distal breakpoints because the lethal phenotype associated with these deletions has not yet been examined.](#)
would not have been predicted based on the histological description of the lethal phenotype associated with the homozygous state of the two deletions.

An interesting aspect of the $c^{11DSD}$ lethal phenotype is that the mesodermal layer of the amnion appears to be thicker and the development of the allantois more extensive than expected. The size of these structures relative to that of the embryonic ectoderm indicates either an overproduction of extra-embryonic mesoderm, or normal proliferation of the embryonic ectoderm coupled to a progressively slower-dividing embryonic ectoderm. When these day-8.5 homozygous embryos were cultured in vitro for two days and then sectioned, all that remained was an internal core of mesenchyme-like cells surrounded by what appeared to be endoderm (unpublished observations).

The lethal phenotype of the $c^{11DSD}/c^6H$ compound heterozygote is similar to that of the $c^{11DSD}$/homozygous embryos. These results suggest that the $c^{11DSD}$ chromosome partially complements the $c^6H$ chromosome by providing additional genetic material that allows normal development of the extraembryonic structures. However, because it was not possible to derive stem-cell lines from $c^6H$ or $c^{11DSD}$ homozygotes, both deletions seem to be missing a gene(s) that is needed for viability and development of the embryonic ectoderm. Given the consistent phenotype produced by the $c^6H$ (over ten years on different genetic backgrounds) and $c^{11DSD}$ deletions, it is unlikely that the differences between the two deletions result from segregating background genes. One possible explanation for the partial complementation is that closely linked genes are affecting the homozygous deletion (null) phenotype. A more likely explanation, however, would be that the distal breakpoint for the $c^{11DSD}$ deletion lies more proximal than the distal breakpoint for the $c^6H$ deletion (see Fig. 4). If this were the case, new functional units of chromosome 7 would be defined such that a gene(s) important for normal development of the extraembryonic ectoderm would be located in the distal region of non-overlap between the two deletions, and a gene(s) important for the development of the embryonic ectoderm would be located in the region deleted by both chromosomes. The $c^6H$ deletion would be missing both genes and belong to one complementation group; whereas the $c^{11DSD}$ deletion would be missing only the gene(s) affecting the development of the embryonic ectoderm and, therefore, belong to another complementation group. This latter hypothesis, which we favour, will be tested as molecular markers become available for this chromosomal region.

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