Sidelights
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The Sad paradox: Mutations with dominant *and* recessive phenotypes

Robert Metzenberg (June 11, 1930 – July 15, 2007) was described as 'a geneticist extraordinaire and "model human"' (Selker 2008). Claudio Scazzocchio (28 July 1938 –), a colleague and friend of Bob Metzenberg, is since his retirement a visiting professor at Imperial College, London, 'actively writing old work, spending quite a few hours a day in front of a computer; trying to learn some bioinformatics' and 'following quite closely everything that has to do with epigenetics of fungi'. In 2001, Metzenberg and colleagues reported the fascinating discovery, in *Neurospora crassa*, of meiotic silencing by unpaired DNA (MSUD). MSUD is a presumed RNAi-mediated dousing of the ascus-expression of any gene lacking a sequence homologue at the same allelic position on the homologous chromosome (e.g. the transposase gene of a transposable element inserted into a novel location; also see figure 1) (Shiu *et al*. 2001). Somewhat counter-intuitively, MSUD leads deficiencies (*Df*) to exert an ascus-dominant phenotype. In a *Df* × WT cross, genes uncovered by the *Df* on the WT chromosome remain unpaired in meiosis, and are silenced. Interestingly, the gene, *suppressor of ascus dominance-1*$^{+}$ (*sad-1*$^{+}$), which encodes a putative RNA-dependent RNA polymerase essential for MSUD, silences itself when opposite a deletion allele (*Sad-1*$^{\Delta}$), and, consequently, *Sad-1*$^{\Delta}$ suppresses MSUD in heterozygous crosses (i.e. *Sad-1*$^{\Delta}$ × WT) (figure 1). Such self-silencing is reminiscent of Bertrand Russell's famous paradox about the village barber who shaves all those who don't shave themselves: Who shaves the barber? Additionally, the homozygous *Sad-1*$^{\Delta}$ × *Sad-1*$^{\Delta}$ cross is infertile. In 2002, I wrote a 'Commentary' article describing the findings of Metzenberg and colleagues, and in it I also made reference to the paradox (Kasbekar 2002). Chancing upon my article last year, Scazzocchio graciously emailed his appreciation of it, and very soon a cordial correspondence developed between us. This correspondence brought to my possession three emails exchanged by Metzenberg and Scazzocchio in 2004, together with permission from Scazzocchio and Stan Metzenberg to use this exchange in any way I see fit. Nothing could be fitter than to publish this exchange in a new 'Sidelights' section in *Journal of Biosciences*. Interestingly, Scazzocchio also refers to Russell's paradox in this scientific correspondence, and Metzenberg seems to suggest the barber shaves himself, but so incompletely as to create doubt about whether he shaved or merely trimmed his beard.

(1) Date: 27 October 2004
To: Robert Metzenberg <rmetzenberg@yahoo.com>
From: Claudio Scazzocchio <claudio@igmors.u-psud.fr>
Subject: MSUD, of course!

Dear Bob:
I hope this finds you well, and still busy with the MSUD fascinating story.

I have been using your Cell article on MSUD and SAD as one of the articles on silencing I get first year graduate students to analyse and dissect. I had done that once in a course I gave in Chile in the spring, and last Friday with the first year graduate students here in Orsay.

While one of the students was presenting the data (actually he was very good) it occurred to me that in your article there is implicit the evidence that SAD acts twice during meiosis. And that the one 'act' that is necessary for fertility of the asci takes place BEFORE the time of MSUD.

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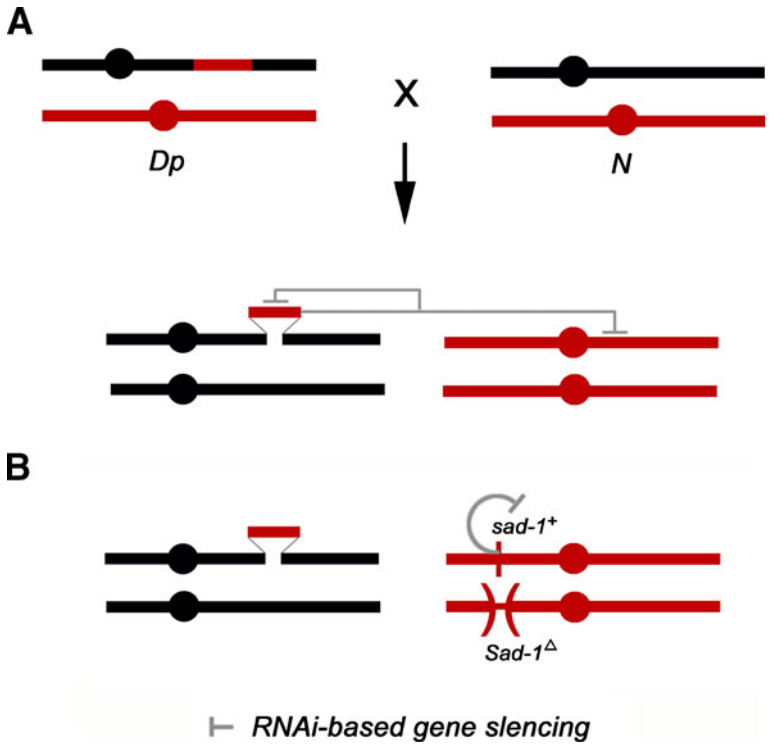

Figure 1. Genes borne on chromosome segment duplication (*Dp*) are silenced by MSUD in a *Dp*-heterozygous cross. (**A**) The cross *Dp* x WT (top panel) produces diploid zygote nuclei that undergo homologous chromosome pairing and meiosis (lower panel). *Dp*-borne genes fail to pair properly with a homolog in meiosis and produce RNAi that silences them, and genes homologous to them, regardless of whether the homologous genes themselves are paired. The silenced genes include some that are essential for meiosis and ascus formation, therefore the *Dp*-heterozygous cross is rendered barren. (**B**) *Sad-1*$^{\Delta}$ induces *sad-1*$^{+}$ to silence itself, and thereby suppresses silencing of the *Dp*-borne genes, consequently, the cross *Dp* × *Sad-1*$^{\Delta}$ shows an increase in productivity.

The argument goes like that: A SAD deletion or UV-grossly-altered-mutation is dominant because it elicits MSUD of the wild type copy. This you discuss and show clearly in the article. But you also show that this mutation is recessive in relation to fertility. And you show cytological evidence that the arrest is in the first division of meiosis, at pachytene/diplotene. So there are two alternatives. Either, the silencing by MSUD is not complete and you need far less active SAD protein for fertility than for MSUD; or, and I like this much more, the role on fertility occurs BEFORE the role for MSUD, before the wild type copy is inactivated, the latter taking place after the diplotene stage, perhaps in the second division. I think that your data are in favour of the second alternative. Your crosses heterozygous for the sad deletion or sadUV look like they have 100% of well developed asci. So it looks to me that the mutation is completely recessive for the transition from diplotene to the diakinesis stage and dominant for MSUD, which it seems to me only compatible with roles on different times of the meiotic process.

What do you think of this?

Best wishes
Claudio

(2) Date: 30 October 2004
To: Claudio Scazzocchio <claudio@igmors.u-psud.fr>
From: Robert Metzenberg <rmetzenberg@yahoo.com>
Subject: Re: MSUD, of course!

Dear Claudio,
Thank you for your interesting and provocative thoughts! I think your logic about two different times of action for the wild type SAD-1 protein is solid, and I think your conclusion is probably right. However, I am disinclined to push the interpretation to that point because the facts themselves are not as sharp-edged as one might wish. Let me explain.

First, about dominance and recessiveness of Sad-1 mutations. It is tempting to call the mutant form dominant in terms of suppressing the effects of unpairing, but the dominance is never quite complete. For example, a cross that is heterozygous for deletion of sad-1 and heterozygous for the dominant mutation 'Round spore' gives mostly spindle-shaped spores (>90%), but there is always a minority of Round spores produced. When one thinks about it, it becomes clear that Sad-1 could 'never' be completely dominant, because it requires SAD-1 product to shut down the synthesis of SAD-1 product! So it always is with autogenous control systems.

Second, it is tempting to call the mutant form recessive with respect to fertility of the cross, but once again, this recessiveness is not complete. A heterozygous cross of Sad-1 to wild type is qualitatively fertile, but, depending on genetic background etc., it is perhaps only 1/3 as fertile as a fully wild-type cross – say, a few hundred thousand ascospores per plate instead of a million.

As you know, classifying a mutant allele as recessive, co-dominant, or dominant depends on one's mode of detection. What is the correct way to classify the classical sickle-cell mutation in human beings? As I used to tell my classes when I talked about gene action, if you ask whether the heterozygote is well or sick, the answer is that the individual is well, and the mutant allele is recessive. If one classifies by running a red cell lysate, the mutant allele is co-dominant. If one classifies by resistance of the heterozygote to malaria, the mutant allele is dominant. And so it may be with *Sad-1*, so I have pushed the question to the back of my mind.

Best always,
Bob Metzenberg

(3) Date: 1 November 2004
To: Robert Metzenberg <rmetzenberg@yahoo.com>
From: Claudio Scazzocchio <claudio@igmors.u-psud.fr>
Subject: Re: MSUD, of course!

Dear Bob,
Thanks for your answer and clarification of the facts. Of course, you are right and I had proposed that other interpretation myself, all you need is that the intracellular concentration you need for fertility is lower than the one you need for MSUD, even if on aesthetic grounds I liked more the idea that SAD acted twice.

And again, you are completely right that the deletion cannot be ever totally dominant, it is almost like Russell's paradox

The example of Sickle cell anaemia is the one I use every year in my lectures! And I add that it is recessive at sea level, but dominant in La Paz, Bolivia (4000 m altitude). Well it is always fun to think aloud and correspond with you,

Very best wishes
Claudio

Acknowledgements

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References

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DURGADAS P KASBEKAR
Centre for DNA Fingerprinting and Diagnostics,
Hyderabad, 500 001
(Email, kas@cdfd.org.in; kas@ccmb.res.in)