resulted in a 20-fold increase of RHAMM on the cell surface (see Table 1 of Hall et al., 1995). Curiously, the same RHAMM1v4 isoform expressed in the same cells was later reported to be located exclusively in the cytoplasm (Zhang et al., 1998).

Questions about the physiological significance of the RHAMM transformation data are raised by the fact that the link between surface hyaluronan binding and transformation has become doubtful and that the transformation studies used a truncated and incompletely processed RHAMM cDNA clone. The same is true of other work using these truncated murine RHAMM constructs (e.g., Zhang et al., 1998). Nonetheless the role of this protein in transformation still warrants further investigation and could yet represent a novel pathway of oncogenic activity.

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Response to Hofmann et al.

RHAMM belongs to a group of hyaladherins that regulate cell motility and cell cycle and that are expressed in the cytoplasm, nucleus, and cell surface, in spite of a lack of signal peptide or transmembrane domain. Complexity of RHAMM distribution and transient expression of its small isoforms lies at the heart of the current controversy. We first reported the full-length long form of the human RHAMM cDNA (Wang et al., 1996). This cDNA was later recloned by Assmann et al. (1998). Hofmann et al. (1998) obtained the murine homolog. A smaller RHAMM isoform (v4; Hall et al., 1995) was variably detected in 3T3 cells with 5′ RACE, primer extension, and RT-PCR and corresponded to a minor 70–73 kDa protein (references in Zhang et al., 1998). This isoform is constitutively detected by RT-PCR in ras-transformed cells, the 5′ UTR is present in the RHAMM gene (unpublished data), and this isoform is transforming when overexpressed in 10T1/2 fibroblasts. Regrettably, in our *Cell* manuscript, we did not report a comparison between the transfected v4 and native v4 proteins. In RHAMMv4 transformed cells, surface RHAMM was elevated and we mistakenly predicted this surface population to be v4 (Hall et al., 1995). Subsequent epitope-tagging of this cDNA established its cytoplasmic location (Zhang et al., 1998) suggesting that surface RHAMM, whose cDNA structure has not yet been determined, was secondarily upregulated. While the Herrlich groups have been unable to find a v4 isoform, they and we noted the presence of multiple RNA transcripts and proteins, the latter even in transfected cells (Hofmann et al. 1998), suggesting RHAMM is indeed subject to extensive alternative splicing. Further, although their 95 kDa protein is widely expressed, we and others (Zhang et al., 1998; references in Masellis-Smith et al., 1996, Lovvorn et al., 1998, and Nagy et al., 1998) have noted additional, smaller, specific RHAMM protein bands including a 70–73 kDa isoform, whose high expression is transient and depends upon culture confluence (e.g., references in Zhang et al., 1998). It is not obvious whether these transient RHAMM forms are detected under the culture conditions used by the Herrlich group, making the disappearance of only 95 kDa RHAMM from RHAMM null mice difficult to assess. Several labs have noted, by FACS, EM, and function blocking, that cell surface RHAMM is constitutively expressed in migratory thymocytes (see references in Masellis-Smith et al., 1996 and Gares et al., 1998) and transiently expressed after plating or injury of adherent cells, although the precise level of expression varies (e.g., Hall et al., 1995 versus Zhang et al., 1998) depending upon which of at least six reported antibodies are used. Although the location of RHAMM in multiple cell compartments is unusual, it is not without precedence (Sheller et al., 1998). This novel class of hyaladherins, currently incompletely understood, promises to widen our understanding of how hyaluronic acid exerts its biological effects.

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