

Tumour development due to stroma permissiveness

It is widely believed that the development of the most common tumour types or ‘carcinomas’, is triggered by somatic mutations in epithelial cells (Lengauer *et al* 1998). It is thought that these mutations are, among other things, responsible for discontinuities in basement membrane reflecting changed protein production by the tumour cells, severe immune responses introducing cytokines into the tumour environment, and the formation of new blood vessels. However, it is also well known that during tumour development the neighbouring tumour microenvironment is greatly altered. The collective process of such mesenchymal alterations, denoted ‘stromagenesis’ (Ruiter *et al* 2002), occurs parallel to tumorigenesis (Beacham and Cukierman 2005) and resembles an inflammatory response during wound healing or fibrosis. Among the many host responses are additional alterations to the mesenchyme (also known as stroma) in the vicinity of the tumour (Bissell and Radisky 2001). While the microenvironment initially plays an active role in suppressing tumour development (Hochedlinger *et al* 2004; Mintz and Illmensee 1975), it is believed that at later stages it changes to support and promote tumour progression (Bhowmick *et al* 2004; Cunha and Matrisian 2002). Moreover, it has been suggested that alterations in the stroma are necessary and also sufficient to induce malignant behaviour (Maffini *et al* 2004). Hence, the concept of the stroma being recruited by the cancerous epithelia is being contested by the view that tumours originate as a consequence of alterations in reciprocal interactions between epithelium and stroma (Sonnenschein and Soto 2004).

Recently, Maffini and colleagues have elegantly demonstrated in a rat model that stroma permissiveness, either promoting or inhibiting breast carcinomas, is dependent upon both age- and reproductive-state (figure 1). In the above-mentioned manuscript featured last month in the *American Journal of Pathology*, Maffini and colleagues injected tumour cells directly into cleared (lacking epithelium) mammary fat pads of rats ranging 24 to 150 days of age (Maffini *et al* 2005). Their results showed that the stroma of younger rats, where developmental tissue-remodelling is extensive, is more permissive for developing neoplasia than that of older rats. Alternatively, the stroma of older rats is relatively protective compared to those of younger rats. Interestingly, the more permissive developmental age coincided with the period of “maximal vulnerability” to chemical carcinogenesis (Russo and Russo 1978). Remarkably, the mammary gland stroma of older rats, as well as that of twice-parous rats, were not only protective of carcinogenesis but could induce normal ductal development by reprogramming the injected tumour cells.

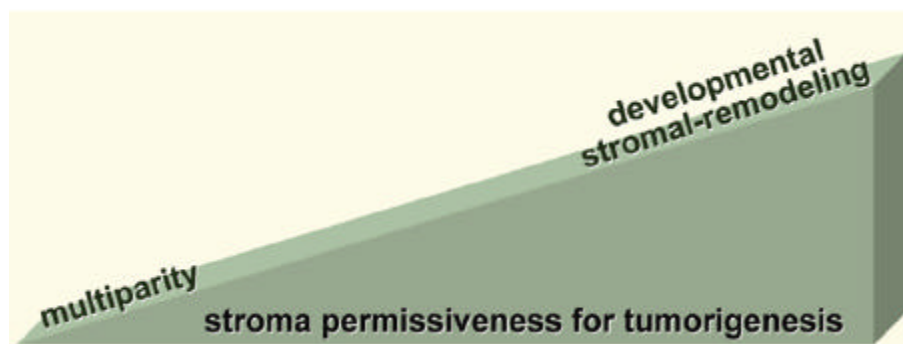


Figure 1. Model of stroma permissiveness for tumour development. The model indicates that stroma from multiparous rats is protective while developmental stages where vast stroma remodelling takes place, support and/or promote tumour development.

The above-mentioned work proposes the possibility of stromal-prevention or stromal-restriction of tumorigenesis and, thus, supports the argument stating that the stroma has the potential of re-programming neoplastic cells towards normal phenotypes in spite of their irreversible genetic alterations (Hochedlinger *et al* 2004; Mintz and Illmensee 1975). In other words, this work (Maffini *et al* 2005) suggests that future studies designed to dissect out mechanisms of stroma-mediated normalization could lead to the development of stroma targeted therapies that are able to restrict or reverse mammary gland neoplasia.

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