TUMOUR IMMUNOLOGY

Suppressing tumorigenic inflammation

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Inflammation is known to be a causal factor in tumorigenesis, and pathological inflammation in mice and humans is associated with the loss of tumour necrosis factor-α-induced protein 8-like protein 2 (TIPE2). So, Zhang, Chen and colleagues investigated the role of TIPE2 in inflammation-associated tumorigenesis.

To uncover the signalling pathways that are regulated by TIPE2, the authors looked for binding partners of TIPE2 and found that three RAL guanine nucleotide exchange factors (GEFs) — RGL, RALGDS and RGL2 — interact with TIPE2. RAL GEFs are activated by RAS GTPases, and these activate RAL GTPases (which promote cell motility) and AKT (which promotes cell survival). Focusing on RGL, they found that TIPE2 binds to the carboxyl terminus of RGL, which contains the RAS-interacting domain that is bound by activated RAS. Exogenous expression of TIPE2 inhibited RAS binding to RGL and decreased RAL-GTP levels in a mouse macrophage cell line and the 293T human embryonic kidney cell line. This suggests that TIPE2 binding prevents RAS-mediated activation of RGL, which in turn prevents the activation of RAL GTPases.

The authors investigated whether TIPE2 affects cell survival and cell motility. Exogenously expressed TIPE2 induced the death of 293T cells, and this was dependent on TIPE2–RGL binding, but not on RAL GTPase activity. RGL has previously been shown to bind 3-phosphoinositide-dependent protein kinase 1 (PDK1), which promotes preferential phosphorylation of AKT by PDK1 and hence AKT activation. TIPE2 expression reduced RGL–PDK1 binding and phosphorylated AKT levels. RAL GTPases regulate cell motility in both lymphocytes and tumour cells owing to their roles in modulating actin dynamics, and these were also inhibited by the expression of TIPE2. Therefore, TIPE2 seems to prevent RGL-mediated activation of AKT by PDK1 and activation of RAL GTPases, which could account for alterations to cell survival and cell motility.

Does TIPE2 affect tumorigenesis? The authors found that HRAS-G12V-transformed NIH3T3 mouse embryonic fibroblasts that stably expressed TIPE2 exhibited reduced growth and colony formation in soft agar. Moreover, injection of these cells into nude mice delayed tumour formation, and TIPE2 protein — but not mRNA — expression was lost in cells from these tumours in a proteasome-dependent manner. This suggests that TIPE2 is a tumour suppressor. As the development of hepatocellular carcinoma (HCC) is associated with inflammation, the authors investigated the expression of TIPE2 in 116 human HCC samples. TIPE2 was expressed in normal adjacent hepatocytes but TIPE2 protein levels were significantly reduced in tumour cells, and exogenous expression of TIPE2 significantly reduced the growth of three HCC cell lines.

This suggests that inflammation can activate RAL GEFs, an important arm of the RAS signalling cascade, to induce RAL GTPase-mediated motility and AKT-mediated cell survival by downregulating the expression of TIPE2.

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