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BASIC RESEARCH

Rebooting rhabdomyosarcoma's operating system

Embryonal rhabdomyosarcoma (ERMS)—one of the most common and deadly paediatric soft-tissue sarcomas—arises when self-renewing tumour cells arrest at early stages of muscle-cell differentiation. ERMS remains a clinical challenge as drugs that target self-renewal and differentiation of tumour cells have not been identified. Now, teams led by Xu Wu and David M. Langenau, have described a large-scale chemical screen of FDA approved—as well as novel—drugs for the ability to differentiate human ERMS into cells that express markers of terminally differentiated muscle cells, such as myosin.

In total, 40,000 compounds were screened. "Then, we took the best hits and assessed their role in modulating growth and differentiation in a zebrafish transgenic model to identify drugs that were efficacious in differentiating the cancer-stem-cell pool into non-proliferative, non-metastatic cell types," explains Wu.

Among 11 drugs that reduced tumour growth, the authors focused on characterizing the role of GSK3 inhibitors in inducing differentiation of the ERMS cells. Treatment of ERMS-bearing zebrafish with GSK3 inhibitors activated the Wnt/β-catenin pathway, which, interestingly, suppressed ERMS growth and diminished self-renewal capacity. "To our knowledge, this is the first demonstration of differentiation therapy in ERMS. We are currently moving these findings into preclinical mouse models with the long-term hope of moving the work into the clinic," concludes Langenau.

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Original article Chen, E. Y. *et al.* Glycogen synthase kinase 3 inhibitors induce the canonical WNT/β-catenin pathway to suppress growth and self-renewal in embryonal rhabdomyosarcoma. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1317731111