

Forsteronia refracta holds the key to breast cancer treatment

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Throughout human history plant products have been shown to be valuable sources of novel anti-cancer drugs. More than 120,000 plant extracts from over 6000 genera have been tested, resulting in the development of a large number of widely structurally divergent 'natural products' as candidate anti-cancer agents. The species are selected on the basis of a potentially useful phytochemical composition using ethnopharmacological, chemosystemic and ecological information. The collected samples are dried and first extracted with an organic solvent, and then with distilled water. Some of these proved clinically useful, and others served as tools to unravel the biochemical mechanisms involved in the growth and regulation of tumours. *Vinca* alkaloids derived from Madagscan periwinkle plant *Catharantus roseus*¹, the taxanes from the Pacific yew *Taxus brevifolia*² and the camptothecins derived from the Chinese tree *Camptotheca acuminata*³ have been successfully tested for anti-tumour properties.

Recent studies (*Cancer Res.*, 1 February 2005) on tumour inhibitory compounds of plant origin have yielded an impressive array of novel structures. A compound extracted and purified from the plant

Forsteronia refracta, a member of the dogbane family (Apocynaceae) found in South American Amazonian rainforest, holds the key to cure breast cancer, the leading killer disease in women. The plant has been tested for the first time for its medicinal properties and the compound has been named as SL0101. Structural studies identified SL0101 as a kaempferol glycoside. The compound works like a key in the molecular lock, inhibiting the action of cancer-linked protein RSK (ribosomal S6 kinase), which plays a role in cancer proliferation by blocking the cell cycle during G₁ phase. RSK family is Ser/Thr protein kinases that are downstream effectors of mitogen-activated protein kinase, but its biological functions are not well understood. The major determinant of SL0101-binding specificity is the unique ATP-interacting sequence in the amino-terminal kinase domain of RSK. SL0101 inhibits proliferation of the human breast cancer cell line MCF-7, producing a cell cycle block in the G₁ phase, with an efficacy paralleling its ability to inhibit RSK in intact cells⁴. RNA interference of RSK expression confirmed that RSK regulates MCF-7 proliferation.

Interestingly, SL0101 does not alter proliferation of a normal human breast cell line MCF-10A, although SL0101 inhibits RSK in these cells. RSK has an unexpected role in proliferation of transformed cells and may be a useful new target for chemotherapeutic agents. The compound is ready for clinical trials and can prove to be a new powerful tool to dissect the molecular functions of RSK in cancer cells and help in breast cancer therapy and prevention.

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