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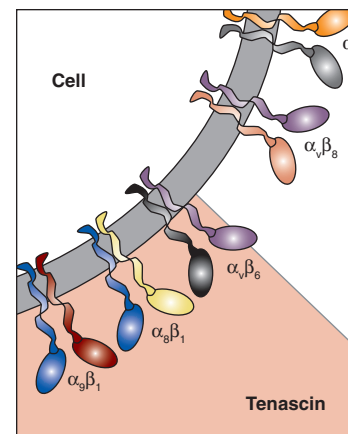
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

132 Caspase-8—Mediated Apoptosis Can Suppress Successful Metastases

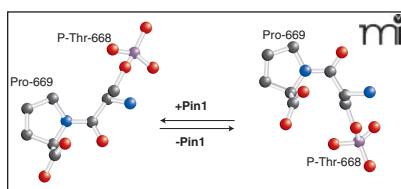
Successful metastasis is determined by the ability of tumor cells to invade surrounding tissue, survive in the circulation, extravasate, arrest, and proliferate within the secondary organ. During this process, mutations in oncogenes and tumor suppressor genes lead to genetic instability, which bestows tumor cells with a selective growth advantage and aids the acquisition of the malignant phenotype. Altered expression and activity of various components of the apoptotic pathway, including receptors, ligands, adaptors, and caspases, can contribute to malfunction of the apoptotic machinery and, ultimately, to a more malignant phenotype. The expression of caspase-8, a key apoptotic factor involved in both the extrinsic and the intrinsic apoptotic pathways, is very frequently lost in high-risk neuroblastomas, the most common group of early childhood tumors. Stupack et al. report a much higher incidence of apoptosis in caspase-8⁺, locally invasive extratumoral cells as compared with that of caspase-8⁻ cells. Conversely, knockdown of caspase-8 expression by RNA interference promotes metastasis but has no effect on primary tumor growth. Caspase-8-expressing neuroblastomas undergo apoptosis in a caspase-8-dependent manner that is independent of death receptor activation but rather might be controlled by integrin-mediated death (IMD), a process that occurs in adherent cells and that is distinct from anoikis, a form of programmed cell death resulting from a loss of integrin-mediated cell-matrix contact.

Izabela Podgorski and Bonnie F. Sloane



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Caspases and
integrin-mediated death

137 Untangling Tau and APP: The Underpinnings of Alzheimer Disease



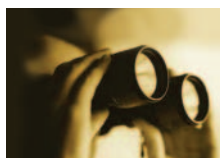
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Oh, what a tangled web
phosphorylation weaves

The neuropathological hallmarks of Alzheimer Disease (AD) are neurofibrillar tangles composed of tau protein and neuritic plaques containing the amyloid β -peptide ($A\beta$) that is derived from proteolytic processing of the amyloid precursor protein (APP). Proline is the sole α -imino acid in nature's repertoire and, therefore, the only peptide residue that can exist in *cis* or *trans* conformation. When phosphorylated on serine or threonine found adjacent to proline, both tau and APP undergo conformational changes that promote the formation of tangles and, in the case of APP, processing to $A\beta$. Now, new findings on the role of the Pin1, a peptidyl-prolyl *cis/trans* isomerase (PPIase) that catalyzes rotation of the protein backbone at proline residues, appear to indicate that Pin1 binds to and isomerizes distinct proline residues located in the commonly found phospho-Ser/Thr-Pro motif within APP to detangle APP fibers.

Interestingly, the expression of Pin1 is decreased in degenerating neurons of AD patients and causes age-dependent neurodegeneration when deleted in mice.

Thomas E. Willnow and Olav M. Andersen

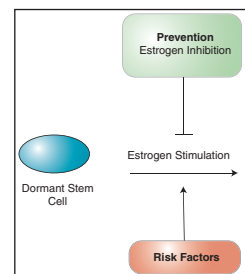


REVIEWS

140 Altering Cancer Treatment Paradigms

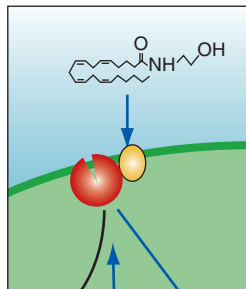
Cancer cells divide rapidly and are immortal, as are embryonic stem cells. Indeed, the term “cancer stem cells” has arisen to describe self-renewing cells within a tumor. The cancer stem cells appear to be a minority of cells in a tumor capable of immortal growth and allowing tumor transplantation. Many researchers now suspect all cancers are composed of a mixture of renewing stem cells and “committed” cells that continue to proliferate but have a limited life span. The implications of this concept are important for basic science as well as cancer therapy, because cancers that are refractory to chemotherapy, typically comprised of cells that express drug transporters and DNA repair systems, could represent the survival of cancer stem cells.

Michael Dean



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Cancer stem cells
get activated

149 Beyond the Cannabinoid Receptors



page 149
Tuning into anan-
damide transport

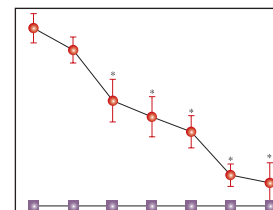
Anandamide is an endogenous lipid agonist of cannabinoid CB₁ and CB₂ receptors, and drugs that mimic or block anandamide agonism are currently being sought to treat numerous ailments, including pain, anxiety-related disorders, and obesity. But the unique routes of anandamide synthesis, turnover, and reuptake may offer avenues for therapeutic intervention other than modulation of cannabinoid receptor activation per se. Anandamide is generated from *N*-arachidonoyl phosphatidylethanolamine within the plasma membrane, and the cellular activities that must be engaged for its arrival at the cannabinoid receptor, as well as its hydrolysis by enzymes that appear primarily in the cytoplasm, continue to be unraveled by investigators. As the mechanisms for anandamide transport become elucidated, novel targets within the endocannabinoid signaling system may be identified for drug design.

Christian C. Felder, Amy K. Dickason-Chesterfield, and Steven A. Moore

162 Opening the DOR on Antidepressant Effects

Initially, it was expected that agonists of the delta-opioid receptor (DOR) would have antinociceptive properties similar to those of other opioids, without negative side effects such as respiratory depression, physical dependence, and abuse potential. Indeed, nonpeptidic delta-opioid agonists, which have greatly advanced our appreciation of DOR function, are devoid of undesirable effects, such as respiratory depression, reinforcing effects, and withdrawal symptoms, but they also have minimal pain-relieving qualities. Most intriguing is the finding that DOR agonists may have antidepressant-like effects, but the development of these compounds as antidepressants is hindered by their apparent convulsive activity. Although polypharmacy may circumvent the convulsive properties of delta-opioid agonists, the development of new nonpeptidic delta-opioid antidepressants without side effects is an ongoing goal.

Emily M. Jutkiewicz



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Treating depression with
DOR agonists