MEDICINE ELSEWHERE

Prepared by

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Chen LT, Gilman AG, Kozasa T. A candidate target for G protein action in brain. J Biol Chem 1999;274:26931-26938.

Heterotrimeric G-proteins play an essential role as transducers of information by coupling many cell surface receptors to effectors at the plasma membrane.They are classified in 4 main subgroups: Gs, Gi, Gq, G12.

Members of the Giα subfamily (Giα, Goα , Gtα, Ggα, Gzα) , particularly Goα and Giα, constitute roughly 1% of brain membrane protein; the only effector known so far to be coupled to these two proteins and also to some isoforms of Gzα, is adenylyl cyclase .

In this study, Chen et al. have elucidated a new effector candidate for G-protein action, named GRIN1 and they have also identified a homolog of that protein using public databases, designated as KIAA0514 (GRIN2). GRIN1, shown to be a novel protein without substantial homology to known protein domains, was homologous to GRIN2 for ~100-150 amino acid residues at the carboxyl terminus which is the Goα-binding domain.Both proteins interacted preferentially with activated members of the Gi subfamily of G-protein α-subunits. GRIN1 was specifically expressed in the brain and found in substantial enrichment in membranes from neuronal growth cones, as Goα.

Go is responsible for receptor-mediated inhibition of voltage sensitive N-type or P/Q-type Ca^{2+} channels in presynaptic nerve terminals, but this effect appears to be mediated by the G-protein βγ subunit complex. Goα is a weak inhibitor of some isoforms of adenylyl cyclase, but the pysiological significance of this is difficult to evaluate. Goα has also been hypothesized to regulate neurite extension. Binding of GTPγS to Goα is stimulated by GAP43, an abundant growth cone protein that is important for neural pathfinding. The expression of both GAP43 and Goα starts in brain regions when differentiated neurons begin to extend neurites.

In this paper, Chen et al. have shown that GRIN1 and GRIN2 induces extensive outgrowth of neurites from Neuro2a cells when coexpressed with activated forms of Goα. The result implies interaction between proteins *in vivo*, although not necessarily a direct one. However, the fact that Goα does interact directly with both GRIN1 and GRIN2 *in vitro* suggests that these proteins may function physiologically as downstream targets for Goα and/or other members of the Giα subfamily to regulate neurite outgrowth.

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Van Keymeulen A, Roger PP, Dumont JE, Dremier S. TSH and cAMP do not signal mitogenesis through Ras activation. Biochem Biophys Res Commun 2000; 273:154-158.

Activation of the small G protein Ras by receptor tyrosine kinases or serpentine receptors is generally considered to be essential for G1 phase progression and mutagenesis. In various systems, Ras function is required throughout G1 phase for D1 expression, $p27^{kip1}$ downregulation, pRb phosphorylation and S phase initiation.

Dog thyroid epithelial cells in primary culture constitute a well-characterized model for

studying cell cycle regulation by TSH and cAMP. In response to TSH, cAMP is generated in these cells; but interestingly, the cAMP-dependent mitogenesis is not associated with p42/ p44 MAP kinases phosphorylation and activation, suggesting that Ras is not involved in activation of this pathway. However, in the thyroid cell line, WRT, the inhibition TSH/cAMP stimulated DNA synthesis with mutants of Ras suggests an intermediary role of Ras in cAMP-dependent mitogenesis.

This study by Van Keymeulen et al. aims to reevaluate the involvement of Ras in cAMP-dependent mutagenesis. The contents of Ras-GTP were assessed in normal dog thyrocytes using an assay based on immunoreactivity between GTP-bound Ras and Raf-RBD. EGF, HGF and TPA, which trigger mitogenesis in dog thyrocytes by cAMP-independent pathway, have previously been shown to activate p42 and p44 MAP kinases in these cells. These agents were shown to lead to strong activation of Ras in this study. Insulin and carbachol which when used alone are not mitogenic factors in thyrocytes but trigger a tyrosine kinase cascade and increase the cell size, were found to activate Ras, but more weakly, than growth factors and TPA. By contrast, the basal level of GTP-Ras was slightly reduced by TSH and forskolin, a direct activator of adenylyl cyclase. In summary, this study demonstrates that TSH and cAMP which induce both proliferation and differentitation expression, do not activate Ras in dog thyrocytes.

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Pozniak CD, Radinovic S, Yang A, McKeon F, Kaplan DR, Miller FD. An anti-apoptotic role for the p53 family member, p73, during developmental neuron death. Science 2000;289:304-306.

p53 is a tumor supressor protein. A large number of functions have been attributed to p53, including apoptosis, DNA repair and maintanence of genetic stability. p73 and p63 are members of the p53 family. p73 and p63 genes have several alternatively spliced mRNA transcripts. Pozniak and colloborators have investigated whether a truncated isoform of p73 (lacking the transactivation domain) plays an antiapoptatic role or not and they have also explored the role p73 and its truncated isoform plays during mouse development.

Expression of p73 variants in the neonatal mouse brain and in the sympathetic superior cervical ganglia was characterized by RT-PCR and analysed by one and two - dimensional Western blot analysis. Full length isoforms and truncated forms (ΔNp73) were expressed in the developing brain and super cervical ganglion(SCG). ΔNp73 was characterized as the predominant isoform in neonatal sympathetic neurons *in vivo* and in cultured cells.

An adenovirus delivery system was used to maintain expression of ΔNp73 after NGF withdrawal.

This study has demonstrated that adenovirus-infected sympathetic neurons were rescued from cell death; whereas, control adenovirus-infected sympathetic neurons were not. Truncated p73 was also found to prevent cell death during normal development of sympathetic neurons in vivo.

In conclusion, Pozniak et al. have demonstrated that ΔNp73, an isoform of p73, inhibits p53 mediated neuronal apoptosis.

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Mainprize KS, Gould SWT, Gilbert JM. Surgical management of polypoid lesions of the gallbladder. Br J Surg 2000; 87: 414-417.

As ultrasound technology improves an increasing number of polypoid lesions of the gallbladder (PIGs) are being detected. They are often incidentally identified during radiographic

evaluation of abdominal pain. The distinction between benign, malignant and potentially malignant lesions is a major diagnostic dilemma and proper management of these lesions remain controversial.

In a recent study performed by Mainprize et al, 38 patients with ultrasonographically detected PLGs were reviewed for patient demography, symptoms, radiological and pathological findings. Thirty-six patients out of 38 were symptomatic of whom 34 had symptoms that could be attributable to the gallbladder. Those 34 symptomatic patients underwent cholecystectomy. There were only 11 who had macroscopic and histopathologically proven PLG in the operative specimen, giving a sensitivity of ultrasonography of 32 per cent. Of these, seven had colesterol polyps, two had adenomas, one had a carcinoid tumour and one had a tubulo villous adenoma with a focus of invasive adenocarcinoma. One patient had a histopathologically normal gallbladder. The remainder had chronic cholecystitis with or without gallstones. The malignancy rate was therefore 3 per cent (one of 34).

There was no difference in the mean age at presentation of those with chronic cholecystitis, neoplasia or non-neoplastic polyps, although the only adenocarcinoma was diagnosed in the oldest patient (80 years). All of the patients with neoplastic lesions of the gallbladder had solitary polyps greater than 1.0 cm in diameter, whereas those with non-neoplastic PLGs all had multiple lesions less than 1.0 cm in diameter.

PLGs are being found more frequently owing to improvements in ultrasound technology. Their reported frequency varies greatly, from 0.004 to 13.8 per cent of resected gallbladders.

Cholesterol polyps are the commonest form of PLG, responsible for over 60 percent of resected lesions. Benign true tumours and malignant tumours occur with a similar frequency of 5-10 percent. This is a problem as it is very difficult to distinguish benign polyps from malignant or potentially malignant ones on ultrasongraphy. Ultrasonography has a reported sensitivity of 45 to over 90 percent whereas oral cholecystography has a sensitivity of only 20 percent in most series. Endoscopic ultrasonography differentiates among polypoid lesions more precisely than ultrasonography (97% vs. 71%). Computed tomography has a reported sensitivity of 60 percent and endoscopic retrograde cholangiopancreatography is of little help.

Factors that increase the chances of a polyp in the gallbladder being malignant include age greater than 50 years, the presence of a single polyp, a polyp greater than 1.0 cm in size, the presence of gallstones, a sessile lesion even if less than 1.0 cm in size, and a rapid change in size on serial ultrasonography.

Taking into account the inaccuracy of ultrasonography in the diagnosis of these lesions, authors have proposed a protocol for the management of ultrasonographically detected PLGs. In this protocol it is suggested that all patients with a PLG should undergo surgery if they are symptomatic, or if the PLG is 1.0 cm or more in diameter. As the sensitivity of ultrasonography is variable, asymptomatic patients are rescanned and the patient is offered a laparoscopic cholecystectomy if a PLG is identified a second time. If the repeat ultrasonographic scan does not show a PLG then a further scan is performed 6 months later and the patient is dischared if no PLG is seen a second time. Patients declining operation are followed with 6-monthly scans and if the lesion increases in size they are once again offered surgery.

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Kraimps JL, Bouin-Pineau MH, Mathonnett M, et al. Multicenter study of thyroid nodules in patients with Graves' disease. Br J Surg 2000;87:1111-1113.

Thyroid nodules are common in patients with Graves' disease. The authors have previously reported that patients with Graves' disease and a thyroid nodule have a very high risk of thyroid cancer. The aim of this study was to review

patients who had surgery for Graves' disease associated with thyroid nodules, and to evaluate the risk of thyroid carcinoma...

Five hundred and fifty seven patients who had thyroidectomy for Graves' disease were studied retrospectively. All patients had undergone surgery because of recurrence of hyperthyroidism after 18 months of medical treatment or because a thyroid nodule was detected and each patient underwent clinical, biochemical, ultrasonographic and scintigraphic evluation. Surgery consisted of either a subtotal or a total thyroidectomy.

In 140 patients, a thyroid nodule was detected before operation (25.1 percent of population). Thyroid carcinoma was diagnosed histologically in 21 patients, always inside a nodule. The overall incidence of thyroid carcinoma associated with Graves' disease was 3.8 percent, rising to 15.0 percent in patients with Graves' disease and a thyroid nodule. Pathological findings consisted of 20 papillary and 1 follicular carcinoma.

In conclusion this report confirms that one-quarter of patients with Graves' disease have associated thyroid nodules. 15.0 percent of these nodules were malignant. Because of the high incidence of carcinoma in a thyroid nodule, the authors and others recommend surgery when nodules are detected during evaluation for Graves' disease. Total thyroidectomy should be considered because of the agressive nature of carcinomas in this condition.

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Fon LJ, Spence RAJ. Sportman's hernia. Br J Surg 2000;87:545-552.

This review article briefly says that keep in mind that there are conditions such as osteitis pubis and musculotendinious injuries other than hernia that make chronic groin pain. Sportsman hernia is a debilitating condition which presents as chronic groin pain. A tear occurs at the external oblique which may result in an occult hernia. The definition, investigation and the treatment of this condition remain unclear. In many cases, clinical signs are lacking despite the patient's symptoms and it is known that there is a high incidence of symptomatic impalpable hernia in patients with obscure groin pain. A medline search was performed from 1962 to 1999 pertaining to chronic groin pain, groin injury and sportsman's hernia. Routine use of CT and MR for assessment of patients with groin pain cannot be justified. They may, however, be employed in difficult cases to help define the anatomical extent of a groin injury. There is no consensus view supporting any particular surgical procedure for sportsman's hernia. Appropriate repair of the posterior wall results in therapeutic benefit in selected cases.

In conclusion the diagnosis of sportsman's hernia is difficult. The condition must be distinguished from the more common osteitis pubis and musculotendinous injuries. When conservative management has failed, surgical intervention is usually, although not always, successful.

MEETINGS

4 - 5 January 2001, London, UK

IBDG January Meeting - Copper Chemistry in Biology and Medicine

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24 - 30 March 2001, Edinburgh, UK

Society for General Microbiology 148th Ordinary Meeting:

New Challenges to Health

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ANSWER TO PHOTO QUIZ

Congenital constriction band syndrome

This is a congenital deformity of the extremities. Incidence is 1:875 births. Two common features of this syndrome are acrosyndactyly and acral absences. As the remnants of web spaces there are rings on the extremities. There is a swelling distal to the ring and the proximal part of it is normal. Neural tube defects, craniofacial abnormalities and abdominal and thoracic wall defects can occur with extremity deformities.

Simple constriction often does not require treatment. Treatment is indicated more on a cosmetic than on a functional basis. For a simple constriction ring, staged excision of the ring and staged Z-plasty of the defect can be done. Rings with large defects can be reconstructed by local flaps. In the case of increasing edema and decreasing circulation, amputation may be considered. Associated congenital abnormalities must be treated.

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