

Issue 4

Tuesday November 23, 2010

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug Management

Invest Ophthalmol Vis Sci. 2010 Nov 18. [Epub ahead of print]

Predictors for Short Term Visual Outcome after Anti-VEGF Therapy of Macular Edema due to Central Retinal Vein Occlusion.

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Abstract

Purpose: The purpose was to analyze predictive factors for best corrected visual acuity (BCVA) after anti-VEGF treatment in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO). **Methods:** This prospective study enrolled treatment-naïve patients with ME secondary to CRVO. BCVA, ophthalmoscopy, fundus photography, and spectral domain OCT (SD-OCT) imaging was performed. SD-OCT was analyzed for integrity of external limiting membrane (ELM), photoreceptor inner segments (IS) and outer segments (OS). Patients were treated with intravitreal bevacizumab (1.25 mg) or ranibizumab (0.5 mg). BCVA outcome was analyzed four weeks after the first injection. **Results:** Sixty-two eyes from 62 patients (39 m, 23 f, mean age of 67 ±16 years) were included. In 55% ELM was intact. These eyes showed also intact photoreceptor IS/OS in horizontal and vertical single scans. Disturbed ELM was seen in 45% and was accompanied by focal disintegration of IS/OS. Four weeks after injection 58% showed clinical relevant increase of BCVA (≥5 letters). Mean BCVA ranged from 20-86 letters. Mean BCVA increase was 18 ±12 letters in eyes with intact ELM versus 4 ±10 letters with disturbed ELM (p<0.001). **Discussion:** Depending on integrity of outer retinal layers we observed fast and clinical relevant improvement of BCVA after the first anti-VEGF injection. In the development of an optimal treatment regime indication for treatment and re-treatment should be based on functional and morphological findings, e.g. deterioration of outer retinal layers. **Conclusion:** Intact ELM in SD-OCT imaging is associated with better visual outcome after intravitreal anti-VEGF treatment in patients with ME secondary to CRVO.

PMID: 21087958 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2010 Nov 8;5(11):e13885.

Distinct signature of altered homeostasis in aging rod photoreceptors: implications for retinal diseases.

Parapuram SK, Cojocaru RI, Chang JR, Khanna R, Brooks M, Othman M, Zareparsis S, Khan NW, Gotoh N, Cogliati T, Swaroop A.

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Abstract

BACKGROUND: Advanced age contributes to clinical manifestations of many retinopathies and represents a major risk factor for age-related macular degeneration, a leading cause of visual impairment and blindness in the elderly. Rod photoreceptors are especially vulnerable to genetic defects and changes in microenvironment, and are among the first neurons to die in normal aging and in many retinal degenerative diseases. The molecular mechanisms underlying rod photoreceptor vulnerability and potential biomarkers of the aging process in this highly specialized cell type are unknown.

METHODOLOGY/PRINCIPAL FINDINGS: To discover aging-associated adaptations that may influence rod function, we have generated gene expression profiles of purified rod photoreceptors from mouse retina at young adult to early stages of aging (1.5, 5, and 12 month old mice). We identified 375 genes that showed differential expression in rods from 5 and 12 month old mouse retina compared to that of 1.5 month old retina. Quantitative RT-PCR experiments validated expression change for a majority of the 25 genes that were examined. Macroanalysis of differentially expressed genes using gene class testing and protein interaction networks revealed overrepresentation of cellular pathways that are potentially photoreceptor-specific (angiogenesis and lipid/retinoid metabolism), in addition to age-related pathways previously described in several tissue types (oxidative phosphorylation, stress and immune response).

CONCLUSIONS/SIGNIFICANCE: Our study suggests a progressive shift in cellular homeostasis that may underlie aging-associated functional decline in rod photoreceptors and contribute to a more permissive state for pathological processes involved in retinal diseases.

PMID: 21079736 [PubMed - in process]PMCID: PMC2975639

Ophthalmic Res. 2010 Nov 16;45(4):191-196. [Epub ahead of print]

Toll-Like Receptor 3 Polymorphism rs3775291 Is Not Associated with Choroidal Neovascularization or Polypoidal Choroidal Vasculopathy in Chinese Subjects.

Sng CC, Cackett PD, Yeo IY, Thalamuthu A, Venkatraman A, Venkataraman D, Koh AH, Tai ES, Wong TY, Aung T, Vithana EN.

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Abstract

Background/Aims: Age-related macular degeneration (AMD) is a leading cause of visual impairment. A single-nucleotide polymorphism (SNP; rs3775291) in the Toll-like receptor 3 (TLR3) gene has recently been implicated in the pathogenesis of AMD in Caucasian populations. The aim of this study was to examine this association in Chinese persons with choroidal neovascularization (CNV) secondary to AMD and polypoidal choroidal vasculopathy (PCV). **Methods:** This was an observational cross-sectional study in Singapore. Study subjects were of Chinese ethnicity and included patients with exudative maculopathy and normal control subjects. The diagnoses of CNV and PCV were made based on fundus examination, fluorescein angiography and indocyanine green angiography findings. Genomic DNA was extracted, and genotypes were determined by bidirectional DNA sequencing. We compared the allele and genotype frequencies between subjects with CNV and PCV with controls using the software PLINK. **Results:** A total of 246 subjects with exudative maculopathy (consisting of 126 with CNV and 120 with PCV) and 274 normal control subjects were recruited. The distribution of rs3775291 SNP genotypes for CNV and PCV was not significantly different from that for normal controls. **Conclusion:** This study indicates that the TLR3 rs3775291 gene polymorphism is not associated with CNV and PCV in Singaporean Chinese patients.

PMID: 21079408 [PubMed - as supplied by publisher]

Other Management & Epidemiology

Invest Ophthalmol Vis Sci. 2010 Nov 18. [Epub ahead of print]

FIGURE GROUND DISCRIMINATION IN AGE-RELATED MACULAR DEGENERATION.

Tran TH, Guyader N, Guerin A, Despretz P, Boucart M.

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Abstract

Purpose: To investigate impairment in discriminating a figure from its background, and to study its relation with visual acuity and lesion size in patients with neovascular age-related macular degeneration (AMD). **Methods:** Seventeen patients, with neovascular AMD and a visual acuity of less than 20/50 were included. Seventeen age-matched healthy subjects participated as controls. Complete ophthalmologic examination was performed on all participants. The stimuli were photographs of scenes containing animals (targets) or other objects (distractors), displayed on a computer monitor screen. Performance was compared in four background conditions: the target in the natural scene; the target isolated on a white background; and the target separated by a white space from either a structured scene or a non-structured shapeless background. Target discriminability (d') was recorded. **Results:** Performance was lower for patients than for controls. For the patients, it was easier to detect the target when separated from its background (under isolated, structured and nonstructured conditions) than it was when located in a scene. The performance of patients was improved with increasing exposure time, but remained lower in controls. Correlations were found between visual acuity, lesion size and sensitivity for patients. **Conclusions:** Figure/ground segregation is impaired in patients with AMD. A white space surrounding the object is sufficient to improve its detection and to facilitate figure/ground segregation. The results may have practical applications to the rehabilitation of the environment in patients with AMD.

PMID: 21087956 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2010 Nov 18. [Epub ahead of print]

Stereotactic radiosurgery for AMD: A Monte Carlo-based assessment of patient-specific tissue doses.

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Abstract

Purpose. To define the radiation doses to non-targeted ocular and adnexal tissues with a Monte-Carlo simulation using the IRay stereotactic low-voltage X-ray irradiation system for treatment of wet age-related macular degeneration. **Methods.** Thirty-two right/left eye models were created from 3D reconstructions of 1 mm CT images of the head and orbital region. The resulting geometric models were voxelized and imported to the MCNPX 2.5.0 radiation transport code for Monte Carlo-based simulations of AMD treatment. Clinically, treatment is delivered non-invasively by three divergent 100 kVp photon beams entering through the sclera and overlapping on the macula cumulating in a therapeutic dose. Tissue-averaged doses, localized point doses, and color-coded dose contour maps are reported from Monte Carlos simulations of x-ray energy deposition for several tissues of interest including the lens, optic nerve, macula, brain, and orbital bone. **Results.** For all eye models in this study ($n=32$), tissues at risk did not receive tissue-averaged doses over the generally accepted thresholds for serious complication, specifically the formation of cataracts or radiation-induced optic neuropathy (RON). Dose contour maps are included for three patients, each from separate groups defined by the coherence to clinically realistic treatment setups. Doses to the brain and orbital bone were found to be insignificant. **Conclusions.** The computational assessment

performed indicates that a previously established therapeutic dose can be delivered effectively to the macula with the scheme described so that the potential for complications to non-targeted radiosensitive tissues might be reduced.

PMID: 21087954 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2010 Nov 11;21(S6):69-74. [Epub ahead of print]

Macular edema: Miscellaneous.

Creuzot-Garcher C, Jonas J, Wolf S.

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Abstract

Abstract. This article provides the reader with practical information to be applied to the various remaining causes of macular edema. Some macular edemas linked to ocular diseases like radiotherapy after ocular melanomas remained of poor functional prognosis due to the primary disease. On the contrary, macular edemas occurring after retinal detachment or after some systemic or local treatment use are often temporary. Macular edema associated with epiretinal membranes or vitreomacular traction is the main cause of poor functional recovery. However, the delay to observe a significant improvement of vision after surgery should be long, as usually observed in tractional myopic vitreoschisis. Finally, some circumstances of macular edemas such as hemangiomas or macroaneurysms should be treated, if symptomatic, with the treatments currently used in diabetic macular edema or exudative macular degeneration.

PMID: 21082613 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2010 Nov 11;21(S6):62-68. [Epub ahead of print]

Postsurgical cystoid macular edema.

Zur D, Fischer N, Tufail A, Monés J, Loewenstein A.

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Abstract

Abstract. Cystoid macular edema (CME) is a primary cause of postoperative reduced vision. It may occur even when the intraoperative course is successful for operations such as cataract and vitreoretinal surgery. Its incidence following modern cataract surgery is 0.1%-2.35%. This risk is increased if there are certain preexisting systemic or ocular conditions and when there are intraoperative complications. The etiology of CME is not completely understood. Prolapsed or incarcerated vitreous and postoperative inflammatory processes have been proposed as causative agents. Pseudophakic CME is characterized by poor postoperative visual acuity. Fluorescein angiography is indispensable in the workup of CME, showing the classical perifoveal petaloid staining pattern and late leakage of the optic disk. Optical coherence tomography is a useful diagnostic tool, which displays cystic spaces in the outer nuclear layer. The most important differential diagnoses include age-related macular degeneration and other causes of CME such as diabetic macular edema. Most cases of pseudophakic CME resolve spontaneously. The value of prophylactic treatment is doubtful. First-line treatment of postsurgical CME should include topical nonsteroidal anti-inflammatory drugs and corticosteroids. Oral carbonic anhydrase inhibitors can be considered complementary. In cases of resistant CME, periocular or intraocular corticosteroids present an option. Antiangiogenic agents, though experimental, should be considered for nonresponsive persistent CME. Surgical options should be reserved for special indications.

PMID: 21082612 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2010 Nov 11;21(S6):3-9. [Epub ahead of print]

Blood-retinal barrier.

Cunha-Vaz J, Bernardes R, Lobo C.

AIBILI, Azinhaga Santa Comba, Celas, Coimbra - Portugal.

Abstract

Abstract. The blood-ocular barrier system is formed by 2 main barriers: the blood-aqueous barrier and the blood-retinal barrier (BRB). The BRB is particularly tight and restrictive and is a physiologic barrier that regulates ion, protein, and water flux into and out of the retina. The BRB consists of inner and outer components, the inner BRB being formed of tight junctions between retinal capillary endothelial cells and the outer BRB of tight junctions between retinal pigment epithelial cells. The BRB is essential to maintaining the eye as a privileged site and is essential for normal visual function. Methods of clinical evaluation of the BRB are reviewed and new directions using optical coherence tomography are presented. Alterations of the BRB play a crucial role in the development of retinal diseases. The 2 most frequent and relevant retinal diseases, diabetic retinopathy and age-related macular degeneration (AMD), are directly associated with alterations of the BRB. Diabetic retinopathy is initiated by an alteration of the inner BRB and neovascular AMD is a result of an alteration of the outer BRB. Macular edema is a direct result of alterations of the BRB.

PMID: 21082604 [PubMed - as supplied by publisher]

Ophthalmic Res. 2010 Nov 16;45(4):197-203. [Epub ahead of print]

Associations between Gender, Ocular Parameters and Diseases: The Beijing Eye Study.

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Abstract

Background: To assess relationships between gender, ocular parameters and ocular diseases. **Methods:** The Beijing Eye Study is a population-based study including 4,439 Chinese. All participants underwent a detailed ophthalmic examination, anthropometric measurements and analytic blood examinations. **Results:** In multivariate regression analysis, female gender was significantly associated with a shallower anterior chamber ($p < 0.001$) and narrower anterior chamber angle ($p = 0.001$), higher prevalence of dry eye ($p = 0.002$), lower best-corrected visual acuity ($p = 0.04$) and lower presenting visual acuity ($p = 0.046$), and with the systemic parameters of lower educational level ($p < 0.001$), rural region ($p = 0.002$), lower frequency of smoking ($p < 0.001$) and alcohol consumption ($p < 0.001$), lower body height ($p < 0.001$), lower diastolic blood pressure ($p < 0.001$) and higher systolic blood pressure ($p < 0.001$), and higher serum concentrations of triglycerides ($p = 0.005$), low-density lipoproteins ($p < 0.001$) and high-density lipoproteins ($p < 0.001$). Men and women did not vary significantly in refractive error, intraocular pressure, central corneal thickness, size of the optic disk and parapapillary atrophy, and prevalences of retinal microvascular abnormalities, trachoma, pterygia, nuclear cataract, posterior subcapsular or cortical cataract, angle-closure glaucoma, open-angle glaucoma, age-related macular degeneration and retinal vein occlusions. **Conclusions:** After controlling for systemic factors, females have a shallower anterior chamber, a narrower anterior chamber angle and a higher prevalence of dry eye.

PMID: 21079409 [PubMed - as supplied by publisher]

Hum Mol Genet. 2010 Nov 15. [Epub ahead of print]

Comparison of an expanded ataxia interactome with patient medical records reveals a relationship between macular degeneration and ataxia.

Kahle JJ, Gulbahce N, Shaw CA, Lim J, Hill DE, Barabási AL, Zoghbi HY.

Department of Molecular and Human Genetics.

Abstract

Spinocerebellar ataxias 6 and 7 (SCA6 and SCA7) are neurodegenerative disorders caused by expansion of CAG repeats encoding polyglutamine (polyQ) tracts in CACNA1A, the α 1A subunit of the P/Q-type calcium channel, and ataxin-7 (ATXN7), a component of a chromatin-remodeling complex, respectively. We hypothesized that finding new protein partners for ATXN7 and CACNA1A would provide insight into the biology of their respective diseases and their relationship to other ataxia-causing proteins. We identified 118 protein interactions for CACNA1A and ATXN7 linking them to other ataxia-causing proteins and the ataxia network. To begin to understand the biological relevance of these protein interactions within the ataxia network, we used OMIM to identify diseases associated with the expanded ataxia network. We then used Medicare patient records to determine if any of these diseases co-occur with hereditary ataxia. We found that patients with ataxia are at 3.03 fold greater risk of these diseases than Medicare patients overall. One of the diseases comorbid with ataxia is macular degeneration (MD). The ataxia network is significantly ($p=7.37 \times 10^{-5}$) enriched for proteins that interact with known MD-causing proteins, forming a MD subnetwork. We found that at least two of the proteins in the MD subnetwork have altered expression in the retina of Ataxin-7(266Q/+) mice suggesting an in vivo functional relationship with Atxn7. Together these data reveal novel protein interactions and suggest potential pathways that can contribute to the pathophysiology of ataxia, MD, and diseases comorbid with ataxia.

PMID: 21078624 [PubMed - as supplied by publisher]

Phys Med Biol. 2010 Dec 7;55(23):7037-7054. Epub 2010 Nov 12.

Assessment of targeting accuracy of a low-energy stereotactic radiosurgery treatment for age-related macular degeneration.

Taddei PJ, Chell E, Hansen S, Gertner M, Newhauser WD.

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Abstract

Age-related macular degeneration (AMD), a leading cause of blindness in the United States, is a neovascular disease that may be controlled with radiation therapy. Early patient outcomes of external beam radiotherapy, however, have been mixed. Recently, a novel multimodality treatment was developed, comprising external beam radiotherapy and concomitant treatment with a vascular endothelial growth factor inhibitor. The radiotherapy arm is performed by stereotactic radiosurgery, delivering a 16 Gy dose in the macula (clinical target volume, CTV) using three external low-energy x-ray fields while adequately sparing normal tissues. The purpose of our study was to test the sensitivity of the delivery of the prescribed dose in the CTV using this technique and of the adequate sparing of normal tissues to all plausible variations in the position and gaze angle of the eye. Using Monte Carlo simulations of a 16 Gy treatment, we varied the gaze angle by $\pm 5^\circ$ in the polar and azimuthal directions, the linear displacement of the eye ± 1 mm in all orthogonal directions, and observed the union of the three fields on the posterior wall of spheres concentric with the eye that had diameters between 20 and 28 mm. In all cases, the dose in the CTV fluctuated $< 6\%$, the maximum dose in the sclera was < 20 Gy, the dose in the optic disc, optic nerve, lens and cornea were < 0.7 Gy and the three-field junction was adequately preserved. The results of this study provide strong evidence that for plausible variations in the position of the eye during treatment, either by the setup error or intrafraction motion, the prescribed dose will be delivered to the CTV and the dose in structures at risk will

be kept far below tolerance doses.

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Pre-Clinical

Invest Ophthalmol Vis Sci. 2010 Nov 18. [Epub ahead of print]

Polarized Secretion of PEDF from Human Embryonic Stem Cell-Derived RPE Promotes Retinal Progenitor Cell Survival.

Zhu D, Deng X, Spee C, Sonoda S, Hsieh CL, Barron E, Pera M, Hinton DR.

Pathology, Keck School of Medicine, Los Angeles, United States.

Abstract

Purpose: Human embryonic stem cell-derived RPE (hES-RPE) transplantation is a promising therapy for atrophic age-related macular degeneration (AMD); however, future therapeutic approaches may consider co-transplantation of hES-RPE with retinal progenitor cells (RPC) as a replacement source for lost photoreceptors. The purpose of this study was to determine the effect of polarization of hES-RPE monolayers on their ability to promote survival of RPC. **Methods:** The hES-3 cell line was used for derivation of RPE. Polarization of hES-RPE was achieved by prolonged growth on Transwell inserts. RPC were isolated from 16-18 week gestation human fetal eyes. ELISA was performed to measure pigment epithelial derived factor (PEDF) levels from conditioned media. **Results:** Pigmented RPE-like cells appeared as early as 4 weeks in culture and were subcultured at 8 weeks. Differentiated hES-RPE had a normal chromosomal karyotype. Phenotypically polarized hES-RPE showed expression of RPE-specific genes. Polarized hES-RPE showed prominent expression of PEDF in apical cytoplasm and a marked increase in secretion of PEDF into the medium compared to non-polarized culture. RPC grown in presence of supernatants from polarized hES-RPE showed enhanced survival, which was ablated in the presence of anti-PEDF antibody. **Conclusions:** hES-3 cells can be differentiated into functionally polarized hES-RPE cells that exhibit characteristics similar to those of native RPE. Upon polarization, hES-RPE secrete high levels of PEDF that can support RPC survival. These experiments suggest that polarization of hES-RPE would be an important feature for promotion of RPC survival in future cell therapy for atrophic AMD.

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Nat Med. 2010 Nov 14. [Epub ahead of print]

Noninvasive multiphoton fluorescence microscopy resolves retinol and retinal condensation products in mouse eyes.

Palczewska G, Maeda T, Imanishi Y, Sun W, Chen Y, Williams DR, Piston DW, Maeda A, Palczewski K.

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Abstract

Multiphoton excitation fluorescence microscopy (MPM) can image certain molecular processes in vivo. In the eye, fluorescent retinyl esters in subcellular structures called retinosomes mediate regeneration of the visual chromophore, 11-cis-retinal, by the visual cycle. But harmful fluorescent condensation products of retinoids also occur in the retina. We report that in wild-type mice, excitation with a wavelength of ~730 nm identified retinosomes in the retinal pigment epithelium, and excitation with a wavelength of ~910 nm revealed at least one additional retinal fluorophore. The latter fluorescence was absent in eyes of genetically modified mice lacking a functional visual cycle, but accentuated in eyes of older wild-type mice and mice with defective clearance of all-trans-retinal, an intermediate in the visual cycle. MPM, a noninvasive imaging modality that facilitates concurrent monitoring of retinosomes along with potentially harmful products in aging eyes, has the potential to detect early molecular changes due to age-related

macular degeneration and other defects in retinoid metabolism.

PMID: 21076393 [PubMed - as supplied by publisher]

J Biol Chem. 2010 Nov 12. [Epub ahead of print]

Deuterium enrichment of vitamin A at the C20 position slows the formation of detrimental vitamin A dimers in wild-type rodents.

Kaufman Y, Ma L, Washington I.

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Abstract

Degenerative eye diseases are the most common causes of untreatable blindness. Accumulation of lipofuscin - granular deposits - in the retinal pigment epithelium (RPE) is a hallmark of major degenerative eye diseases such as Stargardt disease, Best disease and age-related macular degeneration. The intrinsic reactivity of vitamin A leads to its dimerization and to the formation of pigments such as A2E, and is believed to play a key role in the formation of ocular lipofuscin. We sought a clinically pragmatic method to slow vitamin A dimerization as a means to elucidate the pathogenesis of macular degenerations and to develop a therapeutic intervention. We prepared vitamin A enriched with the stable isotope deuterium at carbon twenty (C20-D3 vitamin A). Results showed that dimerization of deuterium-enriched vitamin A was considerably slower than that of vitamin A at natural abundance as measured in vitro. Administration of C20-D3 vitamin A to wild-type rodents with no obvious genetic defects in vitamin A processing, slowed A2E biosynthesis. This study elucidates the mechanism of A2E biosynthesis and suggests that administration of C20-D3 vitamin A may be a viable, long-term approach to retard vitamin A dimerization and by extension, may slow lipofuscin deposition and the progression of common degenerative eye diseases.

PMID: 21075840 [PubMed - as supplied by publisher]Free Article

Stem Cell Res. 2010 Oct 7. [Epub ahead of print]

Stem cell integrins: Implications for ex-vivo culture and cellular therapies.

Prowse AB, Chong F, Gray PP, Munro TP.

Abstract

Use of stem cells, whether adult or embryonic for clinical applications to treat diseases such as Parkinson's, macular degeneration or Type I diabetes will require a homogenous population of mature, terminally differentiated cells. A current area of intense interest is the development of defined surfaces for stem cell derivation, maintenance, proliferation and subsequent differentiation, which are capable of replicating the complex cellular environment existing in vivo. During development many cellular cues result from integrin signalling induced by the local extracellular matrix. There are 24 known integrin heterodimers comprised of one of 18 α subunits and one of 8 β subunits and these have a diverse range of functions mediating cell-cell adhesion, growth factor receptor responses and intracellular signalling cascades for cell migration, differentiation, survival and proliferation. We discuss here a brief summary of defined conditions for human embryonic stem cell culture together with a description of integrin function and signalling pathways. The importance of integrin expression during development is highlighted as critical for lineage specific cell function and how consideration of the integrin expression profile should be made while differentiating stem cells for use in therapy. In addition this review summarises the known integrin expression profiles for human embryonic stem cells and 3 common adult stem cell types: mesenchymal, haematopoietic and neural. We then outline some of the possible technologies available for investigating cell-extracellular matrix interactions and subsequent integrin mediated cell responses.