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Tatum DamBIO211- Cell BiologyEssay Prompt: Discuss the importance ofintercellular signaling in development.

Total Word Count: 1702Essay Word Count: 1492 Why is intercellular signalling important in development? The differentiation and regulation ofdeveloping cells is controlled through a remarkably small number of signallingpathways. Within these pathways, the propagation of intercellular signalsresults in the transcription of target genes that specify cell fate. Thesesignals are necessary for the development of an undifferentiated stem cell intoits specialized type, which determines the structure and refinement of future bodyparts. Malfunctions during intercellular signalling are associated with issues duringembryonic development and many diseases (Dennis and Bradshaw, 2011). In thisessay, the effects of cell fate specification within three intercellular signallingpathways – TGF-?, Sonic hedgehog, and Notch – will be investigated.

First, the relationship between TGF-? signalling and gastrulation will be explored. Second, the function of Sonichedgehog signalling within the induction of the chick limb bud will beexamined. Third, the way in which Notch signalling creates the adult lung willbe scrutinized.

Fourth, the harmful effects of dysregulation during intercellularsignalling will be considered as well as possible methods for new drug therapy. Overall, intercellular signalling plays a fundamental role in controlling cellfate specification; alterations within the process can hinder survival by creatingdefects within embryos and life-threatening diseases. Additionally, greaterunderstanding of how intercellular signalling is affected by mutations

will bekey for creating future drug therapies. Firstly, the transductionof the TGF-? signalling pathway is essential for embryonic development -specifically the induction of the endoderm, mesoderm, and ectoderm layers ofvertebrates. When turned on, TGF-? receptors activate a signalling cascade thatleads to the downstream activation of substrates and regulatory proteins specifyingcell fate (Park, 2011). The varying levels of Nodal signalling in differentareas of the embryo define their patterning and refinement. For instance, nodalligands and nodal-related Vg1 are highly concentrated in the dorsal vegetalregion of Xenopus, fading ventrally.

In zebrafish, there is a similar gradientwhere a higher concentration of nodal-related genes Squint (Sqt) exists on thedorsal side of the embryo (Massagué, 2012). These nodal gradients are vital for theinduction of the endoderm and mesoderm layer. The third germ layer, ectoderm, is formed in the embryo when Nodal signalling is inhibited (Gilbert 2000).

TGF-? signalling therefore plays a direct role in theinduction of the endoderm and mesoderm layers, while indirectly affecting thecell fate specification of the ectoderm layer. Expectedly, organisms witherrors in this signalling process experience mutated phenotypes. For instance, fish with mutations in short and long range nodal related ligands, Cyclops (Cyc) and Squint (Sqt), have almostno mesoderm and are completely absent of endoderm (Massagué, 2012). Overall, the activation and deactivation of TGF-? signalling controls the nodal gradient that define theendoderm, mesoderm, and, indirectly, ectoderm layers; without this processembryonic gastrulation is at risk. The secondintercellular signalling pathway vital for

embryonic development is the Sonichedgehog signalling (Shh) pathway, which uses long range signalling in order toinduce positional values across the chick limb bud (Tickle and Towers, 2017). When Sonic hedgehog is present, an intercellular signal is propagated thateventually results in the dissociation of a complex and release of CubitusInterruptus (Ci). Cubitus Interruptus then moves to the nucleus in order toturn on target genes (Abidi, 2014). Sonic hedgehog signalling is activatedwithin the polarizing region of the chick, where the Sonic hedgehog protein isbelieved to have morphogenic properties that create the identity of positionalvalues across the antero-posterior axis of the limb.

By inducing theproliferation of mesenchyme cells and regulating the anteroposterior length ofthe apical ectodermal ridge, the Sonic hedgehog signalling pathway is able tocontrol the width of the limb bud (Tickle and Towers, 2017). In order to examine therelationship between Sonic hedgehog signalling and chick development, scientistsgrafted the polarizing region onto the anterior margin of a separate chick wingbud. The experiment demonstrated Sonic hedehog's morphogenic abilities byreplicating the pattern of the host's chick wing digits (Tickle and Towers, 2017). Figure1: The figure showcases the mirror image of the positional values of the graft andhost, which each specify 3 digits. The polarizing region, containing Sonichedgehog genes, was grafted to the anterior margin of another wing bud.

TheSonic hedgehog gradient specified the antero-posterior positional values forthe three digits formed next to cells made from the polarizing region.

Thesedigits are symmetric to the ones specified by the host, which lie directlyopposite. The result is six digits patterned 3-2-1-1-2-3 from anterior toposterior (Tickle and Towers, 2017). By examining the relationshipbetween Sonic hedgehog signalling and the chick limb bud, scientists were ableto make a number of discoveries as to how digits are specified and mutated. Duringthis experiment, scientists discovered the highest threshold concentration inthe tissue closest to the polarizing region, which specified the most posteriordigit (Digit 3).

Meanwhile, the tissue with the lowest threshold concentrationexisted in the tissue farthest away from the most anterior digit (Digit 1). Additionally, further testing showed that inactivity in Gli genes resulted in polydactylousor morphologically similar digits within chick limb bud (Tickle and Towers, 2017). These experiments demonstrate that the identity of digits within thechick limb bud is determined by the threshold concentration possessed atparticular positional value and alterations during Sonic hedgehog signalling isimplicated in limb defects. Without the ability to use long-range Sonichedgehog signalling to specify positional values at varying concentrations acrossthe antero-posterior axis, proper formation of the chick limb bud would notoccur.

Lastly, the third intercellular signallingpathway necessary for embryonic development is the Notch signalling pathway, whichis responsible for the induction of the adult lung. When the Notch ligand is activated, repressorproteins are released from the CSL complex, allowing for the expression oftarget genes (Okajima, 2018). The result of this is the

differentiation ofbasal cells, creating the pseudostratifiedairway epithelial in the developing and adult lung. Basal cells express Jagligands under homeostatic conditions but do not activate Notch signalling untila population of p63+ basal cells is sufficiently grown. Notch3 is thenselectively expressed in cells in the parabasal position, where adjacent basal cellsuse Jag1 and Jag2 to activate additional Notch3 signalling. These p63+ basalcells will remain unspecified until Notch1 and Notch2 signalling is turned onfor the differentiation of secretory multiciliated cells, as shown in Figure 2(Mori et.

al, 2015). Figure 2: Within this air liquid interface culture, Notch3 isselectively activated in cells occupying the parabasal position. On Day 0, there are vivid nuclear signals for Notch3, but signals for Notch1 and Notch2do not occur until later in differentiation (Moriet.

al, 2015). Disruptions in this mechanism will causeexpansion in basal cells and altered pseudo stratification, showcasing thenecessity of Notch signaling in lung development (Mori et. al, 2015). SinceNotch signaling has a vital role in the differentiation of basal cells, research in this process may lead to discoveries related to pathogenesis in thelung. Many diseases are correlated tomutations in these intercellular signallling pathways, due to dysregulationsduring cell fate specification (Dennis and Bradshaw, 2011). For instance, certain basal cell carcinomas are linked to autonomous activation of hedgehogsignaling in the absence of a ligand due to a mutation in PTCH1 that preventsit from binding to SMO, shown in Figure 3 and 4 (Crowson, 2006). Figure3: Amutation in PTCH1 causes the protein to become

truncated, preventing it frombinding to and repressing Smoothened (SMO) in the phospholipid bilayer of theplasma membrane.

Since SMO no longer requires the presence of a Sonic hedgehogligand to inhibit PTCH1, constitutive upregulation of SMO expression occurs (Crowson, 2006). Figure 4: When SMO is freed, it is able to act as a signaltransducer that upregulates expression of Gli-1 and Gli-2 proteins, glioblastomasignalling proteins (Crowson, 2006). Activation of Gli-1 and Gli-2 helps mediateaberrant hedgehog signalling in the nucleus of epidermal cells and inducesoncogenic transcription (Gilbert, 2000). Abnormal activation of the Sonichedgehog pathway transforms adult stem cells into cancer cells that inducetumorigenesis, demonstrating the importance of regulation during cell fatespecification (Crowson, 2006).

However, combatting mutations that stem fromintercellular signalling can be incredibly difficult. For example, one way oftreating basal cell carcinoma is by targeting SMO with inhibitors. This howeverputs the transduction of other signalling pathways at risk since SMO can beindependently activated.

Additionally, clinical trials prove that increasingdrug resistance decrease the efficacy of SMO inhibitors. This leads to the question: how do scientists create drug treatments effective enough to overcome drugresistance without threatening to disrupt the transduction of importantdownstream targets? Dysregulations in intercellular signallingthreaten proper cellular development, however creating innovative drugtherapies may solve this. First off, drugs should be designed to fit the needof each tumor model in

order to minimize dangerous side effects. For instance, patients suffering from ligand independent signalling should receive Sonic hedgehoginhibitors that act at the level of SMO and not the full extent of PTCH1, sincethese cancers are associated with a ligand independent pathway (Abidi, 2014). Secondly, drugs should be developed in order to target multiple sites, including sites that may cause drug resistance. For example, the inhibitorMRT-92 has already been proven effective in treating medulloblastoma patientsby binding onto multiple sites of SMO and attacking the SMO D473H mutant, whichis known for partially blocking drug entry (Rimkus, Carpenter, Qasem, Chan, and Lo, 2016).

By creating inhibitors that are specificyet combat multiple mutant sites, scientists may be able to combat aberrantcell fate specializations that stem from disruptions in intercellular signalling. In total, the development of a stem cellinto its fully functioning cell type is regulated through intercellular signalling, a crucial process that determines the strength, functionality, and appearanceof an organism’s body. The propagation of an intercellular signal allows forthe eventual transcription of target genes that induce cellulardifferentiation. This process is particularly important for the refinement andpatterning of organisms during embryonic development (Basson, 2012). Frominducing the primary germ layers in TGF-? signalling, creating the adult lungin Notch signalling, and specifying the positional values of chick limb buds, intercellular signalling plays an incredibly diverse role in determining cellfate. Alterations within intercellular signalling can result in organisms withmutated phenotypes as well as life-threatening

illnesses, due to issues with propercell fate specification (Crowson, 2006). However, by developing new drugtherapies, such as inhibitors that target multiple sites without hindering thetransduction of other downstream targets, scientists may be able to combat thedysregulations that threaten the development of stem cells (Rimkus, Carpenter, Qasem, Chan, and Lo, 2016). Due to theessential role of intercellular signalling within the activation of targetgenes that regulate cellular differentiation, it is critical to protect this pathwayfrom mutations that give rise to embryonic defects and fatal diseases.

References1. Abidi, A. (2014). Hedgehogsignaling pathway: A novel target for cancer therapy: Vismodegib, a promisingtherapeutic option in treatment of basal cell carcinomas. Indian Journal ofPharmacology, 46(1), 3–12. https://www. ncbi.

nlm. nih. gov/pmc/articles/PMC3912804/2. Basson, M. A.

(2012) Signaling in Cell Differentiation andMorphogenesis. ColdSpring Harbor Perspectives in Biology, 4(6), a008151. 3. Crowson, A.

Neil (2006) Basal cell carcinoma: biology, morphology and clinical implications, Nature Modern Pathology, https://www. nature. com/articles/3800512. 4. Dennis, E. & Bradshaw, R. (2011)Intercellular Signalling in Development and Disease (1st Edition), Academic Press, Massachusetts.

5. Gilbert S. F.

(2003) DevelopmentalBiology (7th Edition) Sunderland: Sinauer Associates, Massachusetts. 6. Massagué, Joan (2012) TGF? signallingin context. Nature Reviews Molecular Cell Biology, https://www.

nature. com/articles/nrm3434. 7. Mori, M., Mahoney, J. E.

, Stupnikov, M. R., Paez-Cortez, J.

R., Szymaniak, A. D., Varelas, X.

, Cardoso, W. V. (2015) Notch3-Jagged signaling controls the pool ofundifferentiated airway progenitors. Development (Cambridge, England), 142(2), 258–267. https://www.

ncbi. nlm. nih. gov/pubmed/255646228. Park, K.-S. (2011)TGF-beta Family Signaling in Embryonic Stem Cells.

International Journal of Stem Cells, 4(1), 18–23. 9. Okajima, Tetsuya (2018) NotchSignalling: A sweet strategy.

Nature Chemical Biology, https://www. nature. com/articles/nchembio.

2532 10. Rimkus, T. K., Carpenter, R. L., Qasem, S., Chan, M.

, & Lo, H.-W. (2016).

Targeting the Sonic HedgehogSignaling Pathway: Review of Smoothened and GLI Inhibitors. Cancers, 8(2), 22. https://www. ncbi. nlm. nih.

gov/pmc/articles/PMC4773745/11. Tickle, C., , M.

(2017). Sonic Hedgehog Signaling in Limb Development. Frontiers in Cell and DevelopmentalBiology, https://www. frontiersin. org/articles/10. 3389/fcell. 2017. 00014/full