

Tatum and regulation of developing cells is controlled



Tatum DamBIO211- Cell Biology Essay Prompt: Discuss the importance of intercellular signaling in development. Total Word Count: 1702
Essay Word Count: 1492 Why is intercellular signalling important in development? The differentiation and regulation of developing cells is controlled through a remarkably small number of signalling pathways. Within these pathways, the propagation of intercellular signals results in the transcription of target genes that specify cell fate. These signals are necessary for the development of an undifferentiated stem cell into its specialized type, which determines the structure and refinement of future body parts.

Malfunctions during intercellular signalling are associated with issues during embryonic development and many diseases (Dennis and Bradshaw, 2011). In this essay, the effects of cell fate specification within three intercellular signalling pathways - TGF- β , Sonic hedgehog, and Notch - will be investigated. First, the relationship between TGF- β signalling and gastrulation will be explored. Second, the function of Sonic hedgehog signalling within the induction of the chick limb bud will be examined. Third, the way in which Notch signalling creates the adult lung will be scrutinized. Fourth, the harmful effects of dysregulation during intercellular signalling will be considered as well as possible methods for new drug therapy. Overall, intercellular signalling plays a fundamental role in controlling cell fate specification; alterations within the process can hinder survival by creating defects within embryos and life-threatening diseases.

Additionally, greater understanding of how intercellular signalling is affected by mutations will be key for creating future drug therapies. Firstly, the transduction of the TGF- β signalling pathway is essential for embryonic

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development -specifically the induction of the endoderm, mesoderm, and ectoderm layers of vertebrates. When turned on, TGF- β receptors activate a signalling cascade that leads to the downstream activation of substrates and regulatory proteins specifying cell fate (Park, 2011). The varying levels of Nodal signalling in different areas of the embryo define their patterning and refinement. For instance, nodal ligands and nodal-related Vg1 are highly concentrated in the dorsal vegetal region of *Xenopus*, fading ventrally. In zebrafish, there is a similar gradient where a higher concentration of nodal-related genes Squint (Sqt) exists on the dorsal side of the embryo (Massagué, 2012).

These nodal gradients are vital for the induction of the endoderm and mesoderm layer. The third germ layer, ectoderm, is formed in the embryo when Nodal signalling is inhibited (Gilbert 2000). TGF- β signalling therefore plays a direct role in the induction of the endoderm and mesoderm layers, while indirectly affecting the cell fate specification of the ectoderm layer. Expectedly, organisms with errors 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 almost no mesoderm and are completely absent of endoderm (Massagué, 2012). Overall, the activation and deactivation of TGF- β signalling controls the nodal gradient that define the endoderm, mesoderm, and, indirectly, ectoderm layers; without this process embryonic gastrulation is at risk.

The

second intercellular signalling pathway vital for embryonic development is

the Sonic hedgehog signalling (Shh) pathway, which uses long range
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signalling in order to induce positional values across the chick limb bud (Tickle and Towers, 2017). When Sonic hedgehog is present, an intercellular signal is propagated that eventually results in the dissociation of a complex and release of Cubitus Interruptus (Ci). Cubitus Interruptus then moves to the nucleus in order to turn on target genes (Abidi, 2014). Sonic hedgehog signalling is activated within the polarizing region of the chick, where the Sonic hedgehog protein is believed to have morphogenic properties that specify positional values across the antero-posterior axis of the limb.

By inducing the proliferation of mesenchyme cells and regulating the anteroposterior length of the apical ectodermal ridge, the Sonic hedgehog signalling pathway is able to control the width of the limb bud (Tickle and Towers, 2017).

In order to examine the relationship between Sonic hedgehog signalling and chick development, scientists grafted the polarizing region to the anterior margin of another wing bud. The experiment proved how the Sonic hedgehog signalling pathway specified positional values in chick limb buds, as seen in Figure 1 (Tickle and Towers, 2017). Figure 1: The figure showcases the mirror image of the positional values of the graft and host. The polarizing region, containing Sonic hedgehog genes, was grafted to the anterior margin of another wing bud. The Sonic hedgehog gradient specified the antero-posterior positional values for the three digits formed next to cells made from the polarizing region. Directly opposite from this are 3 digits that were specified by the host. The result is six symmetric digits patterned 3-2-1-1-2-3 from anterior to posterior (Tickle and Towers, 2017).

By examining the relationship between Sonic hedgehog signalling and the chick limb bud, scientists were able to make a number of discoveries as to how digits are specified and mutated. During this experiment, scientists discovered the highest threshold concentration in the tissue closest to the polarizing region, which specified the most posterior digit (Digit 3).

Meanwhile, the tissue with the lowest threshold concentration existed in the tissue farthest away from the most anterior digit (Digit 1). Additionally, further testing showed that inactivity in Gli genes resulted in polydactylous or morphologically similar digits within chick limb bud (Tickle and Towers, 2017). These experiments demonstrate that the identity of digits within the chick limb bud is determined by the threshold concentration possessed at the positional value and alterations during Sonic hedgehog signalling is implicated in limb defects. Without the ability to use long-range Sonic hedgehog signalling to specify positional values across the antero-posterior axis, proper formation of the chick limb bud would not occur.

Lastly, the third intercellular signalling pathway necessary for embryonic development is the Notch signalling pathway, which is responsible for the induction of the adult lung. When the Notch ligand is activated, repressor proteins are released from the CSL complex, allowing for the expression of target genes (Okajima, 2018). The result of this is the differentiation of basal cells, creating the pseudostratified airway epithelium in the developing and adult lung. Basal cells express Jag ligands under homeostatic conditions but do not activate Notch signalling until a population of p63+ basal cells is fully grown. Notch3 is then selectively expressed in

cells in the parabasal position, where adjacent basal cells use Jag1 and Jag2 to activate additional Notch3 signalling.

These p63+ basal cells will remain unspecified until Notch1 and Notch2 signalling is turned on for the differentiation of secretory multiciliated cells, as shown in Figure 2 (Moriet. al, 2015). Figure 2: Within this air liquid interface culture, Notch3 is selectively activated in cells occupying the parabasal position.

On Day 0, there are clear nuclear signals for Notch3, but signals for Notch1 and Notch2 do not occur until later in differentiation (Moriet. al, 2015). Disruptions in this mechanism will cause expansion in basal cells and altered pseudo stratification, showcasing the necessity of Notch signaling in lung development (Mori et. al, 2015). Since Notch signaling has a vital role in the differentiation of basal cells, research in this process may lead to discoveries related to pathogenesis in the lung. Many diseases are correlated to mutations in these intercellular signalling pathways, due to dysregulations during cell fate specification (Dennis and Bradshaw, 2011).

For instance, certain basal cell carcinomas are linked to autonomous activation of hedgehog signaling in the absence of a ligand due to a mutation in PTCH1 that prevents it from binding to SMO, shown in Figure 3 and 4 (Crowson, 2006). Figure 3: A mutation in PTCH1 causes the protein to become truncated, preventing it from binding to and repressing Smoothed (SMO) in the phospholipid bilayer of the plasma membrane. Since SMO no longer requires the presence of a Sonic hedgehog ligand to inhibit PTCH1, constitutive upregulation of SMO expression occurs (Crowson, 2006).

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Figure 4: When SMO is freed, it is able to act as a signal transducer that upregulates expression of Gli-1 and Gli-2 proteins, glioblastoma signalling proteins (Crowson, 2006). Activation of Gli-1 and Gli-2 helps mediate aberrant hedgehog signalling in the nucleus of epidermal cells and induces oncogenic transcription (Gilbert, 2000). Abnormal activation of the Sonic hedgehog pathway transforms adult stem cells into cancer cells that induce tumorigenesis, demonstrating the importance of regulation during cell fate specification (Crowson, 2006). However, combatting mutations that stem from intercellular signalling can be incredibly difficult. For example, one way of treating basal cell carcinoma is by targeting SMO with inhibitors. This however puts the transduction of other signalling pathways at risk since SMO can be independently activated. Additionally, clinical trials prove that increasing drug resistance decrease the efficacy of SMO inhibitors.

This leads to the question: how do scientists create drug treatments effective enough to overcome drug resistance without threatening to disrupt the transduction of important downstream targets? Dysregulations in intercellular signalling threaten proper cellular development, however creating innovative drug therapies may solve this. First off, drugs should be designed to fit the need of each tumor model in order to minimize dangerous side effects. For instance, patients suffering from ligand independent signalling should receive Sonic hedgehog inhibitors that act at the level of SMO and not the full extent of PTCH1, since these 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 inhibitor MRT-92 has already been proven effective in treating medulloblastoma patients by binding onto multiple sites of SMO and attacking the SMO D473H mutant, which is known for partially blocking drug entry (Rimkus, Carpenter, Qasem, Chan, and Lo, 2016). By creating inhibitors that are specific yet combat multiple mutant sites, scientists may be able to combat aberrant cell fate specializations that stem from disruptions in intercellular signalling. In total, the development of a stem cell into its fully functioning cell type is regulated through intercellular signalling, a crucial process that determines the strength, functionality, and appearance of an organism's body. The propagation of an intercellular signal allows for the eventual transcription of target genes that induce cellular differentiation.

This process is particularly important for the refinement and patterning of organisms during embryonic development (Basson, 2012). From inducing the primary germ layers in TGF- β signalling, creating the adult lung in Notch signalling, and specifying the positional values of chick limb buds, intercellular signalling plays an incredibly diverse role in determining cell fate. Alterations within intercellular signalling can result in organisms with mutated phenotypes as well as life-threatening illnesses, due to issues with proper cell fate specification (Crowson, 2006). However, by developing new drug therapies, such as inhibitors that target multiple sites without hindering the transduction of other downstream targets, scientists may be able to combat the dysregulations that threaten the development of stem cells (Rimkus, Carpenter, Qasem, Chan, and Lo, 2016). Due to the essential role of intercellular signalling within the activation of target genes that

regulate cellular differentiation, it is critical to protect this pathway from mutations that give rise to embryonic defects and fatal diseases.

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