and ZPA, maintaining proliferation of the cells underneath. Shh is responsible for posterior patterning, while Fgfs are responsible for distal patterning. Also included in this feedback loop is the secreted factor, wingless-7a (Wnt-7a). This factors region of expression is in the dorsal aspect of the limb bud, while Engrailed-1 (En-1) is expressed in the ventral region. En-1 is an inhibitor of Wnt-7A, setting up the dorsoventral axis (figure 2). Another important factor upregulated during injury is Msx1, a Hox gene, which is also found in the limb bud, supporting both the undifferentiated and proliferating cells (Simon et al., 1995). There is massive complexity in the maintenance of all these signalling molecules.

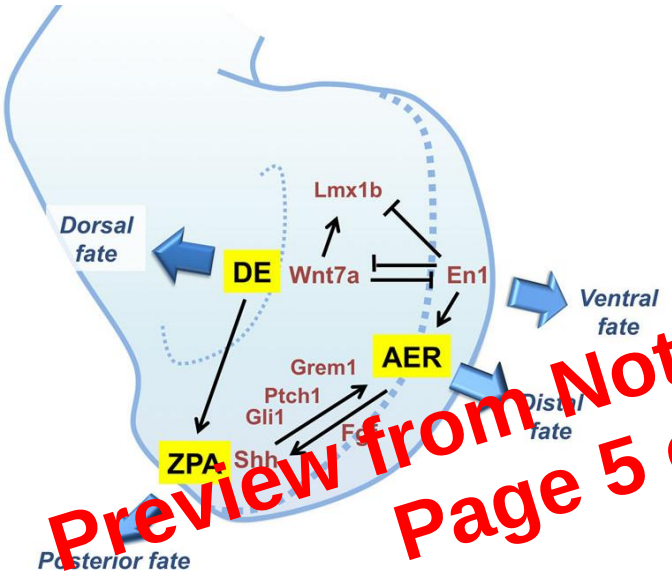

***Figure 2**- shows a limb bud with its key signalling centres; the ZPA, AER and DE (dorsal ectoderm). Also shown are the signalling molecules required for limb bud and blastema formation.*

(Taken from Yamamoto et al., 2012).

This describes a large similarity between limb regeneration and limb development, as the outgrowth of both is reliant upon the key signalling molecules mentioned above. However, in the limb bud Fgf expression originally comes from lateral plate mesoderm, while in the blastema the nerves are responsible for secretion of these factors (Zenjari et al., 1997). This seems to suggest that the fundamentals of limb regeneration are a repetition of the former limb development. The signals from the AER initiate differentiation of cells in the limb bud, while the signals from the AEC are required for the dedifferentiation of adult tissue cells, followed by the differentiation of these blastema cells into functioning, regenerated limb structures. This is the key feature required for amphibians remarkable ability to regenerate