Figure II Pancreatic genes mutations

Procaspase 9 which will convert Procaspase 3 into caspase 3 from caspase 9.

***INTRINSIC PATHWAY OF APOPTOSIS***

Bl2

Apoptosis

Caspase 3

Activate nucleus enzymes

Chromosome and DNA degrade

In response to signaling molecules, a protein P53 will be activated which will halt the cell in the current stage and will recruit proteins such as Bax which makes mitochondrial pore

Caspace 3 will activate nucleus enzymes and this does so by degrading the inhibiting enzyme of nucleus

this active nucleus enzymes can go inside and find chromosome and start degrading them and with this degraded DNA, cell cannot survive and hence cell undergo apoptosis via intrinsic pathway

Protease result in protein and nucleic acid breakdown with the formation of bulges known as apoptotic belbs/apoptotic bodies. These cells will shrink and condense destroy the cells and Macrophage will engulf those bodies

MMP pores

Cytochrome c release to cytosol by mitochondria acting as a death signal

Procaspase 9

Afaf-1

Apoptosome

Caspase9

Procaspase 3

BAD

Cytohrome c will pair with Afaf-1 to activate caspase 9 from its precursor procaspase 3

Bcl-2

BIM

tBID

Extrinsic Pathway

Inhibition of anti-apoptotic factors

Activation of pro-apoptotic factors

Cell signaling molecules Receive damage signal

Damage to DNA (cellular stress)

Figure III Intrinsic apoptosis pathway for programmed cell death

Caspase 8 can activate the molecule bid to tbid which will activate Bax and Bak which will trigger intrinsic pathway

Bid

Tbid

Cell stress signal DNA damage

Death receptors

Death domain signal DISC (death inducing signaling cascade)

Caspase 8

Procaspase 8

DISC complex active caspase 8 from precursor procaspase 8. Caspase 8 can activate caspase 3 from procaspase 3

Procaspase 3

Caspase 3

Bax , Bak activation

Intrinsic pathway

Apoptosis

Caspase 8 can degrade inhibitor holding on to nuclear enzyme freeing the nucleus making it active which will breakdown DNA, chromosome and will eventually lead to death of cell

Death domain containing receptors are fast receptors. The signal when received from outside the cell due to infection or DNA damage attach to the fast ligand receptor and activate intracellular death domain receptors. Due to multiple receptors of close proximity death receptors will be activated and give death domain signal DISC

**EXTRINSIC PATHWAY OF APOPTOSIS**

Figure IV Extrinsic pathway of Apoptosis

Figure I Pancreatic Receptors with treatment options

Reduction in cell migration and invasion[[15](#_ENREF_15)]

farnesoid X receptor

Guggulsterone-mediated FXR inhibition

sigma-2 receptors

sigma-2 ligand SW43

Augment Gemicitabine, Stabalize tumor volume[[16](#_ENREF_16)]

chemokine receptor CXCR4

Treatment of fresh human PDA slices with combination PD-1 and CXCR4 blockade[[2](#_ENREF_2)]

Apoptosis

Migration of CD8+ towards Epithelial tumor cells [[10](#_ENREF_10)]

mesothelin receptors

Engineered T cells to transiently express a mRNA encoding a chimeric antigen receptor (CAR) specific for [mesothelin](https://www.sciencedirect.com/topics/medicine-and-dentistry/mesothelin) [[18](#_ENREF_18)]

 Autologous T cells genetically modified with a CAR that recognizes mesothelin [[22](#_ENREF_22), [23](#_ENREF_23)]

Ephrine receptor EPHA4

knockdown of EPHA4 by siRNA inhibits the motility and invasion of pancreatic cancer cells. [[12](#_ENREF_12)]

GRIA3 receptor

Inhibitors of glutamate receptors such as GYKI52466 and SYM2206 significantly decreased survival of pancreatic cancer cells[[17](#_ENREF_17)]